Hyperkalemia in Chronic Kidney Disease

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Potassium balance and serum potassium level are maintained until very late in chronic kidney disease (CKD), mainly because of an increase in renal and colonic excretion. Hyperkalemia may develop earlier in the course of CKD in patients with hyporeninemic hypoaldosteronism. Hyperkalemia in CKD patients may occur in association with excess dietary potassium intake, constipation or prolonged fasting. It may also be seen with the use of potassium-sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs. If suspected, pseudohyperkalemia should be excluded to avoid unnessary treatments. Acute treament of hyperkalemia in marked or symptomatic hyperkalemia, particularly in the presence of electrocardiographic changes includes combinations of intravenous calcium gluconate and infusions of glucose and insulin with or without bicarbonate. In patients with kidney failure, dialysis may be required. Either asymptomatic and mild hyperkalemia or chronic hyperkalemia in CKD patients can be treated by potassium restriction, a loop diuretic at high doses, and cation exchange resin.

Kew Words : Potassium, Hyperkalemia, Chronic kidney disease

Hyperkalemia is a common, potentially life-threatening disorder in patients with chronic kidney disease (CKD). Hyperkalemia is usually defined as plasma potassium greater than 5.0 mEq/L, even though exact cut-off is arbitrary. The incidence of hyperkalemia in hospitalized patients varies from 1.4% to 10% depending on the arbitrary level of potassium[1]. In the largest study in a single hospital overall incidence of hyperkalemia (defined as serum potassium >6.0 mEq/L) was 1.4%. Hyperkalemia has been associated with a higher mortality rate. In patients with end-stage renal disease (ESRD), the prevalence of hyperkalemia is 5% to 10%. Hyperkalemia accounts for or contributes to 1.9% to 5% of deaths among patients with ESRD[2].

Under almost all conditions, hyperkalemia not due to redistribution of potassium is related to impaired renal potassium excretion. If potassium intake is normal, CKD does not produce significant hyperkalemia until the glomerular filtration rate (GFR) is less than 5 ml/min[3]. Preservation of normokalemia results from an adaptive increase in potassium excretion by remnant nephrons and increased bowel loss. However, hyperkalemia may be an early feature of renal failure in patients with (hyperchloremic) metabolic acidosis and hyporeninemic hypoaldosteronism, which occur particularly in patients with tubulointerstitial disease and diabetes mellitus.

Hyperkalemia also complicates an acute potassium load or administration of medication, which interferes with potassium excretion or causes a transcellular shift, for example, potassium sparing diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), β-blockers, and non-steroidal anti-inflammatory drugs (NSAIDs).

Clinical management for hyperkalemia in patients with CKD requires exclusion of pseudohyperkalemia, assessmemt of the urgency for treatment, and operation of appropriate acute and chronic therapy.

In this article, potassium homeostasis in patients with CKD and many medications that affect potas-

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sium balance in CKD are reviewed initially. Then clinical management of hyperkalemia including acute and chronic treatment of hyperkalemia in CKD will be discussed. In this review, we will focus on potassium balance and chronic therapy for hyperkalemia in CKD patients.

Potassium balance in CKD

1. Renal excretion of potassium

Under normal conditions, the kidney can excrete large quantities of potassium. The daily ingestion of 400 mEq of KC1, which is several-fold greater than the usual daily intake, increases plasma potassium on average by less than 1 mEq/L if renal function is normal and potassium excretion mechanisms are intact[4].

Less than 1% normal healthy adults develop hyperkalemia. This low frequency is a testament to the potent mechanisms for renal potassium excretion. Accordingly, hyperkalemia should suggest an underlying impairment of renal potassium excretion[5]. This may be due to either advanced CKD, which decreases the number of nephron units available for potassium secretion, or to factors that impair the rate of collecting duct potassium secretion.

