Original Article

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Use of Fludrocortisone for Hyperkalemia in Chronic Kidney Disease Not Yet on Dialysis

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Background: Hyperkalemia is a frequent and potentially lethal complication of chronic kidney disease (CKD). We retrospectively examined the potassium-lowering effect of oral fludrocortisone and its adverse effects in hyperkalemic CKD patients not yet on dialysis.
Methods: Thirty-three patients (23 men and 10 women, ages 69±14 years) were included. To control hyperkalemia at the outpatient clinic, twenty-one patients (Group 1) received fludrocortisone (0.05–0.1 mg/day) without changes in angiotensin II receptor blockers (ARBs) and calcium polystyrene sulfonate (CPS), while twelve patients (Group 2) were treated with fludrocortisone in addition to stopping ARBs and/or adding low-dose CPS.
Results: Fludrocortisone was administered for a median of 169 days (interquartile range, 47–445). At the first follow-up after fludrocortisone administration, serum potassium dropped from 6.14±0.32 mEq/L to 4.52±1.06 mEq/L ($p<0.001$) in Group 1 and from 6.37±0.35 mEq/L to 4.08±0.74 mEq/L ($p<0.01$) in Group 2. Ten patients in Group 1 and five patients in Group 2 measured serum potassium levels at four outpatient visits before and after fludrocortisone administration, respectively. The frequency of serum potassium ≥6.0 mEq/L decreased from 19/40 (48%) to 2/40 (5%) ($p<0.001$) in Group 1 and from 11/20 (55%) to 0/20 (0%) ($p<0.001$) in Group 2. Eleven patients experienced sodium retention-related problems after fludrocortisone administration: 7 with worsening leg edema, 2 with pleural effusions, and 2 with pulmonary edema.
Conclusion: In pre-dialysis CKD patients, fludrocortisone at low doses effectively reduced serum potassium levels; however, sodium retention was a common adverse effect.

Key Words: Calcium polystyrene sulfonate, Chronic kidney disease, Fludrocortisone, Hyperkalemia

INTRODUCTION

Hyperkalemia is a common complication of chronic kidney disease (CKD), since potassium is primarily eliminated through the kidneys[1]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) that are used to reduce proteinuria also contribute to decreased potassium excretion. Clinically, hyperkalemia may cause life-threatening arrhythmias, especially when the serum potassium exceeds 6.5 mEq/L[2]. As a result, hyperkalemia is a potentially serious issue for CKD patients.

Cation-exchange resins, such as sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS), have been extensively used to control hyperkalemia in CKD outpatients[3,4]. In the gastrointestinal tract, SPS and CPS take potassium in exchange for sodium or calcium ions, respectively,

and promote potassium excretion. However, many patients find the drugs intolerable because of their adverse effects, which are most commonly nausea and constipation[4]. Loop diuretics may lower serum potassium by increasing renal potassium excretion, but their use may be inappropriate in the absence of volume overload since they could exacerbate renal dysfunction[5]. Sodium bicarbonate may decrease serum potassium by transferring potassium into the cells, but its effectiveness is limited[6]. Most recently, sodium zirconium cyclosilicate and patiromer have been introduced[7]. Like SPS and CPS, these drugs take up potassium in exchange for sodium or calcium ions in the gastrointestinal tract. These new agents have been shown to effectively reduce serum potassium and have fewer side effects. However, they are not yet available in many countries, including Korea.

Despite dietary education for potassium restriction and administration of a potassium-binding agent, hyperkalemia is frequent in CKD outpatients, and it is a tough problem to control. If hyperkalemia is severe, referral to the emergency room is required for rapid correction of it with intravenous insulin/glucose infusions, repeated enemas with a potassium-binding agent, or even hemodialysis.

Fludrocortisone is a synthetic mineralocorticoid receptor agonist that lowers potassium levels by increasing potassium and hydrogen excretion instead of sodium reabsorption[8]. Due to sodium retention, however, fludrocortisone may have adverse effects such as peripheral edema, congestive heart failure, and hypertension. In addition, activation of mineralocorticoid receptors may contribute to interstitial inflammation, fibrosis, and proteinuria in CKD patients[9,10]. Mineralocorticoid receptor antagonists, on the other hand, have been shown in animal models of diabetic kidney disease to reduce mesangial expansion, interstitial fibrosis, and proteinuria[9,10]. Thus, sodium retention and the potential adverse mineralocorticoid effects on the kidney make fludrocortisone unattractive for chronic therapy, and fludrocortisone has not traditionally been used for hyperkalemia in CKD patients.

