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Hyperkalemia: A Cause of Non-adherence to Renin-Angiotensin-Aldosterone System Inhibitors in Chronic Kidney Disease: A Retrospective Study

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ABSTRACT

Introduction: There is increasing awareness of non-adherence to renin-angiotensin- aldosterone system inhibitors (RAASi) in chronic kidney disease (CKD). This study aimed to evaluate the incidence of hyperkalemic adult CKD patients who were prescribed RAASi and to determine variations in pharmacological interventions to uncover reasons for non-adherence to RAASi treatment.

Methods: The incidence of hyperkalemia and non-adherence to RAASi [angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blockers (ARBs)] in CKD patients was examined among 471 patients over the age of 18 years who had estimated-glomerular filtration rate (e-GFR) measurements and were diagnosed with CKD between stages 1 and 5. Hyperkalemia was defined as serum potassium ($K+$) ≥5 mmol/L. The number of hyperkalemic patients not reaching the target dose, hyperkalemia as a reason for not reaching the target dose, patients receiving sodium polystyrene sulfonate patients discontinuing ACEi/ARBs, having a decreased dose of ACEi/ARBs, or treated with the addition or increasing dose of diuretics were compared between the hyperkalemia groups.

Results: Hyperkalemia was detected in 29.1% of the patients (n=137), being mild in 21.7%, moderate in 6.2%, and severe in 1.3%. The main finding was that the frequency of patients not reaching the target dose of ACEi/ARBs treatment due to hyperkalemia, hypotension, or e-GFR increase higher than 30% was dramatically higher among patients having moderate/severe hyperkalemia ($p<0.0001$). In 12.41% of hyperkalemic patients, hyperkalemia was cited as the cause for not achieving the target dosage of ACEi/ARB therapy. 25.71% of these patients discontinued ACEi/ARBS treatment, 14.29% had decreased dose of this treatment, and 11.43% had increased dose of diuretics or newly prescribed diuretics. However, none of the patients with mild hyperkalemia experienced these events during treatment.

Conclusion: These findings suggest that serum K^+ concentration may be related to major adverse clinical outcomes and affect the type of pharmacological intervention in CKD, resulting in ACEi-ARB discontinuation and halting to reach the target dose.

Keywords: Chronic kidney disease, hyperkalemia, renin-angiotensin-aldosterone system inhibitors

Introduction

Hyperkalemia is a potential metabolic disease and a fatal complication of chronic kidney disease (CKD). It is defined as an elevated potassium (K^+) concentration in the blood serum. Recent studies have shown that K^+ fluctuation may be related to increased mortality or poor cardiovascular (CV) outcomes in patients with CKD (1,2). Hyperkalemia also arises because of renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, which is commonly used to treat CKD (3,4). The use of RAASis in treating CKD is usually recommended by current treatment guidelines because it has been demonstrated to lower blood pressure and proteinuria, delay the decline in estimated-glomerular filtration rate (e-GFR), and lessen the risk of kidney failure (5).

The CREDIT study (Chronic Renal Disease in Turkey) conducted by Süleymanlar et al. (6) depicted that RAASis [especially angiotensin-converting enzyme (ACE) inhibitors (ACEs) and angiotensin II receptor blockers (ARBs)] need to be used in CKD treatment due to their successful renoprotective properties, despite the risk of severe side effects such as hyperkalemia. Therefore, raising awareness about RAASis non-adherence has to be enlightened.

For this purpose, this study aimed to evaluate the incidence of hyperkalemic adult CKD patients who were prescribed RAASi, to determine the variations in the pharmacological interventions, which included the ratio of patients who could reach the maximum RAASi dose, and to uncover the reasons for drug non-adherence to RAASi treatment.

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Methods

Study Design and Patient Selection

The data of patients with chronic renal failure diagnosed at the outpatient clinic of a tertiary hospital between 31.01.2021-31.01.2022 were retrospectively collected. The electronic database of the automation system of the tertiary hospital was examined between these dates, including patients with newly initiated ACEi/ARBs, and the potassium levels of these patients within 180 days after the start of treatment were screened. A total of 512 patients over the age of 18 years who had a baseline e-GFR measurement, were diagnosed with CKD between stages 1 and 5, and were receiving RAASi treatment were recruited to the study. Patients were included if they received one of the following treatments within 180 days of the initial measurement of hyperkalemia: RAASi discontinuation, RAASi dose reduction, diuretic dose increase, or new diuretic or sodium (Na) polystyrene sulfonate (SPS) prescription. Patients who received the same dose of RAASi without receiving any extra medication to address hyperkalemia were also included.