Approximately two-thirds of the hyperkalemic patients with CKD whose GFR is able to maintain normokalemia manifest the syndrome of hyporeninemic hypoaldosteronism[6]. Hypoaldosteronism, especially when combined with a decrease in GFR and/or a reduction in the delivery of salt and fluid to the distal nephron, can substantially impair renal potassium excretion. As a result of the decline in renin and aldosterone, along with a modest fall in GFR, elderly patients are at increased risk to develop hyperkalemia[7].

2. Extra-renal excretion of potassium in CKD

The colon also secretes small amounts of potassium. Some regulation of colonic potassium secretion occurs, particularly in CKD stage 4 or 5. Adaptation is detectable when the GFR is reduced to one-third of normal, is maximal at a GFR of less than 10 mL/min, and accounts for 10-20 mEq/day of the potassium elimination[8]. Since uremic patients eliminate potassium via the gastrointestinal tract by as much as 25% of their daily potassium excretion, whereas normal healthy subjects eliminate 5-10% of their intake, the constipation occasionally observed in patients with kidney failure can be one of the sources for inadequate potassium elimination from the body[9].

Both the proximal and distal portions of the colon secrete potassium. Proximal colon reabsorbs Na^+ and secretes K^+ predominantly via transcellular mechanisms, but also by a paracellular, voltage-dependent pathway. Aldosterone enhances sodium and potassium transport without effects on either transmural potential difference or short-circuit current. Distal colon can either reabsorb or secrete potassium. Aldosterone also increases Na^+ absorption and K^+ secretion by this segment together with a raised transmural potential difference. In contrast to proximal colon, these effects are inhibited by amiloride. The enhanced capacity to secrete potassium in response to a high potassium diet is more prominent in the distal colon, whereas the diminution in potassium secretion in response to a low-potassium diet is more prominent in the proximal colon[10].

3. Redistribution of potassium

Acidosis also results in hyperkalemia due to exchange of intracellular potassium for extracellular hydrogen ions. The increase in the plasma potassium concentration occurs only with not organic acid-induced forms of metabolic acidosis. Hyperglycemia produces hyperkalemia in diabetic patients by the combined effects of hyperosmolarity and insulin deficiency on transcellular potassium distribution[11].

4. Potassium loads from diet and others in CKD

When hyperkalemia is considered with respect to the degree of GFR reduction, there are two categories : uremic hyperkalemia (GFR<5-10 mL/min) on dialysis and non-uremic hyperkalemia (GFR>10-15 mL/min) not yet on dialysis. Most cases of non-uremic hyperkalemia and uremic hyperkalemia may be partially related to excess intake of potassium. However, since the remaining nephrons in CKD stage 3 and 4 can often excrete the usual exogenous intake of potassium, a modestly high potassium intake is unlikely to induce hyperkalemia without other contributing factors[12].

The Dietary Approaches to Stop Hypertension (DASH) diet contains more potassium (approximately 4,500 mg/d) than a typical American diet that contains approximately 1,700 mg/d (40 to 45 mEq/d). Consumption of a diet high in fruits and vegetables may lead to hyperkalemia in patients with CKD stage 3, 4 and 5 or with concurrent use of ACE inhibitors, ARBs, or potassium-sparing diuretics. Potassium supplements and salt substitutes such as potassium chloride can also increase potassium load in CKD patients[13]. Some currently popular weight loss diets may contain excessive protein or potassium for later stages of CKD.

Apart from diet, exogenous and endogenous potassium load is increased in transfusion of old blood, hemolysis, rhabdomyolysis, tumour lysis, and following trauma and surgery.

Drugs that interferes with potassium balance in CKD

1. Drugs that affect a transcellular shift of potassium

Beta-blockers (e.g., propranolol) can cause hyperkalemia due to altered transcellular distribution of potassium. Increased cellular uptake of potassium appears to be β_2-receptor specific, with the cellular mechanism involving stimulation of cyclic AMP followed by activation of Na^+-K^+ ATPase. Selective beta-blockers may cause lesser elevation in serum potassium than nonselective beta-blockers. Digoxin and hypertonic solutions can also cause hyperkalemia by inducing a transcellular shift.