However, fludrocortisone may be used if there are no other effective ways to prevent fatal, severe hyperkalemia. The use of fludrocortisone as a potassium-lowering agent has been reported in hemodialysis patients[11-14] and organ transplant recipients receiving calcineurin inhibitors[15-19], but there has been little data regarding the use of fludrocortisone for hyperkalemia control in patients with CKD who are not yet on dialysis.

In this study, we retrospectively examined the potassium-lowering effect of oral fludrocortisone and its adverse effects in hyperkalemic pre-dialysis CKD patients who did not tolerate adding CPS or increasing the dose of CPS.

Materials and Methods

1. Patients

We reviewed the medical records of patients registered at Asan Medical Center, a tertiary hospital in Seoul, Korea, and included adult CKD patients (≥18 years) who received oral fludrocortisone at the outpatient clinic to control hyperkalemia (K^+ >5.1 mEq/L) between January 1, 2011, and December 31, 2022. Patients with CKD who have hyperkalemia have been treated with CPS. The included patients were given oral fludrocortisone, mostly because they were unable to tolerate adding CPS or increasing the CPS dosage.

Patients with normal renal function or patients with end-stage renal disease on hemodialysis or peritoneal dialysis were excluded. Patients who received fludrocortisone to manage orthostatic hypotension but not hyperkalemia were also excluded.

In cases of severe hyperkalemia (K^+ ≥6.0 mEq/L), some patients received 10 g of CPS three times per day for the first five days. ACEI/ARBs were prescribed at the divisions of nephrology, cardiology, and endocrinology and the department of neurology. ACEI/ARBs were stopped or reduced in some patients but not in others, especially in those who received them from departments other than nephrology.

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. S2022-1461-0001).

2. Clinical and laboratory parameters

We collected data from the medical records, such as age, gender, underlying renal disease, medication use (including CPS and antihypertensive drugs), weight, blood pressure, and laboratory data, including creatinine, potassium, and

estimated glomerular filtration rate (eGFR). The CKD-EPI 2021 equation was used to calculate eGFR using sex, age, and serum creatinine[20]. The normal range of serum potassium was 3.5-5.1 mEq/L.

3. Statistical analyses

Results are expressed as mean±SD or median (interquartile range), depending on the data type. Serum potassium levels, body weights, and blood pressure before and after fludrocortisone administration were compared using Wilcoxon signed rank test. The frequency of serum potassium ≥6.0 mEq/L was compared before and after fludrocortisone administration using the chi-squared test. Statistical analyses were performed using SPSS version 21 (IBM Co., Armonk, NY, USA). P values less than 0.05 were considered statistically significant.

Results

1. Patient characteristics

Thirty-three patients (23 men and 10 women) with a mean age (±SD) of 69±14 years were included. Serum creatinine was 2.84 (2.01-4.49) mg/dl and estimated GFR was 23±12 ml/min/1.73m^2. Fludrocortisone was administered at doses of 0.05-0.1 mg/day for a median of 169 (47-445) days.

Baseline demographic and clinical characteristics are presented in Table 1. One patient had liver transplantation, and another had lung transplantation, receiving tacrolimus as an immunosuppressant.

To control hyperkalemia, twenty-one patients received

Table 1. Clinical and laboratory data of the study population at the time of initiating fludrocortisone

	Group 1# (n=21)	Group 2## (n=12)
Age (years)	70±15	67±12
Male/female	14/7	9/3
Creatinine (mg/dL)	2.84 (1.77-4.68)	3.04 (2.45-4.48)
eGFR (mL/min/1.73m^2)	24±13	21±10
Potassium (mEq/L)	6.14±0.32	6.37±0.35
Total CO_2 (mEq/L)	19.3±3.1	18.7±3.7
Underlying Kidney Diseases		
Diabetes nephropathy	5	4
IgA nephropathy	2	-
Membranous nephropathy	1	-
Polycystic kidney disease	1	-
Reflux nephropathy	1	-
Myeloma kidney	1	-
Chronic kidney disease of unknown etiology	10	8
Comorbidities		
Hypertension	16	8
Diabetes mellitus	9	6
Medications at the time of fludrocortisone administration		
ARB	8	10
ACEI	1	-
CCB	15	9
Beta blocker	8	2
CPS dose (g/day)	15 (10-17.5)	7.5 (0-15)
Furosemide	2	1
Thiazide	1	1
K-sparing diuretic	-	-
Sodium bicarbonate	13	7

#Patients in Group 1 received fludrocortisone with no changes in ARB or CPS.
##Patients in Group 2 were given fludrocortisone as well as the discontinuation of ARBs and/or the addition of low-dose CPS.
ARB; angiotensin II receptor blocker, ACEI; angiotensin-converting enzyme inhibitor, CCB; calcium channel blocker, CPS; calcium polystyrene sulfonate

fludrocortisone without changes in ARB and CPS (Group 1), while the remaining twelve patients received fludrocortisone as well as discontinuation of ARBs and/or addition of low-dose CPS (Group 2).