The exclusion criteria wereas follows:

- A disease other than CKD, including a known inflammatory disease and/or severe psychological disorder,

- Being on dialysis,

- History of kidney transplantation,

- Taking SPS and/or diuretic prescriptions started earlier than 30 days or exclusively in the emergency room,

- Having an initial hyperkalemia value greater than 7.0 mEq/L,

- No repeat K^+ measures,

- Hospitalization within 30 days of the initial measurement.

The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee of Non-invasive Clinical Research (approval number: 311, date: 14.10.2022) in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net).

Data Collection

All data were collected from the hospital database. The patients' characteristics included gender, age (years), body mass index (BMI) (kg/m^2), their comorbidities [diabetes mellitus (DM), hypertension, CV disease (CVD) and cerebrovascular event]. The laboratory findings included the hematocrit (HCT), white blood cells, glucose, urea, creatinine, uric acid, total protein amount, albumin, albumin/creatinine ratio, calcium (Ca^{+2}), phosphor (P), Na^+, K^+, parathyroid hormone (PTH), bicarbonate (HCO_3), hemoglobin (Hb), hemoglobin A1C (HbA1C), and e-GFR levels. To assess the patients' laboratory results, fasting blood samples were collected from all individuals during the examination and then centrifuged. Roche Cobas 8000 e602 analyzers (Roche Diagnostics, Mannheim, Germany) were used to analyze parameters such as whole blood count, blood urea, creatinine, uric acid, total protein, and albumin. Levels of HCO_3, Hb, and HbA1C were determined using a photometric method, whereas an electrochemiluminescence assay was used to measure PTH.

The e-GFR was calculated using equations established by the CKD epidemiological collaboration (CKD-EPI) (7). CKD was defined as the presence of persistent proteinuria or a reduced e-GFR (<90 mL/min per 1.73 m^2) determined by the CKD-EPI creatinine equation, confirmed in two separate measurements within a 3-month interval. The CKD-EPI equation, presented as a single formula, is as follows: GFR= 141 x minimum (Scr/κ, 1)α x maximum (Scr/κ, 1)-1.209x0.993 age x 1.018 (if female), where Scr represents serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males. The min function indicates the smaller value between Scr/κ and 1, and the maximum function indicates the larger value between Scr/κ and 1.

Diagnosis of Hyperkalemia and Classification

To estimate the peak level of K^+, blood K^+ was measured at least once 180 days after beginning ACE/ARB intake. Hyperkalemia was characterized by a serum K^+ level equal to or greater than 5 mmol/L. It was further categorized as mild (>5.0 to <5.5 mmol/L), moderate (5.5 to <6.0 mmol/L), or severe (≥6.0 mmol/L) based on the K^+ concentration. Patients who had serum K^+ <5 mmol/L were selected as the control group. The patient characteristics and laboratory findings were compared between the control and hyperkalaemic patients. As the target dose, we accepted the maximum dose stated in the prospectus or product information sheet. Among the patients with serum K^+ ≥5 mmol/L, the number of patients not reaching the target dose, hyperkalemia as cause of not reaching the target dose, patients receiving SPS, patients discontinuing ACEi/ARBs, having a decreased dose of ACEi/ARBs, or treated with addition or increasing dose of diuretics were compared between the groups of hyperkalemia.

Statistical Analysis

The Graph Pad Instat application was used to statistically evaluate all data. The mean, standard deviation, median, minimum, and maximum values were identified as descriptive statistics. The homogeneity of the variance and the normality of the variable distribution were examined using the Kolmogorov-Smirnov test. The parametric analysis of variance test (Student's t-test) was used to evaluate two groups after the assumption was satisfied. Non-parametric testing (Mann-Whitney U test) was used to evaluate the two groups when the requirements for parametric tests were not satisfied. Categorical variables are analyzed by the chi-square test. At a 95% confidence interval, $p<0.05$ was considered statistically significant level.