2. Drugs that affect excretion of potassium

In patients with CKD, ACE inhibitors, ARBs and aldosterone antagonists may reduce the aldosterone-mediated effect on renal excretion of potassium, resulting in hyperkalemia. The adrenal release of aldosterone due to an increased potassium concentration depends on an intact adrenal-renal angiotensin system; this response is abrogated by systemic ACE inhibitors and ARBs[14]. In one study, ARB appears to have a reduced effect on increasing plasma potassium in patients with a GFR below 60 mL/min/1.73 m^2 [15]. Beside above renin-angiotensin-aldosterone (RAA) inhibitors, NSAIDs, heparin and beta-blockers are also involved in RAA system affecting final action or synthesis of aldosterone.

NSAIDs cause hyperkalemia by a variety of mechanisms. They decrease distal delivery of Na^+ and reduce distal flow rate. Moreover, NSAIDs can reduce and the flow-dependent component of potassium excretion[16]. NSAIDs are also a classic cause of hyporeninemic hypoaldosteronism and blunt the adrenal response to hyperkalemia[17].

Selective cyclooxygenase-2 (COX-2) inhibitors are equally likely to cause hyperkalemia. Such inhibitors can cause sodium retention and a decrease in GFR. Because COX-2-derived prostaglandins stimulate renal renin release and COX-2 inhibitors reduce plasma rennin activity in vivo, they are likely to lead to hyporeninemic hypoaldosteronism[18]. Hypovolemic patients may be particularly prone to hyperkalemia.

Inhibition of apical epithelial sodium channel (ENaC) activity in the cortical collecting duct (CCD) by potassium-sparing diuretics (triamterene, amiloride) predictably results in hyperkalemia[19]. The risk

of hyperkalemia is especially high in patients with GFR <30 mL/min/1.73 m^2 receiving concomitant therapy with ACE inhibitors or ARBs or other conditions that raise plasma potassium. Amiloride is structurally similar to the antibiotics (trimethoprim and pentamidine) which can also inhibit ENaC. Both agents were reported to cause hyperkalemia during high-dose treatment of Pneumocystis carinii pneumonia in HIV-infected patients[20, 21]. In hospitalized patients without HIV infection, treatment with standard doses of trimethoprim also causes significant hyperkalemia in more than 50%[22].

Nafamostat, a protease inhibitor that is widely used in Japan for pancreatitis and other indications, can cause hyperkalemia. The mechanism involves inhibition of amiloride-sensitive Na^+ channels in the CCD[23, 24].

Cyclosporine (cyclosporin A) and tacrolimus cause hyperkalemia[25, 26]. Cyclosporine causes hyporeninemic hypoaldosteronism, in part because of its inhibitory effect on COX-2 expression in the macula densa. Cyclosporine inhibits apical SK secretory K^+ channels in the distal nephron and basolateral Na^+-K^+-APTase[27, 28].

Digoxin may cause hyperkalemia in predisposed patients, such as those with ESRD. Digoxin inhibits the principal cell basolateral Na^+-K^+-ATPase. Digoxin may cause hyperkalemia by both impaired renal excretion and impaired cellular uptake of potassium.

Pseudohyperkalemia

Verifying whether pseudohyperkalemia is present is important to avoid unnecessary treatment. The most common cause of pseudohyperkalemia is hemolysis, which is usually easily noted due to a pink tinge to the plasma resulting from release of hemoglobin from damaged red blood cells. Alternatively, an excessively tight tourniquet surrounding an exercising extremity (e.g., opening and closing a hand) can increase plasma potassium by more than 2 mEq/L[29]. Excessive numbers of either leukocytes greater than 70,000/cm^3, or platelets greater than 1,000,000/cm^3 also can lead to pseudohyperkalemia[13].

