Review Article

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Understanding and Treatment Strategies of Hypertension and Hyperkalemia in Chronic Kidney Disease

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Hypertension and potassium imbalance are commonly observed in chronic kidney disease (CKD) patients. The development of hypertension would be related to several mechanisms. Hypertension is related to body mass index, dietary salt intake, and volume overload and is treated with antihypertensives. In CKD patients, managing hypertension can provide important effects that can slow the progression of CKD or reduce complications associated with reduced glomerular filtration rate. The prevalence of hyperkalemia and hypokalemia in CKD patients was similar at 15-20% and 15-18%, respectively, but more attention needs to be paid to treating and preventing hyperkalemia, which is related to a higher mortality rate, than hypokalemia. Hyperkalemia is prevalent in CKD due to impaired potassium excretion. Serum potassium level is affected by renin-angiotensin-aldosterone system inhibitors and diuretics and dietary potassium intake and can be managed by potassium restriction dietary, optimized renin-angiotensin-aldosterone system inhibitor, sodium polystyrene sulfonate, patiromer, and hemodialysis. This review discussed strategies to mitigate and care for the risk of hypertension and hyperkalemia in CKD patients.

Key Words: Chronic kidney disease, Hypertension, Hyperkalemia, Renin-angiotensin-aldosterone system

INTRODUCTION

Hypertension is commonly observed in patients with chronic kidney disease (CKD)[1], and its prevalence varies from 60% to 90%, depending on the stage and cause of CKD[2]. In CKD, the hypertension mechanisms include sympathetic overactivity, volume overload, endothelial dysfunction, salt retention, and changes in the hormonal system (e.g., increased activity renin-angiotensin-aldosterone system [RAAS]) regulating blood pressure (BP)[2,3].

In addition, serum potassium abnormalities are also commonly observed in CKD patients. In CKD, the severity of CKD, excessive dietary potassium intake, and the use of drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, and potassium-sparing diuretics intake affect serum potassium concentration[4,5,6]. Increased renal and colonic excretion balance potassium until the very late stage of CKD, although hyperkalemia may also occur in the early stage of CKD in patients with hyporeninemia and hypoaldosteronism.

Proper management of hypertension and hyperkalemia in CKD patients may deliver important points for the prognostic management of patients. This article reviews the management strategies to mitigate the risk of hypertension and hyperkalemia for CKD patients.

Controversies of the proper target of blood pressure in CKD management

Up to now, the optimal BP level for hypertension in CKD is still controversial[7-11] since several reasons exist, such as various targets in each guideline, changing targets, and in-

Table 1. Recommended guidelines of blood pressure target for patients with diabetic chronic kidney disease (CKD) and non-diabetic CKD

		KDIGO (2012)[94]	AHA/ACG (2017)[7]	ESH/ESC (2018)[8]	KSH (2018)[95]	KSH (2022)[96]
Non-diabetic CKD	No albuminuria	<140/90	<130/80	130-139/70-79	<140/90	<140/90 (I/A)
	Albuminuria*	<130/80	<130/80	130-139/70-79	<130/80	<130/80 (IIa/B)
Diabetic CKD	No albuminuria	<140/90	<130/80	130-139/70-79	<140/90	<130/80 (IIb/C)
	Albuminuria*	<130/80	<130/80	130-139/70-79	<130/80	
Class/level of recommendation		IB/IID for the presence/absence of albuminuria	IB for the SBP and IC for the DBP target	1A/IIaB for the SBP/DBP target	-	Expert opinion considering the condition of each patient

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; KDIGO, Kidney Disease Improving Global Outcomes; AHA/ACG, American Heart Association/American College of Cardiology; ESH/ESC, European Society of Hypertension/European Society of Cardiology; KSH, Korean Society of Hypertension.
*Albuminuria indicates urinary albumin excretion ≥30 mg/24h or equivalent[9].

sufficient evidence in CKD patients (Table 1).