Results

Among 512 patients over the age of 18 years who had baseline e-GFR and hyperkalemia measurements and were diagnosed with CKD, 41 patients were excluded according to the exclusion criteria. Among the 471 patients diagnosed with CKD and receiving RAASi, hyperkalemia was identified in 29.1% of the cases (n=137) during the initial assessment. Specifically, 21.7% of these cases were categorized as mild (n=102), 6.2% as moderate, and 1.3% as severe (n=6). The general characteristics of patients classified according to hyperkalemia diagnosis are

presented in Table 1. The mean age, BMI, distribution of sex, and comorbidities were comparable between the control group including normokalemic patients and the hyperkalemia group including hyperkalemic patients, except that the ratio of patients with CVD in the hyperkalemia group was significantly higher than that in the control group (25.55% vs. 7.49%, p<0.0001). The mean HCT, total protein, HCO_{3^-}, Hb, and e-GFR levels significantly decreased, whereas the median urea and K^+ levels significantly increased in the hyperkalemia group compared with those in the control group (p<0.05) (Table 1). The distribution of CKD stage significantly varied between the two groups (p<0.0001). The ratios of patients at stages 4 and 5 were 16.06% and 2.92% in the hyperkalemia group and 7.78% and 0.60% in the control groups, respectively.

The distribution of medications classified according to hyperkalemia diagnosis is presented in Table 2. The most common drugs prescribed in the control group were ARBs, thiazide, beta-blockers and ACEi (59.9%, 46.7%, 41.0% and 40.1%, respectively). The most common drugs prescribed in the hyperkalemia group were ARBs, beta-blockers, Ca channel blockers, oral antidiabetics and ACEi (55.5%, 52.6%, 51.8%, 47.4% and 44.5%, respectively).

Table 1. General characteristics of normokalemic and hyperkalaemic patients

Characteristics	Total, (n=471)	Control, (n=334)	Hyperkalemia, (n=137)	p-value
Age (y), $\bar{x}$ ± SD	66.07±10.37	66.17±10.86	66.17±10.86	0.309
Sex, (n, %)				
Male	211 (44.80)	149 (44.61)	62 (45.26)	0.979
Female	260 (55.20)	185 (55.39)	75 (54.74)	
BMI (kg/m^2), $\bar{x}$ ± SD	31.64±5.61	31.86±5.88	31.44±5.37	0.546
Comorbidities (n, %)				
DM	270 (57.32)	185 (55.39)	85 (62.04)	0.221
HT	463 (98.30)	328 (98.20)	135 (98.54)	0.797
CVD	60 (12.74)	25 (7.49)	35 (25.55)	**<0.0001**
CVE	5 (1.06)	4 (1.20)	1 (0.73)	0.653
Laboratory findings				
Urea (mg/dL), $\bar{x}$ (min.-max.)	50.8 (18-180)	48 (18-120)	55.2 (25.7-180)	**0.0011**
Creatinine (mg/dL), $\bar{x}$ (min.-max.)	1.28 (0.55-8.2)	1.29 (0.55-4.00)	1.28 (0.66-8.2)	0.182
e-GFR (mL/min/1.73 m2), $\bar{x}$ ± SD	48.01±16.46	49.21±16.88	45.08±15.04	**0.0095**
Uric acid (mg/dL), $\bar{x}$ ± SD	6.45±1.61	6.47±1.68	6.42±1.54	0.793
Total protein (g/L), $\bar{x}$ ± SD	7.10±0.47	7.20±0.41	7.00±0.51	**0.0007**
Albumin (g/L), $\bar{x}$ ± SD	4.44±0.34	4.44±0.35	4.43±0.33	0.867
Ca (mg/dL), $\bar{x}$ (min.-max.)	9.5 (7.9-11)	9.42 (7.9-11.0)	9.5 (8.4-10.6)	0.490
P (mmol/L), $\bar{x}$ ± SD	3.69±0.66	3.65±0.72	3.73±0.61	0.374
Na (mg/dL), $\bar{x}$ ± SD	139.76±3.11	139.81±3.16	139.74±3.09	0.894
K (mmol/L), $\bar{x}$ (min.-max.)	4.76 (2.9-6.38)	4.6 (2.9-4.99)	5.28 (5.0-6.38)	**<0.0001**
Glucose (mg/dL), $\bar{x}$ (min.-max.)	115 (72-375)	116 (79-312)	113.55 (72-375)	0.631
PTH (ng/L), $\bar{x}$ (min.-max.)	61.3 (9.5-1405)	61 (14.3-1405)	62.2 (9.5-458)	0.805
HCO_3^- (mmol/L), $\bar{x}$ ± SD	25.54±3.00	25.73±2.99	25.02±2.98	**0.0293**
A/C ratio (mg/gr), $\bar{x}$ (min.-max.)	146 (0-11665)	145 (0-11665)	153 (1-9326)	0.391
Hb (g/dL), $\bar{x}$ ± SD	12.71±1.71	12.84±1.74	12.39±1.59	**0.0062**
HCT (%), $\bar{x}$ ± SD	38.63±4.74	39.50±4.73	37.83±4.64	**0.0043**
WBC (10^9/L), $\bar{x}$ (min.-max.)	7,770 (3,690-17,100)	7,750 (3,690-17,100)	7,930 (4,150-12,470)	0.856
HbA1C (%), $\bar{x}$ ± SD	7.40±1.59	7.44±1.52	7.29±1.94	0.855
CKD stage (n, %)				
1 (≥90 mL/min/1.73 m^2)	9 (1.91)	9 (2.69)	0 (0)	**<0.0001**
2 (60-89 mL/min/1.73 m^2)	49 (10.40)	26 (7.78)	23 (16.79)	
3 (30-59 mL/min/1.73 m^2)	359 (76.22)	271 (81.14)	88 (64.23)	
4 (15-29 mL/min/1.73 m^2)	48 (10.19)	26 (7.78)	22 (16.06)	
5 (<15 mL/min/1.73 m^2)	6 (1.27)	2 (0.60)	4 (2.92)	

