

# Pathogenesis and Treatment of Dyskalemia in Maintenance Hemodialysis and CAPD

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In end-stage renal disease (ESRD) patients regardless of dialysis modes, i.e. maintenance hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD), potassium (K) homeostasis is regulated primarily via dialysis and extrarenal K regulation in the diverse daily K intake. However, K metabolism has been known to differ greatly between the two main methods of dialysis. Hyperkalemia is a common complication (10-24%) and the most common cause of the death (3-5%) among electrolyte disorders in patients on maintenance HD. On the contrary, hypokalemia (10-36%) is responsible for a rather common complication and independent prognostic factor on CAPD. Although excessive K intake or inadequate dialysis on maintenance HD and poor nutritional K intake on CAPD are accused without doubts upto 50% of ESRD patients as a primary cause of the K-imbalance, i.e. hyperkalemia on HD and hypokalemia on CAPD, other contributory factors including certain medications and unknown causes remain still to be resolved. Accordingly, the effects of medications as another source of K-imbalance on HD with RAS blockades and beta blockers as well as those of conventional and glucose-free dialysates (Icodextrin) for internal K-redistribution on CAPD were evaluated with reviewing the literatures and our data. Furthermore, new developments in the clinical managements of hyperkalemia on HD following the exclusion of pseudohyperkalemia before the initiation of dialysis were suggested, especially, by the comparison of the effects between mono- and dual-therapy with medications for transcellular K shifting in the emergent situation. Also, the intraperitoneal K administration via conventional glucose-containing (2.5%) and glucose-free dialysates (Icodextrin) as a specific route of K-supplementation for hypokalemia on CAPD was examined for its efficiency and the degree of intracellular K shift between these two different types of dialysates.

**Key Words :** Hyperkalemia, Hypokalemia, Hemodialysis, Continuous ambulatory peritoneal dialysis

## Introduction

In ESRD patients on renal replacement therapy, K homeostasis is mainly maintained on adequate dialytic K removal and adapted extrarenal K regulation<sup>1)</sup>. However, due to the different dialysis modes between HD and CAPD, i.e. the episodic (3-4 times/wk) in HD versus the daily continuous dialysis in CAPD, HD patients do not achieve a steady blood [K] leading to

usually highest before dialysis and lowest immediately after dialysis while CAPD patients approach a steady state for it's level, so that wide variations in blood [K] are not present. Excessive dietary K gain before dialysis in HD can temporarily contribute to the development of hyperkalemia but poor dietary K intake in CAPD may lead to hypokalemia. Therefore, hyperkalemia would be more frequent in hemodialysis than in CAPD, especially predialysis stage, and hypokalemia more frequent in CAPD than in HD.

The K imbalance in dialysis patients seems to be primarily related to poor dietary compliance. In fact, too much K intake with poor compliance to diet in interdialytic interval in HD despite adequacy of HD

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contributes to the high frequency of hyperkalemia (10–24%) responsible for the most common cause of death (3–5%) among electrolyte imbalances, whereas malnutrition with poor K intake in CAPD is a well known factor for the high prevalence of hypokalemia (10–36%) leading to the higher cardiovascular mortality than normokalemic CAPD patients in a recent study<sup>2)</sup>.

However, besides dietary factors, there are other important factors to be considered among the causes of K imbalance in dialysis patients regardless of dialysis modes, since they are mostly remediable with identifying and then avoiding or removing them. Those are clinical conditions causing the derangement of the external K regulation including abnormal colonic K secretion, i.e. constipation or diarrhea, as well as administration of drugs affecting internal K balance in K homeostatic mechanism related to neurohormones such as insulin, catecholamines, and renin-angiotensin-aldosterone (RAS), such as non-selective beta-blockers, ACE-inhibitors and/or ARBs, and aldosterone receptor blocker (spironolactone, eplerenone). As another factor for K homeostasis in the patients on CAPD, daily continuous infusion of standard glucose containing dialysates might be involved in intracellular K shift related to insulin hormone and showed high intracellular K contents in muscles as shown in a few studies. Recently, Icodextrin with glucose-polymer solution leading to less glucose load and less insulin secretion has been replaced for the patients on CAPD with ultrafiltration failure during long overnight dwell, which might affect K distribution in them<sup>3)</sup>.