The Kidney Disease Improving Global Outcomes guidelines recommended a target of 130/80 mmHg only for patients with albuminuric CKD in 2012, whereas the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommended a BP target of 140/90 mmHg for CKD, regardless of albuminuria. In 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) was prematurely discontinued due to the interim analysis results showing that the group with a target of 120 mmHg systolic BPs had a 25% lower risk of cardiovascular disease and a 27% lower risk of all-cause mortality than those of 140 mmHg. Subsequently, the American College of Cardiology/American Heart Association guidelines committee selected the systolic BP target as 130 mmHg, an intensive target in the SPRINT rather than 120 mmHg[12,13]. This selected systolic BP target included concerns about SPRINT application to a broader population and considerations related to SPRINT's highly automated BP measurements, which on average, may be lower than routine clinic measurements. In 2018, for CKD patients, the ESH/ESC guidelines recommended a systolic blood pressure of 130 to 139 mmHg and diastolic blood pressure of 70 to 79 mmHg[8]. A previous study using the data from the Irbesartan in Diabetic Nephropathy Trial indicated decreasing cardiovascular mortality and heart failure with progressively lower achieved systolic BPs to 120 mmHg[14]. Another study involving over 70,000 veterans with eGFR <60 ml/min/m^2 and uncontrolled hypertension demonstrated a mortality hazard ratio was about 1.7 between the veteran groups with systolic BPs less than 120 mmHg and 120 to 139 mmHg[15]. Although these results show lower risks of death and cardiovascular events in people with lower than higher systolic BPs, it will be cautioned that these situations do not necessarily indicate the treatment of hypertension to the same values reduces risks proportionately.

Strategic approaches to hypertension management in CKD

Control of obesity

Obesity is a risk factor for hypertension and the progression of CKD[16-18]. Obesity increases arterial blood pressure by causing excessive renal sodium reabsorption, renal pressure natriuresis, and extracellular fluid volume expansion[19,20]. Increased blood pressure and GFR offset increased renal sodium reabsorption, maintaining sodium balance despite high arterial pressure and renal pressure natriuresis. However, chronically elevated blood pressure, renal vasodilation, and glomerular hyperfiltration may affect renal damage. These phenomena further impair renal pressure

natriuresis and exacerbate hypertension and renal impairment[21].

The results that weight gain increases blood pressure in the relationship between hypertension and obesity are supported by various studies. Population studies have shown that blood pressure is strongly related to anthropometric indicators of obesity, such as waist circumference, waist-to-hip ratio, or body mass index (BMI)[22,23]. A strong relationship between overweight and hypertension has been observed in diverse populations worldwide[23,24]. Thus, excess weight gain is a good predictor of future hypertension development. In a previous study[25], 63 patients with biopsy-proven, obesity-related glomerulopathy participated weight loss program, including diet and exercise. After two years, these patients resulted in a reduction in blood pressure and dyslipidemia, 51% of proteinuria, and 9.2% of BMI. Moreover, a systematic review showed that nonsurgical weight reduction interventions in a small, short-term study of CKD patients reduced proteinuria and BP and seemed to prevent further decline in renal function[26]. The results among three studies with 66 patients also indicated that nonsurgical interventions significantly decreased systolic BP at the end of the study period (95% CI 14.23 to 3.74; p <0.001)[27-29]. In a previous study of 112 obese patients (mean eGFR of 32 ml/min/1.73m^2) with CKD, 22% or more of the participants lost 10% or more of their body weights within 24 months, and systolic BP was also significantly reduced[30]. However, even the researchers of the previous study indicated a limitation in generalizing the results because more than half of the subjects were dialysis patients and were in a specific situation where they could receive medical advice or checkups on regular weight control. Several results have shown a positive effect of weight reduction, but data on weight loss intervention and effects on BP and renal function in CKD patients are still limited. Therefore, it is necessary to proceed with more research efforts on CKD patients' safety and prognosis through appropriate weight reduction.

Dietary salt intake reduction

In a previous study, the interaction between dietary salt intake and RAAS blockade was evaluated in CKD patients, and the effect of dietary sodium intake was also assessed through 24-hour urine sodium excretion[31]. The results of dietary sodium intake showed an apparent decrease in 24-hour urine albumin to creatinine ratio, and systolic BP was most significant in those with the lowest baseline urinary sodium to creatinine ratio.