$\bar{x}$ ± SD: Mean ± standard deviation, $\bar{x}$ [min.-max.]: Median [minimum value-maximum value], min.: Minimum, max.: Maximum, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, CHD: Coronary heart disease, CVE: Cerebrovascular event, e-GFR: Estimated-glomerular filtration rate, min.: Minute, Ca: Calcium, P: Phosphorus, Na: Sodium, K: Potassium, PTH: Parathyroid hormone, HCO_3^-: Bicarbonate, A/C: Albumin/creatinine ratio in spot urine, Hb: Hemoglobin, HCT: Hematocrit, WBC: White blood cells, HbA1C: Hemoglobin A1C, CKD: Chronic kidney disease

The general characteristics of patients classified according to the severity of hyperkalemia are presented in Table 3. The mean age of patients with moderate/severe hyperkalemia was significantly lower than that of patients with mild hyperkalemia (p=0.0034). The mean BMI, distribution of comorbidities, and medications did not differ according to the severity of hyperkalemia, except the number of sodium-glucose transport protein 2 (SGLT2) inhibitor users, which was significantly lower among patients with moderate/severe hyperkalemia than among patients with mild hyperkalemia (14.29% vs. 32.35%, p=0.0488). The mean e-GFR level was significantly lower, whereas the median Na^{+2} and K^{+} levels were significantly higher in patients with moderate/severe hyperkalemia compared to the mild hyperkalemic patients (p<0.05). The other laboratory findings were comparable between the two groups (Table 3). The distribution of CKD stage did not differ between the two groups (p=0.538).

Among the hyperkalemic patients receiving a pharmacologic intervention with RAASi (Table 4), 54 (39.42%) could not reach the target dose of ACEi/ARBs. This ratio was significantly higher in patients with moderate/severe hyperkalemia than in those with mild hyperkalemia (74.29% vs. 27.45%, p<0.0001). The cause of not reaching a target dose was hyperkalemia in 48.57% of patients with moderate/severe hyperkalemia, whereas none of the mild hyperkalemic patients had this cause. 27 (19.71%) hyperkalemic patients were prescribed SPS as treatment for hyperkalemia, which did not differ between the two groups (p=0.076). Among the patients with moderate/severe hyperkalemia, 9 (6.57%) underwent ACEi/ARBs discontinuation, 5 (3.65%) underwent ACEi/ARBs dose decrease, 4 (2.92%) were newly prescribed a diuretic or prescribed an increased dose of a preexisting diuretic. None of the patients with mild hyperkalemia did not undergo ACEi/ARBs discontinuation or ACEi/ARBs dose decrease or were newly prescribed a diuretic or had an increased dose of a preexisting diuretic.