When the serum potassium is >0.3 mEq/L as compared with a simultaneous plasma potassium, pseudohyperkalemia should be diagnosed. Plasma potassium can be measured by obtaining a heparinized blood specimen. If pseudohyperkalemia exists, all further potassium levels should be measured using plasma.

Clinical manifestations of hyperkalemia

Hyperkalemia may be asymptomatic or life-threatening. The main danger of hyperkalemia is a cardiac arrhythmia. Electrocardiograms are considered to be sensitive indicators of the presence of hyperkalemia. Electrocardiographic abnormalities consistent with hyperkalemia in the hospitalized hyperkalemia patients

Table 1. Drug-Induced Hyperkalemia in CKD

Mechanism		Examples
Reduced Potassium Excretion	RAA involvement	ACEIs, ARBs, β-blockers, Heparin, NSAIDs, COX-2 inhibitors
	RAA non-involvement	Potassium-sparing diuretics, Cyclosporine, Tacrolimus, Trimethoprim, Pentamidine, Digoxin, Lithium
Transcellular Shifting	Insulin antagonists, Hypertonic solutions, Digoxin, β-blockers	
Potassium Loading	Potassium-supplements, Herbal supplements, Packed red blood cell infusions	

CKD, chronic kidney disease; RAA, renin-angiontensin-aldosterone; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers
Adapted from Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43(5 Suppl 1):S1-S290, 2004

were observed in only 14% of episodes[1]. Serum potassium levels higher than 8 mEq/L are almost invariably associated with ECG abnormalities. However, minimal or atypical ECG changes have been observed in some cases of severe hyperkalemia[30, 31]. Minor electrocardiographic abnormalities (tall-peaked T waves) may be the first indication of hyperkalaemia but by the time serious changes occur, the patient usually complains of muscle weakness, paresthesia, and lethargy. Severe hyperkalemia can cause bilateral flaccid paralysis of extremities, and weakness of repiratory muscles. However unlike hypokalemia, complete paralysis is uncommon.

Treatment of hyperkalemia

1. Acute or emergency treatment of hyperkalemia

Acute reduction of serum potassium is required at levels exceeding 7.0 mEq/L, because of the risk of cardiac arrest. For acute therapy of hyperkalemia in an urgent situation, regardless of the underlying cause, following treatments have been recommended.

Emergency treatment should be started by the administration of calcium (10-30 mL of 10% calcium gluconate over 10 min intravenously). Intravenous infusion of calcium is the most rapid and effective way to antagonize the myocardial toxic effects of hyperkalemia.

Furthermore, intravenous glucose (50 mL dextrose 50 %, preferably by central venous infusion) should be given followed by or combined with 10 units of short-acting regular insulin, because combined administration of glucose and insulin results in a greater decline in serum potassium levels. Intravenous insulin rapidly stimulates uptake of potassium into cells, primarily the muscle and liver.

β_2-adrenergic agonists, which also induce cellular potassium uptake, are useful for the acute therapy of hyperkalemia. A direct comparison between intravenous (0.5 mg) and nebulized (10 mg) albuterol in ESRD patients revealed a similar potassium-lowering effect[32]. However, 20-40% of ESRD patients are refractory to the potassium-lowering effect of albuterol and it is not possible to predict non-responders. Combined use of β_2-adrenergic agonists with glucose and insulin will maximize the reduction in serum potassium[33].

When especially used alone, bicarbonate is probably less effective than either β_2-agonist or insulin in the acute treatment of hyperkalemia[13]. Recent studies show conflicting evidences whether bicarbonate can act in a synergistic fashion with either insulin or β_2 -adrenergic agonists[34-36].

Dialysis should be considered the primary method of potassium removal when hyperkalemia is persistent or severe. Hemodialysis is the most rapid method of potassium removal. Removal rates of potassium can approximate 35 mEq/hr with a dialysate bath potassium concentration of 1-2 mEq/L. A glucose free dialysate is preferable to minimize a glucose-induced shift of potassium into cell, lessening the removal of potassium[37]. Peritoneal dialysis and chronic hemodiafiltration are effective in chronic hyperkalemia, but do not remove potassium fast enough to be recommended for use in acute, severe hyperkalemia. Although dialysis is the most rapid method available to treat most cases of hyperkalemia, other modes of treatment should not be delayed while waiting to institute dialysis.