At the time of fludrocortisone initiation, furosemide was maintained at the current dose in 2 patients in Group 1, increased in 1 patient in Group 2, and not prescribed in the other patients.

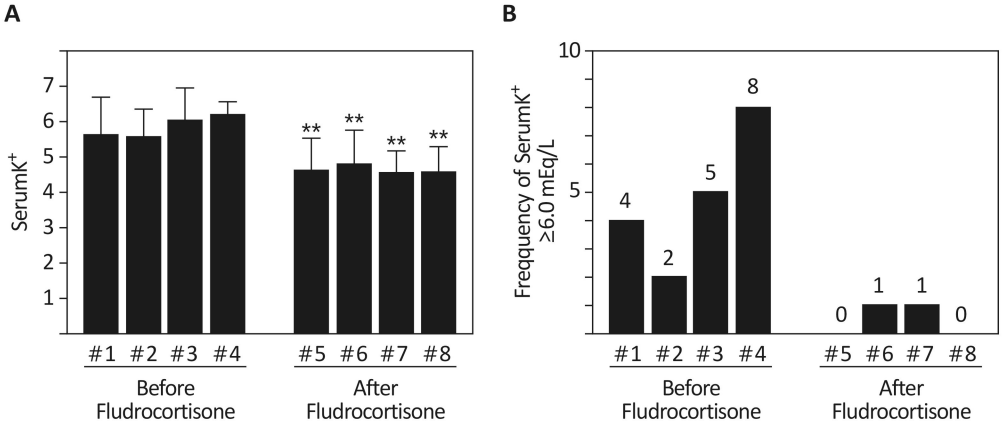
2. Changes in serum potassium after fludrocortisone administration

The serum potassium in Group 1 dropped from 6.14±0.32 mEq/L to 4.52±1.06 mEq/L ($p<0.001$) at the first follow-up after a median of 35 (18-60) days. Similarly, in Group 2, it dropped from 6.37±0.35 mEq/L to 4.08±0.74 mEq/L at the first follow-up after a median of 30 (19-42) days ($p<0.01$).

To evaluate whether the potassium-lowering effect is sustained while fludrocortisone is taken, we analyzed 15 patients (10 patients in Group 1 and 5 patients in Group 2) in whom serum potassium levels were measured at four outpatient visits before and after fludrocortisone administration. The intervals between the measurements are shown in Figs. 1 and 2.

In Group 1, the four consecutive serum potassium levels were 5.63±1.06 mEq/L, 5.56±0.79 mEq/L, 6.02±0.93 mEq/L, and 6.18±0.37 mEq/L before fludrocortisone administration, and 4.60±0.91 mEq/L, 4.79±0.96 mEq/L, 4.55±0.60 mEq/L, and 4.56±0.72 mEq/L after fludrocortisone administration, respectively (Fig. 1A). The frequency of serum potassium ≥6.0 mEq/L was 4/10, 2/10, 5/10, and 8/10 before fludrocortisone administration and 0/10, 1/10, 1/10, and 0/10 after fludrocortisone administration (Fig. 1B); thus, it decreased from 19/40 measurements (48%) to 2/40 measurements (5%) after fludrocortisone administration ($p<0.001$).