In this paper, the etiologies responsible for hyperkalemia in HD and for hypokalemia in CAPD with evaluation of their prevalence and incidence as well as their treatments based on the contributing factors for the K imbalances are reviewed with collected data from the literature and our data.

### Hyperkalemia on Hemodialysis

HD patients with ESRD are continuously exposed to

the risk of hyperkalemia due to episodic removal of body K through dialysis for 3 to 4 hrs with 3 or 4 times per week in frequency rather than continuous K excretion by the intact kidneys. However, the degree of hyperkalemia in HD during the interdialytic period depends on several factors: 1) a dietary K intake, 2) the amount of dialysate K removal by HD related to the [K] gradient and to the K passive refilling from ICF to ECF, 3) increased intestinal excretion of K as an adaptive extrarenal K homeostasis<sup>4)</sup>, and 4) the transcellular K shifts as in healthy subjects.

Hyperkalemia was pointed out as a “potential silent killer” and suggested even one of the leading causes of sudden death in HD patients<sup>5)</sup>. In our survey of HD patients during past 10 yrs, 108 out of 548 patients (20%) expired, and its most common causes are cardiovascular disorder (44%) and infection (17%) same as reported in the world literature, but other notable causes included unknown etiologies (22%) and hyperkalemia (6%)<sup>6)</sup>. In the admitted patients with severe hyperkalemia, the most common causes of hyperkalemia were related to inadequate dialysis with non-compliance to HD frequency per week (55%) and excessive K intake with noncompliance to dietary regimen (35%) followed by others including medications<sup>7)</sup>.

Nonselective beta-blockers have been shown to increase serum [K] in patients with ESRD due to preventing intracellular K shift by the inhibition of beta-2 adrenergic receptors.<sup>8–9</sup> However, nonselective beta-adrenergic blocker with a selective alpha-1 blocking activity, carvedilol, did not enhance the hyperkalemic effect of moderate physical exercise on HD, but in our observation predialysis-serum [K] with carvedilol was significantly higher than that without it ( $5.13 \pm 1.0$  mEq/L vs  $5.7 \pm 1.0$  mEq/L)<sup>10)</sup>.

Though renin-angiotensin-aldosterone system (RAAS) blockers such as ACEi, ARB and spironolactone or Eplerenone currently are recommended in HD patients for the cardio-protective effects, it has been reported to be independently associated with an increased risk of developing hyperkalemia<sup>11)</sup>. Recently, low-dose spiro-



basis, the administration of laxative such as bisacodyl increasing colonic K secretion<sup>20)</sup>, and exogenous mineralocorticoid or mineralocorticoid-like substance may provide simple means of reducing interdialytic hyperkalemia in HD<sup>21, 22)</sup>.

### Hypokalemia on CAPD

In our analysis of serum [K] profile in stable CAPD patients (n=253)<sup>23)</sup>, normokalemia (83%) and hypokalemia (16%) were much more frequent than hyperkalemia (1%), being similar to the recent data of Chinese CAPD patients, i.e. normokalemia (80%), hypokalemia (20%), and none in hyperkalemia<sup>21)</sup>. The Chinese data revealed that serum [K] is correlated with serum albumin level ( $r=0.17$ ;  $p=0.005$ ) suggesting close relation between hypokalemia and malnutrition. Also, on analysis of serum [K] profile in admitted CAPD patients for 3 yrs, we observed the significant differences between groups of hypokalemia (11/48, 23%) and without hypokalemia (37/48, 77%) in serum albumin, BUN, and creatinine levels. Furthermore, the history of poor dietary intake was more prominent in hypokalemic patients (9/11 vs 6/37,  $p<0.01$ ), but daily K loss via dialysates was similar in two groups. These data support strongly that high prevalence of hypokalemia in CAPD as well as the close correlation of hypokalemia with malnutrition and poor dietary K intake<sup>24)</sup>. However, one study investigated for the pathogenetic mechanism of hypokalemia in CAPD with measuring the amount of K intake minus that of urinary and peritoneal K excretion and considering stool K losses of around 6–50 mEq/day. External K imbalance (i.e. K losses) alone was not enough to justify the hypokalemia. Therefore, the deranged internal K balance, i.e. intracellular K shift by mostly insulin hormone stimulated by the continuous glucose peritoneal infusion in CAPD, was proposed as a contributory factor for the development of hypokalemia even in the context of a low K excretion<sup>25)</sup>. In our recent study, the mean serum [K] was higher in the