2. Chronic treatment of hyperkalemia in CKD

In chronic treatment of hyperkalemia, it is important to determine underlying causes for hyperkalemia. One should find modifiable causes of hyperkalemia in CKD patients. Common modifiable causes are concomitant medications (Table 1) and excessive dietary intake. A careful history on the dietary habit and the medication is necessary.

Measures for chronic therapy of hyperkalemia in outpatient management of CKD patients can be divided into three general categories (1) to avoid or replace drugs that cause hyperkalemia; (2) to pre-

Table 2. Dosage of Loop Diuretics in Hyperkalemia of CKD Stage 4 and 5

	Usual daily dose	Maximum daily dose
Furosemide (mg)	20-160	320-400
Bumetanide (mg)	0.5-4	10
Torsemide (mg)	20-80	100-200

CKD, chronic kidney disease
Adapted from Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43(5 Suppl 1):S1-S290, 2004

Table 3. Treatment of Asymptomatic and Mild Hyperkalemia or Chronic Hyperkalemia in CKD Patients

mEq/L	Measures to low serum potassium
5-5.5	Dietary potassium restriction to 2-3 g/d (50-75 mEq/d)
	Discontinuation of any offending drug
5.6-6	Loop diuretic with or without thiazide with above measures
6-6.5	Cation exchange resin, given orally or by colonic enema with above measures

CKD, chronic kidney disease

scribe a low-potassium diet and avoid constipation, and (3) to enhance potassium excretion by residual functioning nephrons or to remove it more efficiently by dialysis and/or by the gastrointestinal tract[12].

Follow-up should be in 2 weeks if serum potassium >5.1 mEq/L for outpatients management of CKD. If mild hyperkalemia develops after medications, reduce the dose of medications that interfere potassium balance by 50% and reassess the serum potassium every 5 to 7 days until serum potassium has returned to baseline. If serum potassium does not return to baseline within 2 to 4 weeks, discontinue that medications and select an alternate medications[38].

Target potassium intake of a "low potassium diet is <2 to 3 g/d (approximately 50 to 75 mEq/d). The DASH diet should not be routinely recommended to patients with CKD stage 3, 4 and 5 (GFR<60 mL/min/1.73 m^2) because of its high content of fruits and vegetables. Salt substitutes should not be recommended in CKD. Beside excess potassium dietary intake and constipation, it is also important to look for prolonged fasting[39]. Overnight fasting in preparation for surgery in dialysis patients may induce hyperkalemia due to a fall in the concentration of insulin. This can be avoided by continuous infusion of 10% glucose at 50 mL/h mixed with or without regular insulin[12].

Promoting diuresis with a loop diuretic (Table 2) can control chronic, mild hyperkalemia. Thiazide and loop diuretics increase the delivery of sodium to the distal tubule, thereby increasing urinary potassium excretion. This may be a useful side-effect in CKD, especially in patients treated with an ACE inhibitor or ARB. However, most of thiazides are effective in kaliuresis in patients with GFR greater than approximately 30 mL/min/1.73 m^2.

An active component of licorice, glycyrrhetinic acid might be considered as one of the therapeutic agents for chronically hyperkalemic patients on maintenance hemodialysis[40].

Either after acute hyperkalemia has been corrected or in chronic management of less severe hyperkalemia in CKD patients, the more slowly acting cation exchange resin may be given orally or rectally (e.g. sodium/calcium polystyrene sulfonate 15-30 g, with an equal amount of sorbitol to prevent fecal impaction). Cation exchang resin may be given in order to prevent a further increase in serum potassium.