Discussion

In this retrospective study, the outcomes of hyperkalemia and non-adherence to RAASi (ACEi/ARBs) in patients with CKD were examined. The study found a hyperkalemia prevalence of 29.1% (n=137). Mild hyperkalemia was detected in 74.5% of the hyperkalemic patients, whereas 29 had moderate hyperkalemia (21.2% of hyperkalemic patients), and 6 had severe hyperkalemia (4.4% of hyperkalemic patients). These ratios were consistent with other studies in the literature (8,9). Patients with CKD cannot reach the target dose of treatments with ACEi/ARB mainly because of hyperkalemia. However, hypotension and e-GFR increases higher than 30% also seem to be related to inappropriate ACEi/ARB dosing (10). The key finding of the present study was that the frequency of patients not reaching the target dose of ACEi/ARB treatment was moderate/severe hyperkalemia. Second, within this patient group, it was discovered that hyperkalemia was the presumed cause for the failure to achieve the target dosage of treatments with ACEi/ARBs. Third, 25.71% of these patients discontinued ACEi/ARBS treatment, 14.29% had a decreased dose of this treatment, and 11.43% had an increased dose of diuretics or newly prescribed diuretics. However, none of the patients with mild hyperkalemia experienced these events during treatment.

Several factors can affect serum K^{+} concentration in CKD patients, including demographic variables, e-GFR level, medications frequently prescribed, acid- base status, BMI, and the existence of comorbidities (11). In our study, no relationship was found between age, gender, BMI, and hyperkalemia. However, the prevalence of CVD was significantly higher among hyperkalemic patients (25.55% vs. 7.49%), probably because of the medications used in these patients. In fact, in a previous study, hyperkalemia was reported to be frequent in patients with established CVD who were using antihypertensive drugs and was associated with increases in all-cause mortality and hospitalizations. Advanced CKD, diabetes mellitus, CVD, and peripheral vascular disease were also found to be independent predictors of hyperkalemia (12).

Table 2. Distribution of medications classified according to hyperkalemia diagnosis

Medications (n, %)	Total, (n=471)	Control, (n=334)	Hyperkalemia, (n=137)
ACEi	195 (41.4)	134 (40.1)	61 (44.5)
ARBs	276 (58.6)	200 (59.9)	76 (55.5)
CCBs	130 (27.6)	59 (17.7)	71 (51.8)
Alpha-blocker	27 (5.7)	7 (1.5)	20 (14.6)
Beta-blocker	209 (44.4)	137 (41.0)	72 (52.6)
Allopurinol	23 (4.9)	15 (4.5)	8 (5.8)
Thiazide	203 (43.1)	156 (46.7)	47 (34.3)
Furosemide	48 (10.2)	29 (8.7)	19 (13.9)
Spironolactone	12 (2.6)	9 (2.7)	3 (2.2)
ASA	84 (17.8)	33 (9.9)	51 (37.2)
Statin	69 (14.6)	28 (8.4)	41 (29.9)
Oral antidiabetics	123 (26.1)	58 (17.4)	65 (47.4)
Insulin	42 (8.9)	19 (5.7)	23 (16.8)
SGLT2 inhibitor	137 (29.1)	99 (29.6)	38 (27.7)

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blockers, CCBs: Calcium channel blockers, ASA: Acetylsalicylic acid, SGLT2: Sodium-glucose transport protein 2

Table 3. General characteristics of patients classified according to the severity of hyperkalemia