Reduction of excessive body water

Volume overload accompanying salt retention in CKD patients is a significant cause of hypertension, and body composition can be measured using bioimpedance spectroscopy (BIS) to evaluate the volume status of dialysis patients[32,33]. Mitsides et al. assessed fluid status in CKD patients to evaluate the accuracies of BIS outputs, which may vary with changing tissue ionic sodium concentration (Na^+)[34]. Ten healthy control and 20 CKD patients participated, and the extracellular and intracellular resistance, tissue capacitance, extracellular and total body water were measured using BIS. BIS-derived volumes were 0.4±0.9 L (control group) and 0.5±1.9 L (CKD group) without significance (p=0.13). However, the CKD group showed significantly higher Na^+ (25.3±7.4 mmol/L) than the control group (21.2±3.0 mmol/L, p=0.04). The extracellular resistance in the CKD group (609±74.3 Ohms) was significantly lower than the control group (693±93.6 Ohms, p=0.01), and intracellular resistance and capacitance did not vary. Moreover, Na^+ showed a significant inverse linear relationship to extracellular resistance (r=-0.598, p<0.01), and tissue Na^+ concentration has a significant inverse linear relationship to extracellular resistance. Khan et al. performed a prospective observational study to assess the relationship between fluid overload and hypertension using diuretic therapy with BIS[35]. 312 CKD patients were enrolled and categorized in five different parts of hydration reference plot (HRP) generated by BIS (5.1% [normal BP and fluid status], 20.5% [hypertensive with severe fluid overload], 29.5% [hypertensive with mild fluid overload], 22% [hypertensive with normohydration], 10.2% [underhydration with normal/low BP] and 12.5% [normal BP with severe fluid overload]). Diuretics were administered to 46% of all patients due to BP and edema and were prescribed to most patients with [hypertensive with severe fluid overload] and [hypertensive with mild fluid overload]. The results showed that the BIS

helps classify CKS patients according to body fluid status and to manage hypertensive CKD patients. Verdalles et al. performed an evaluation study using BIS[36]. They divided patients with the dilatation of extracellular volume (ECV) measured by BIS into two groups as follows; the patients with ECV dilatation injected with a diuretic (n=30) and those without ECV dilation injected with an additional antihypertensive (n=20). After six months of follow-up, it was confirmed that the systolic BP decreased more in the patients with the ECV dilation group compared with those without ECV dilatation (21 mmHg vs. 9 mmHg, respectively; $p < 0.01$). In addition, nine patients in the ECV dilatation group and two in the other group reached a target BP of less than 140/90 mmHg. Although the BIS can be used as an effective approach for evaluating volume status, the BIS still needs further study in larger cohorts before it can become a generalized method.

Antihypertensives

Antihypertensives are often used in CKD and hypertension patients to achieve target BP. The selective renin inhibitor Aliskiren[37,38] and the selective endothelial antagonist Sitaxentan[39] have been shown to affect BP. In addition, a 36-week randomized clinical trial using Aldactone, a steroid mineralocorticoid receptor antagonist, showed well tolerated in early stage 3 CKD patients with fewer than 1% episodes of hyperkalemia ($K^+ \geq 6$ mmol/l)[40]. However, these antihypertensive trials and the accurate results are not yet widely adopted in CKD patients. Although Aliskiren has antihypertensive properties, large randomized trials of Aliskiren in combination with ACEi or ARB therapy in diabetes or heart failure found no renal benefit, with the adverse event for the combination, such as hyperkalemia[41,42]. Aldactone is also used for treatment-resistance and control of hypertension, but caution is needed in CKD patients because of hyperkalemia risk[43]. Therefore, additional researches on antihypertensives based on key factors that can achieve the goal of BP control, renal protection, and slowing the progression of CKD need to be studied to improve treatment strategies.

Hyperkalemia in CKD

Hyperkalemia, commonly defined as plasma potassium greater than 5.5 mEq/L[44], is associated with a higher mortality rate, contributing to 1.9%-5% of deaths in patients with ESRD[45,46]. Hyperkalemia is strongly associated with impaired renal potassium excretion and not a redistribution of potassium[45]. Since the kidney in a normal condition can excrete a large amount of potassium, even if 400 mEq of KCl is consumed daily, several times higher than usual, plasma potassium will increase to less than 1 mEq/L on average if normal renal function and potassium excretion mechanism are ensured[46]. Therefore, hyperkalemia may indicate a fundamental impairment in renal potassium excretion[47]. These phenomena are possibly due to progressive CKD reducing the number of nephron units available for potassium secretion or impairing the rate of collecting duct potassium secretion. In addition, hypoaldosteronism can lead to decreased renal potassium excretion and acidosis, especially in metabolic acidosis, which may affect hyperkalemia by intracellular potassium exchanging for extracellular hydrogen[45,48]. In CKD, particularly in stages 4 or 5, potassium can be excreted extrarenal from sites such as the colon[45,49]. This phenomenon can be detected when GFR decreases to 1/3 and accounts for potassium elimination of 10-20 mEq/day[50]. Moreover, a normal person eliminates 5-10% of their intake, but patients with uremia may remove up to 25% of their daily potassium excretion from the body inappropriately through the gastrointestinal tract[51].