In Group 2, the four consecutive serum potassium levels were 5.74±0.63 mEq/L, 5.66±0.55 mEq/L, 5.84±0.36 mEq/L, and 6.48±0.48 mEq/L before fludrocortisone administration, and 4.20±0.88 mEq/L, 4.66±0.51 mEq/L, 5.32±0.58 mEq/L,



C

eGRF (ml/min/1.73m²; mean with standard deviation)

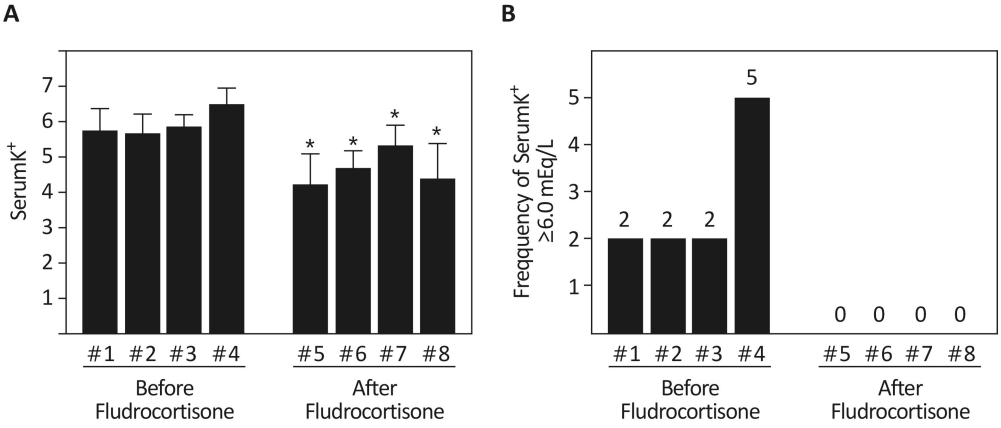
#1	#2	#3	#4	#5	#6	#7	#8
27.3±12.9	25.8±14.7	23.5±14.1	26.2±13.9	27.8±16.9	25.9±16.5	24.6±17.5	22.7±15.9

D

Intervals between measurements (days; median with interquartile range)

#1~#2	#2~#3	#3~#4	#4~#5	#5~#6	#6~#7	#7~#8
59 (21~95)	59 (26~92)	28 (8~63)	30 (19~54)	49 (26~63)	50 (30~56)	60 (45~67)

Fig. 1. Serum potassium levels (**A**) and the frequency of serum potassium ≥6.0 mEq/L (**B**) in patients who received fludrocortisone without changes in ARB and CPS, and measured serum potassium at four outpatient visits before and after fludrocortisone administration (n=10, **p<0.01 compared with #4 before fludrocortisone).



C

eGRF (ml/min/1.73m²; mean with standard deviation)

#1	#2	#3	#4	#5	#6	#7	#8
21.4±11.7	21.0±14.0	19.2±14.4	17.2±12.3	18.2±14.6	14.0±9.1	13.2±10.7	12.2±9.8

D

Intervals between measurements (days; median with interquartile range)

#1~#2	#2~#3	#3~#4	#4~#5	#5~#6	#6~#7	#7~#8
91 (66~109)	91 (57~105)	92 (77~138)	27 (13~71)	66 (49~92)	45 (22~93)	41 (33~77)

Fig. 2. Serum potassium levels (**A**) and the frequency of serum potassium ≥6.0 mEq/L (**B**) in patients who received fludrocortisone as well as discontinuation of ARBs and/or the addition of low-dose CPS to control hyperkalemia, and measured serum potassium at four outpatient visits before and after fludrocortisone administration (n=5, *p<0.05 compared with #4 before fludrocortisone).

and 4.36±1.01 mEq/L after fludrocortisone administration, respectively (Fig. 2A). The frequency of serum potassium ≥6.0 mEq/L was 2/5, 2/5, 2/5, 5/5 before fludrocortisone administration and 0/5, 0/5, 0/5, 0/5 after fludrocortisone administration (Fig. 2B); thus, it decreased from 11/20 measurements (55%) to 0/20 measurements (0%) after fludrocortisone administration (p<0.001).

3. Changes in body weight and blood pressure after fludrocortisone administration

In 15 patients, blood pressure and body weight were measured at four outpatient visits before and after fludrocortisone administration.

Body weight was 67.5±10.8 kg, 67.2±10.3 kg, 67.1±10.4 kg, and 67.3±10.3 kg before fludrocortisone administration, and 68.6±10.3 kg, 68.2±10.9 kg, 68.6±11.1 kg, and 68.1±10.1 kg after fludrocortisone administration, with small but significant increases after fludrocortisone administration (Fig. 3).