Characteristics	Mild, (n=102)	Moderate/severe, (n=35)	p-value
Age (y), $\bar{x} \pm$ SD	67.17±8.86	61.91±8.77	**0.0034**
Sex (n, %)			
Male	48 (47.06)	14 (40)	0.598
Female	54 (52.94)	21 (60)	
BMI (kg/m^2), $\bar{x} \pm$ SD	31.45±5.26	31.40±5.75	0.968
Comorbidities (n, %)			
DM	62 (60.78)	23 (65.71)	0.751
HT	101 (99.02)	34 (97.14)	0.424
CHD	26 (25.49)	9 (25.71)	0.979
CVE	0 (0)	1 (2.86)	0.574
Medications (n, %)			
ACEi	45 (44.12)	16 (45.71)	0.870
ARBs	57 (55.88)	19 (54.29)	0.870
CCBs	50 (49.02)	21 (60)	0.355
Alpha-blocker	18 (17.65)	2 (5.71)	0.148
Beta-blocker	52 (50.98)	20 (57.14)	0.664
Allopurinol	7 (6.86)	1 (2.86)	0.650
Thiazide	39 (38.24)	8 (22.86)	0.148
Furosemide	14 (13.73)	5 (14.29)	0.934
Spironolactone	1 (0.98)	2 (5.71)	0.326
ASA	38 (37.25)	13 (37.14)	0.991
Statin	31 (30.39)	10 (28.57)	0.839
Oral diabetics	45 (44.12)	20 (57.14)	0.256
Insulin	17 (16.67)	6 (17.14)	0.948
SGLT2 inhibitor	33 (32.35)	5 (14.29)	**0.0488**
Laboratory findings			
Urea (mg/dL), $\tilde{x}$ (min.-max.)	55.55 (25.7-180)	54.4 (30.6-151.4)	0.696
Creatinine (mg/dL), $\tilde{x}$ (min.-max.)	1.27 (0.66-8.2)	1.5 (0.69-4.52)	0.494
e-GFR (mL/min/1.73m^2), $\bar{x} \pm$ SD	46.56±14.94	40.76±14.68	**0.049**
Uric acid (mg/dL), $\bar{x} \pm$ SD	6.48±1.60	6.27±1.36	0.489
Total protein (g/L), $\bar{x} \pm$ SD	7.03±0.50	6.94±0.54	0.420
Albumin (g/L), $\tilde{x}$ (min.-max.)	4.5 (3.3-5.1)	4.5 (3.5-4.9)	0.755
Ca (mg/dL), $\tilde{x}$ (min.-max.)	9.5 (8.4-10.6)	9.6 (8.5-10.3)	0.581
P (mmol/L), $\bar{x} \pm$ SD	3.70±0.62	3.82±0.55	0.352
Na (mg/dL), $\tilde{x}$ (min.-max.)	140 (130-145)	142 (135-148)	**0.0386**
K (mmol/L), $\tilde{x}$ (min.-max.)	5.2 (5.0-5.49)	5.6 (5.12-6.38)	**<0.0001**
Glucose (mg/dL), $\tilde{x}$ (min.-max.)	113 (72-375)	122 (72-301)	0.148
PTH (ng/L), $\tilde{x}$ (min.-max.)	61.65 (9.5-458)	67.2 (12.2-179.3)	0.913
HCO_{3^-} (mmol/L), $\bar{x} \pm$ SD	25.06±3.09	24.88±2.65	0.767
A/C ratio (mg/gr), $\tilde{x}$ (min-max)	143 [1.0-7483)	213.5 (6.0-9326)	0.337
Hb (g/dL), $\bar{x} \pm$ SD	12.42±1.60	12.29±1.55	0.661
HCT (%), $\bar{x} \pm$ SD	37.89±4.69	37.64±4.53	0.777
WBC (10^9/L), $\bar{x} \pm$ SD	7833.9±1893.6	7744.6±1918.3	0.812
HbA1C (%), $\tilde{x}$ (min.-max.)	7.15 (6.4-11.4)	6.7 (5.3-6.9)	0.478
CKD stage (n, %)			
2 (60-89 mL/min/1.73 m^2)	19 (18.63)	4 (11.43)	0.538
3 (30-59 mL/min/1.73 m^2)	66 (64.71)	22 (62.86)	
4 (15-29 mL/min/1.73 m^2)	14 (13.73)	8 (22.86)	
5 (<15 mL/min/1.73 m^2)	3 (2.94)	1 (2.85)	

$\bar{x} \pm$ SD: Mean ± standard deviation, $\tilde{x}$ (min.-max.): Median [minimum value-maximum value), BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, CHD: Coronary heart disease, CVE: Cerebrovascular event, ACEi: Angiotensin-converting enzyme inhibitor, ARBs: Angiotensin II receptor blockers, CCBs: Calcium channel blockers, ASA: Acetylsalicylic acid, SGLT2: Sodium-glucose transport protein 2, e-GFR: Estimated-glomerular filtration rate, Ca: Calcium, P: Phosphorus, Na: Sodium, K: Potassium, PTH: Parathyroid hormone, HCO_3^-: Bicarbonate, A/C: Albumin/creatinine ratio in spot urine, Hb: Hemoglobin, HCT: Hematocrit, WBC: White blood cells, HbA1C: Hemoglobin A1C, CKD: Chronic kidney disease