Either asymptomatic and mild hyperkalemia or chronic hyperkalemia in CKD patients is common. Several measures to low serum potassium in these patients are summarized in Table 3.

References

1) Acker CG, Johnson JP, Palevsky PM, Greenberg A : Hyperkalemia in hospitalized patients : Causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med* **158**:917-924, 1998
2) Mount DB, Zandi-Nejad K : Disorders of Potassium Balance. In : Brenner & Rector's the Kidney, 7th ed., edited by Brenner BM, Philadelphia, WB Saun-

ders Company, 2004, p997-1040
3) Mitch WE, Wilcox CS : Disorders of body fluids, sodium and potassium in chronic renal failure. *Am J Med* **72:**536-550, 1982
4) Rabelink TJ, Koomans HA, Hene RJ, Dorhout Mees EJ : Early and late adjustment to potassium loading in humans. *Kidney Int* **38:**942-947, 1990
5) Weiner ID, Linas SL, Wingo CS : Disorders of potassium metabolism. In : Clinical Comprehensive Nephrology, 2nd ed., edited by Johnson RJ, Feehally J, Philadelphia, Mosby, 2003, p109-121
6) Schambelan M, Sebastian A, Biglieri EG : Prevalence, pathogenesis, and functional significance of aldosterone deficiency in hyperkalemic patients with chronic renal insufficiency. *Kidney Int* **17:**89-101, 1980
7) Rodriguez-Puyol D : The aging kidney. *Kidney Int* **54:**2247-2265, 1998
8) Panese S, Martin RS, Virginillo M, Litardo M, Siga E, Arrizurieta E, Hayslett JP : Mechanism of enhanced transcellular potassium-secretion in man with chronic renal failure. *Kidney Int* **31:**1377-1382, 1987
9) Martin RS, Panese S, Virginillo M, Litardo M, Gimenez M, Arrizurrieta E, Hayslett JP : Increased secretion of potassium in the rectum of man with chronic renal failure. *Am J Kidney Dis* **8:**105-110, 1986
10) Kunzelmann K, Mall M : Electrolyte transport in the mammalian colon : mechanisms and implications for disease. *Physiol Rev* **82:**245-289, 2002
11) Cox M, Sterns RH, Singer I : The defense against hyperkalemia : the roles of insulin and aldosterone. *N Engl J Med* **299:**525-532, 1978
12) Kim HJ, Han SW : Therapeutic approach to hyperkalemia. *Nephron* **92**(Suppl 1):33-40, 2002
13) Weiner ID, Wingo CS : Hyperkalemia : A potential silent killer. *J Am Soc Nephrol* **9:**1535-1543, 1998
14) Hilbers U, Peters J, Bornstein SR, Correa FM, Johren O, Saavedra JM, Ehrhart-Bornstein M : Local renin-angiotensin system is involved in K^+-induced aldosterone secretion from human adrenocortical NCI-H295 cells. *Hypertension* **33:**1025-1030, 1999
15) Bakris GL, Siomos M, Richardson D, Janssen I, Bolton WK, Hebert L, Agarwal R, Catanzaro D : ACE inhibition or angiotensin receptor blockade : Impact on potassium in renal failure. VAL-K Study Group. *Kidney Int* **58:**2084-2092, 2000
16) Woda CB, Bragin A, Kleyman TR, Satlin LM: Flow-dependent K^+ secretion in the cortical collecting duct is mediated by a maxi-K channel. *Am J Physiol Renal Physiol* **280:**F786-F793, 2001
17) Mactier RA, Khanna R : Hyperkalemia induced by indomethacin and naproxen and reversed by fludrocortisone. *South Med J* **81:**799-801, 1988
18) Roig F, Llinas MT, Lopez R, Salazar FJ : Role of cyclooxygenase-2 in the prolonged regulation of renal function. Hypertension **40:**721-728, 2002
19) Cohen AB : Hyperkalemic effects of triamterene. Ann Intern Med 65:521-527, 1966
20) Choi MJ, Fernandez PC, Patnaik A, Coupaye-Gerard B, D'Andrea D, Szerlip H, Kleyman TR : Brief report : Trimethoprim-induced hyperkalemia in a patient with AIDS. *N Engl J Med* **328:**703-706, 1993
21) Lachaal M, Venuto RC : Nephrotoxicity and hyperkalemia in patients with acquired immunodeficiency syndrome treated with pentamidine. Am J Med **87:** 260-263, 1989
22) Alappan R, Perazella MA, Buller GK : Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med* **124:**316-320, 1996
23) Kitagawa H, Chang H, Fujita T: Hyperkalemia due to nafamostat mesylate. *N Engl J Med* **332:**687, 1995
24) Muto S, Imai M, Asano Y : Effect of nafamostat mesilate on Na^+ and K^+ transport properties in the rabbit cortical collecting duct. *Br J Pharmacol* **109:** 673-678, 1993
25) Perazella MA : Drug-induced hyperkalemia : Old culprits and new offenders. *Am J Med* **109:**307-314, 2000
26) Oishi M, Yagi T, Urushihara N, Takakura N, Inagaki M, Sadamori H, Mastukawa H, Inoue T, Oda S, Tanaka N : A case of hyperkalemic distal renal tubular acidosis secondary to tacrolimus in living donor liver transplantation. *Transplant Proc* **32:**2225-2226, 2000
27) Ling BN, Eaton DC: Cyclosporin A inhibits apical secretory K^+ channels in rabbit cortical collecting tubule principal cells. *Kidney Int* **44:**974-984, 1993
28) Tumlin JA, Someren JT, Swanson CE, Lea JP : Expression of calcineurin activity and alpha-subunit isoforms in specific segments of the rat nephron. *Am J Physiol* **269:**F558-F563, 1995
29) Skinner SL, Adelaide MB : A cause of erroneous potassium levels. *Lancet* **1:**478-482, 1961
30) Martinez-Vea A, Bardaji A, Garcia C, Oliver JA. Severe hyperkalemia with minimal electrocardiographic manifestations. *J Electrocardiol* **32:**45-49, 1999
31) Lee S, Lee MH, Kang KP, Kim W, Park SK, Kang SK : Two Cases of Severe Hyperkalemia with Atypical Electrocardiographic Manifestations. *Electrolyte Blood Press* **3:**52-54, 2005
32) Liou HH, Chiang SS, Wu SC, Huang TP, Campese VM, Smogorzewski M, Yang WC : Hypokalemic effects of intravenous infusion or nebulization of salbutamol in patients with chronic renal failure: comparative study. *Am J Kidney Dis* **23:**266-271,