group of glucose-free dialysates (Icodextrin) than in the group of standard glucose dialysates for long overnight-dwell ( $4.6\pm 0.1$  mEq/L vs  $4.4\pm 0.1$  mEq/L,  $p<0.05$ ).<sup>13</sup> For K supplementation in the management of hypokalemia, K could be generally administered via oral or intravenous routes. Furthermore, K mixed with dialysate solution would be administered thru intraperitoneal route upto 40 mEq in 2 L dialysate safely. In hypokalemic patient ( $<3.5$  mEq/L), 40 mEq KCl in 2 L dialysate was administered safely and efficiently. The degree of K absorption via peritoneum and that of intracellular shift of absorbed K were  $76\pm 6\%$  and  $74\pm 19\%$ , respectively, and the increment of serum [K] was  $0.8\pm 0.2$  mEq/L.<sup>26</sup> A recent study of comparison of intraperitoneal K administration (40 mEq mixed in 2 L dialysate) after one exchange between standard 2.5 % glucose and glucose-free (Icodextrin) dialysates revealed the less increase in serum [K] ( $0.18\pm 0.1$  mEq/L vs  $0.56\pm 0.1$  mEq/L,  $p<0.05$ ), despite the less increment of insulin level from basal value ( $-19\pm 9\%$  vs  $37\pm 12\%$ ) in the latter and similar blood glucose concentrations in two different dialysates<sup>13)</sup>.

Undoubtedly, acute administration of K in hypokalemic patients in CAPD regardless its routes would be necessary for its correction to avoid neuromuscular weakness and serious cardiac arrhythmia. Nevertheless, in the chronic long-term basis, further investigation may be required to investigate the benefits of K supplementation alone, because hypokalemia may simply be surrogate marker of malnutrition and/or other serious comorbid illness.

### Conclusion

In dialysis patients, i.e. HD or CAPD, K imbalance should be always considered as a common condition related to either a potentially lethal condition itself or the important contributory factor for their morbidity and mortality. The pathophysiologic factors for hyperkalemia in HD are well understood, and accordingly its managements are somewhat straightforward, while the

pathogenetic mechanisms of hypokalemia in CAPD need further clarification for the role of intracellular K redistribution.

For the management of K imbalance in dialysis, the foremost step is to improve compliance to dietary K intake and dialysis regimen besides the reversal or removal of pathophysiologic factors and other potential sources including drugs affecting K imbalance should be always considered. However, cautious administration of certain beneficial drugs such as RAAS blockers could be justified in ESRD on dialysis with tremendous burden with cardiovascular morbidity and mortality. As temporizing acute K-lowering regimens in severe life-threatening hyperkalemia, dual-therapeutic regimens, i.e. NaHCO<sub>3</sub> plus insulin with glucose or insulin with glucose plus beta-2 agonist, could be recommended as an efficacious modality. In CAPD patients with hypokalemia, for the long-term management, the correction of malnutrition would be required as one of the essential managements and the selection of glucose-free dialysates such as Icodextrin could be considered rather than the conventional glucose dialysates. Also, as short-term management, K supplements could be administered safely and efficiently via intraperitoneal route, if required.

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