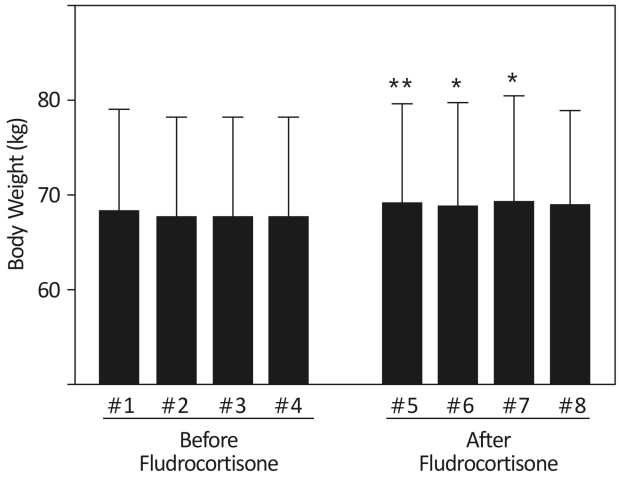


Fig. 3. Body weight changes in patients who were measured at four outpatient visits before and after fludrocortisone administration (n=15, *p<0.05 and **p<0.01 compared with #4 before fludrocortisone)

Systolic blood pressure was 129±18 mmHg, 130±20 mmHg, 131±17 mmHg, and 133±15 mmHg prior to the administration of fludrocortisone and 134±15 mmHg, 134±16 mmHg, 141±

16 mmHg, and 136±19 mmHg after fludrocortisone administration. Diastolic blood pressure was 72±10 mmHg, 74±12 mmHg, 72±7 mmHg, and 74±10 mmHg before fludrocortisone administration, and 74±9 mmHg, 76±11 mmHg, 76±10 mmHg, and 74±10 mmHg after fludrocortisone administration. There were no differences in systolic and diastolic blood pressures before and after fludrocortisone administration. During this time, antihypertensive medications were not changed in 13 patients, the dose of a calcium channel blocker was reduced in one patient, and an ARB was added in another patient.

4. Other adverse effects of fludrocortisone administration

Eleven patients experienced problems related to sodium retention following a median of 71 (51-435) days of fludrocortisone administration. Seven patients had worsening leg edema. Two patients suffered pleural effusions, while the other two developed pulmonary edemas. Diuretics were used to treat pleural effusion and pulmonary edema, and fludrocortisone was discontinued.

Three of the 21 patients in Group 1 and three of the 12 patients in Group 2 experienced hypokalemia (K^+ <3.5 mEq/L) at the first follow-up.

Discussion

In pre-dialysis CKD patients who are unable to tolerate adding CPS/SPS or increasing the dose of CPS/SPS, hyperkalemia detected in the outpatient clinic is a difficult problem to manage. The present study suggests that oral fludrocortisone may be an option in this situation.

So far, there has been little data on the use of fludrocortisone to control hyperkalemia in pre-dialysis CKD patients except a case report[21] in which fludrocortisone was safe and effective in preventing hyperkalemia and maintaining renal function in a woman with type 2 diabetes and CKD stage 3. Despite the lack of data, it has been suggested that CKD patients may require high doses of fludrocortisone (up to 0.4 mg daily) to reduce serum potassium due to aldosterone resistance in damaged renal tubules[22]. In the present study, however, low-dose fludrocortisone (0.05-0.1 mg daily) effectively decreased serum potassium level at 1st follow-up and significantly decreased the frequency of serum potassium ≥6.0 mmol/L from 30/60 (50%) to 2/60 (3%) ($p<0.001$) in 15 patients who measured serum potassium levels at four outpatient visits before and after fludrocortisone administration, respectively, reducing the risk of developing fatal arrhythmia.

Fludrocortisone has previously been studied to prevent hyperkalemia in hemodialysis patients. In a study of 19 hemodialysis patients[11], fludrocortisone (0.1-0.3 mg/day) decreased serum potassium from 5.6±0.1 mEq/L to 4.9±0.1 mEq/L. In another study of 15 patients[12] on hemodialysis receiving fludrocortisone with its dosage gradually increased from 0 to 0.2 mg/day, serum potassium was observed for five successive 4-week periods. The serum potassium concentration decreased from 5.57±0.05 mEq/L to 4.89±0.11 mEq/L at 0.15 mg administration. Such a decrease in serum potassium concentration was more significant in patients with low plasma aldosterone concentrations. In another study[13], 13 hemodialysis patients were treated with fludrocortisone (0.1 mg/day), and fludrocortisone lowered serum potassium levels from 6.1 (5.3-6.8) mEq/L to 5.2 (4.4-6.0) mEq/L at 10 months of treatment. In the other study of 37 hemodialysis patients[14], however, oral fludrocortisone (0.1 mg/day for 3 months) did not significantly reduce serum potassium levels. Thus, fludrocortisone demonstrated modest potassium-lowering effects in hemodialysis patients.