1994
33) Allon M, Copkney C : Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int* **38:**869-872, 1990
34) Kim HJ : Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. *Nephron* **72:**476-482, 1996
35) Kim HJ : Acute therapy for hyperkalemia with the combined regimen of bicarbonate and beta(2)-adrenergic agonist (salbutamol) in chronic renal failure patients. *J Korean Med Sci* **12:**111-116, 1997
36) Allon M, Shanklin N : Effect of bicarbonate administration on plasma potassium in dialysis patients : interactions with insulin and albuterol. *Am J Kidney Dis* **28:**508-514, 1996
37) Halperin ML : Hyperkalemia, in : The ACID truth and BASIC facts with a Sweet Touch, an enLYTEnment. 5th ed., Toronto, RossMark Medical Publishers, 2004
38) Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* **43**(5 Suppl 1):S1-S290, 2004
39) Gifford JD, Rutsky EA, Kirk KA, McDaniel HG : Control of serum potassium disposal in men with end-stage renal disease. *Kidney Int* **35:**90-94, 1989
40) Serra A, Uehlinger DE, Ferrari P, Dick B, Frey BM, Frey FJ, Vogt B : Glycyrrhetinic acid decreases plasma potassium concentrations in patients with anuria. *J Am Soc Nephrol* **13:**191-196, 2002