Hyperkalemia-inducible drugs

Beta-blockers such as propranolol increase potassium uptake, which is β2-receptor-specific, including cyclic adenosine monophosphate stimulation and Na^+-k^+ ATPase activation[45]. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists reduce the aldosterone-mediated effect on renal potassium excretion, induce hyperkalemia, and the resulting adrenal release from aldosterone depends on the adrenal-renal angiotensin system[52,53]. Non-steroidal anti-inflammatory drugs (NSAIDs) cause hyperkalemia by decreasing distal delivery and flow rate of Na+ and reducing the flow-related component of potassium excretion[45,54]. Cyclooxygenase-2 inhibitors that induce sodium retention and decreased GFR can also lead to hyperkalemia[55,56]. Potassium-sparing diuretics, such as triamterene and amiloride, cause hyperkalemia by in-

hibiting apical epithelial sodium channel activity in the cortical collecting duct[57,58]. Digoxin may induce hyperkalemia due to impaired renal excretion and impaired intracellular potassium absorption[59]. In addition, cyclosporine (cyclosporine A) and tacrolimus are known to induce hyperkalemia[60,61].

Strategic approaches to potassium management in CKD

Management of dietary intake

Potassium and sodium intakes need to be considered simultaneously. High dietary K^+ intake blunts diseases associated with an excessive sodium diet, such as hypertension and cardiovascular disease, whereas low dietary potassium increases the outcome of more dietary sodium[62]. In this regard, many previous studies have reported that higher dietary sodium and lower potassium could have detrimental effects on the progression of CKD, hypertension, and diabetes[62,63]. Moreover, Korean and American diets lack potassium and are acid-producing due to the meat-based diets[64]. A meat-based diet that does not involve an intake of fruits and vegetables is related to high net endogenous acid production known to contribute to CKD progression. Therefore, proper intake of dietary fruits and vegetables and administration of endogenous alkalis may not only reduce net endogenous acid production rather, it slows the progression of CKD[65]. However, restricting dietary K^+ is not the only correct method for all CKD patients. For example, a fruit and vegetable diet is recommended for patients with early-stage CKD with clinical hypokalemia or patients with borderline hypokalemia. Therefore, dietary K^+ restriction must be cautiously applied in patients with more advanced CKD and documented hyperkalemia. A low-potassium diet is recommended for patients with advanced CKD and hyperkalemia. Clinical guidelines recommend that patients receive regular advice, such as an individualized diet and nutritionist counseling, when limiting potassium intake[66,67]. In a comprehensive review paper[68], Kalantar-Zadeh and Fouque suggested an intake of 4.7 g/day in the early stages of CKD patients but a dietary potassium restriction of less than 3 g per day in CKD patients who tend to develop hyperkalemia. Ogata et al. found significant but relatively weak associations between serum potassium and dietary potassium intake estimated by urine collections in CKD patients (unadjusted R2 values were 0.08, 0.14, and 0.18 for CKD stages 3, 4, and 5, respectively)[69]. Similarly, Noori et al. also showed a weak association (r=0.14) between dietary potassium and serum potassium among 224 patients[70]. In addition, a low potassium diet may also result in folic acid deficiency in advanced CKD patients. A previous study reported that the incidence of folic acid deficiency in patients with CKD stage 3-4 on a potassium-restricted diet was three times higher than in patients with CKD stage 1-2 on an unrestricted potassium diet[71]. Moreover, severe folic acid deficiency may increase the risk of cancers, cardiovascular disease, and neurological disorders[71].