Because the primary sites of action for fludrocortisone are the collecting ducts of the kidneys, the potassium-lowering effect of fludrocortisone may vary depending on the presence of renal function. The majority of the hemodialysis patients included in the previous studies were oliguric or anuric, and thus fludrocortisone could not increase urinary potassium loss, and the decrease in serum potassium values was considered to occur via extrarenal losses, including gastrointestinal potassium excretion[23]. Fludrocortisone consequently had a limited effect on potassium elimination in HD patients and was well tolerated with no significant adverse effects, such as hypertension and volume overload. In contrast, the current study shows that fludrocortisone significantly lowers serum potassium levels in pre-dialysis CKD patients and, in some cases, even results in hypokalemia. On the other hand, the adverse effects seem to be more common in patients with CKD who are not yet on dialysis. Although the blood pressure was not significantly raised,

fludrocortisone caused pleural effusion and pulmonary edema in some patients. Thus, it may be necessary to co-administer a loop diuretic to prevent sodium retention.

Calcineurin inhibitors are one of the major components of immunosuppressants in patients with a kidney or liver transplant. Calcineurin inhibitors can result in type 4 renal tubular acidosis and hyperkalemia. Fludrocortisone, on the other hand, increases sodium resorption and facilitates potassium excretion in the distal convoluted renal tubule. As a result, fludrocortisone has been used to treat calcineurin inhibitor-induced hyperkalemia. A study[15] of 9 liver transplantation patients receiving tacrolimus has shown that fludrocortisone (0.14±0.08 mg/day) decreased serum potassium from 5.7±1 to 4.3±0.5 mEq/L within 48 h. In another study[16] of 10 renal transplant patients with hyperkalemic metabolic acidosis who were taking calcineurin inhibitors, such as tacrolimus, fludrocortisone decreased potassium from 6.1±0.4 to 5.3±0.3 mEq/L. However, fludrocortisone had no significant effects on blood pressure or serum sodium. Consistent with the previous reports, serum potassium was well controlled in two of our patients, one of whom had liver transplantation and another had lung transplantation, receiving tacrolimus as an immunosuppressant.

After oral administration, fludrocortisone is promptly absorbed and exhibits a two- to three-hour half-life. In normal subjects, fludrocortisone (0.2 mg) was shown to increase the transtubular potassium gradient (TTKG) within 3 h after oral administration[24]. Fludrocortisone may thus be useful for acutely lowering serum potassium. It is unknown, however, how quickly it reduces serum potassium levels in CKD patients. The findings in this study warrant further research into the acute effect of fludrocortisone on serum potassium in pre-dialysis CKD.

The traditionally used potassium-lowering agents, CPS and SPS, are unpalatable and cause constipation. Sodium zirconium cyclosilicate and patiromer, two newly introduced potassium-lowering agents, are known to be effective and have fewer adverse reactions[7]. These agents, however, should also be avoided in patients with severe constipation[25], are significantly more expensive than CPS and SPS[5,26], and are not available in many countries. In this study, low-dose fludrocortisone caused sodium retention-related problems in some patients but effectively lowered serum potassium. Our findings suggest that fludrocortisone may be used selectively in pre-dialysis hyperkalemic CKD patients if no other appropriate option to lower serum potassium levels is available. In CKD patients, renin-angiotensin system (RAS) inhibitors, including ARBs, are often discontinued due to hyperkalemia, but withdrawing RAS inhibitors is associated with a higher risk of mortality[27]. Our data suggest that fludrocortisone may also lower serum potassium levels in ARB-treated patients.

However, because of the retrospective study design, this study has a number of limitations. First, because fludrocortisone has not traditionally been utilized for hyperkalemia in CKD patients, the sample size was limited. Second, evidence of increases in urine potassium or TTKG following fludrocortisone administration is useful in supporting the potassium-lowering effect of the drug, but the data on urinary potassium levels are lacking. Third, the absence of a control group made it impossible to assess the impact of fludrocortisone on cardiovascular events and renal function.

In conclusion, low-dose oral fludrocortisone may be a useful short-term option for lowering high potassium levels in hyperkalemic pre-dialysis CKD patients if CPS/SPS is not tolerated and other potassium-binding agents are not available. However, it should be used with caution due to the potential for adverse effects such as pulmonary edema.

Conflict of Interest

The authors have no conflicts of interest to declare.

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