Renin-angiotensin-aldosterone system inhibitor

Hyperkalemia in CKD patients can be managed by optimized RAAS inhibitor therapy or by limiting K^+ dietary[72,73]. The RAAS inhibitor therapy, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, slows the progression of CKD and improves the prognosis in concomitant diseases such as hypertension and diabetes. Moreover, RAAS inhibitor therapy has advantages in patients with CKD early stage for reducing hypertension and glomerulosclerosis, and patients with CKD late stage and hemodialysis for maintaining residual renal funtional[74]. On the other hand, RAAS inhibitors may also increase the risk of hyperkalemia[75]. It should be cautioned that when RAAS inhibitors are used in patients with reduced renal function, the risk of hyperkalemia may be increased, as aldosterone modulates potassium excretion by the kidneys[76]. Previous studies reported that hyperkalemia related to RAAS inhibitor takes occurrence 5% to 10% in CKD patients, whereas patients without CKD have less than 2% occurrence[77,78]. Therefore, using RAAS inhibitors requires attention and the most optimal dosage considering the patient's benefit. Furthermore, multiple researchers are also studying to verify using new K^+ binding agents such as sodium zirconium cyclosilicate (SZC) and Partiromer that maintains optimal RAAS inhibitor therapy and decreases serum K^+ (More detailed information on newer K^+ binding agents is explained following sections). Note that continuous further studies should accompany long-term clinical studies for evaluating

new K^+ binding agents, although the benefits of these new K^+ binding agents are being reported.

Potassium-lowering drugs

Sodium Polystyrene Sulfonate (SPS) is an insoluble polymeric cation exchange resin applied in oral formulation or by the rectal route to exchange sodium for potassium ions. Potassium binds to SPS and moves through the gastrointestinal tract before being eliminated in the feces[79,80]. SPS acts within 2 to 24 hours after administration and continues for 4 to 6 hours before being eliminated from the body[81]. The exchange capacity of SPS is about 33% or 1 mEq of potassium per gram of resin. SPS is not selective for potassium in the body, such as being able to bind with calcium or magnesium, so the exchange capacity of the resin is not constant and may reduce. A previous study for a randomized controlled trial evaluated the effect of SPS in CKD patients with 5.0 to 5.9 mEq/L serum K^+ concentrations (double-blind test with two groups; with oral sorbitol-free SPS and placebo[82]. The results demonstrated that the SPS group showed an apparent effect in reducing serum K^+ with significance compared to the placebo group. However, caution is needed in using SPS as studies report concerns about poor tolerability and serious gastrointestinal side effects.

SZC is a non-polymeric compound that exchanges K^+ for sodium and hydrogen ions in the gastrointestinal tract, clears bound K^+ via the feces, and is used for the management of hyperkalemia[83]. Previous studies have reported that SZC helps correct hyperkalemia and maintain normokalemia in CKD patients. Roger et al., in a long-term study of 751 outpatients with hyperkalemia, showed that serum K+ levels normalized after initiation of SZC, and normokalemia was maintained for up to 12 months[84]. Ash et al. also showed that SZC significantly reduced serum K^+ levels in a randomized, double-blind, placebo-controlled study of 90 patients with hyperkalemia and stage 3 CKD (eGFR 30-60 mL/min/1.73 m^2)[85]. It has been reported that SZC administration is beneficial for managing serum K^+ concentration in patients with hyperkalemia, while another study reported that caution should be taken for dose-related mild to moderate edema due to reductions of dosage[86,87].

Patiromer and the SZC mentioned above is a new K^+ binding drug that effectively reduces serum K^+ concentrations in CKD patients with hyperkalemia. Patiomer is a spherical and nonabsorbable polymer with higher potassium binding capacity than polystyrene sulfonate polymers[88,89]. It is characterized by low water absorption and includes calcium rather than sodium in the exchange cation[90]. Moreover, patiomer is fully ionized at the physiological pH of the colon for optimal ion exchange with the highest potassium concentration in the gastrointestinal tract[88]. Various studies have shown that in CKD patients receiving RAAS inhibitor therapy, patiromer significantly reduces serum K^+ concentration and positively affects the continuation of RAAS inhibitor therapy[91,92]. However, despite the pharmacological properties and potassium-lowering effect of patiomer, as shown in the previous study and meta-analyses[93], it needs caution for adverse events such as nausea, constipation, and diarrhea.

Future consideration

By monitoring the effects, treatment, and favorable prognosis of hypertension and potassium metabolisms in patients with CKD, medical staff must try to balance the expected benefits and adverse effects caused by potassium restriction and RAAS inhibitors. In the hypertension domain, there is a need to expand attention not only to the use of antihypertensives but also to improving patients' lifestyles, such as sodium intake and obesity control. Moreover, while potassium-lowering therapies with patiromer or SZC have been beneficial in effectively and safely correcting hyperkalemia in patients, it should be noted that research is still ongoing to overcome some concerns about continued efficacy and safety. Thus, developing and continuously researching drugs that can effectively control the potassium level without worrying about adverse effects and a diet for controlling potassium are necessary.

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