Table 4. Distribution of patients classified according to treatment progress

Characteristics	Total, (n=137)	Mild, (n=102)	Moderate/severe, (n=35)	p-value
Patients not reaching the target dose (n, %)	54 (39.42)	28 (27.45)	26 (74.29)	**<0.0001**
Hyperkalemia as a cause of not reaching target dose (n, %)	17 (12.41)	0 (0)	17 (48.57)	**<0.0001**
Patients receiving SPS (n, %)	27 (19.71)	16 (15.69)	11 (31.43)	0.076
Discontinuation of ACEi/ARBs (n, %)	9 (6.57)	0 (0)	9 (25.71)	**<0.0001**
Decreasing dose of ACEi/ARB (n, %)	5 (3.65)	0 (0)	5 (14.29)	**0.0008**
Addition or increasing dose of diuretics (n, %)	4 (2.92)	0 (0)	4 (11.43)	**0.0039**

SPS: Sodium polystyrene sulfonate, ACEi: Angiotensin-converting enzyme inhibitor, ARBs, Angiotensin II receptor blockers

In this study, the urea level was significantly higher in hyperkalemic patients, probably because of a prerenal condition resulting from CVD. We can explain the low Hb and HCT levels in hyperkalemic patients by the fact that the anemia increases as the CKD stage progresses because the rate of hyperkalemia was higher in advanced CKD patients.

The factors linked to K^+ levels in patients under nephrological care were renal function, nephropathy type, age, diabetes mellitus, and plasma HCO_{3^-} concentration, listed in descending order of significance. Among these main factors, only one seems to be modifiable: the plasma HCO_{3^-} level, which reflects the body acidity of patients with CKD (13). This study also supported these statements by showing that hyperkalemic patients have significantly lower HCO_3 concentrations than normokalemic patients. However, HCO_3 concentrations did not differ depending on the severity of hyperkalemia.

The risk of hyperkalemia was discovered to be inversely related to renal function, escalating from 2-fold in stage 2 to 16-fold in stage 5 kidney failure (14). We observed a significantly higher ratio of patients in stages 4-5 in the hyperkalemia group than in the control group, indicating an anticipated complication of advancing CKD. To prevent hyperkalemia in these patients, who gradually lose their ability to excrete dietary K^+, it is advisable to maintain a low dietary K^+ intake (13).

Hyperkalemia may develop in patients with CKD due to hyporeninemic hypoaldosteronism. While beta blockers, NSAIDs, and renin inhibitors reduce renin production in these people, ACEis and ARBs reduce angiotensin 2 production, and the use of these drugs increases the risk of developing hyperkalemia (15). In our study, no significant relationship was found between medications and hyperkalemia. Moranne et al. (16) recruited 1,038 CKD patients and found that the prevalence of hyperkalemia was 2% in the group with a GFR >60 mL/min/1.73 m^2, while it was 42% in the group with GFR <20 mL/min/1.73 m^2 (16). In another study including 13,500 patients with CKD, it was shown that every 5 mL/min/1.73 m^2 decrease in GFR increased the risk of hyperkalemia by 26% (17). In a study including 388 patients whose serum K^+ value was ≥5.1 mEq/L and without renal replacement therapy, as the GFR value decreased, the K^+ value increased (8). Consistent with the literature, we determined that the mean e-GFR level of hyperkalaemic patients was significantly lower than that of normokalemic patients. In addition, patients with moderate/severe hyperkalemia had significantly lower e-GFR levels than those with mild hyperkalemia.

SGLT2 inhibitors have demonstrated significant nephroprotection and cardioprotection in both diabetic and non-diabetic CKD patients, as indicated by reports evaluating long-term outcomes (18). Consequently, these inhibitors might be recommended for non-diabetic CKD patients in the future (19). Research has shown that SGLT2 inhibitors are linked to lower serum K^+ levels in patients with CKD (20-22). The effect of SGLT2 inhibitors on serum K^+ levels appears to be more substantial in clinical trials involving CKD patients than in trials focusing on high CV risk (23). Remarkably, SGLT2 inhibitors seem to have a neutral or even decreasing effect on hyperkalemia in CKD patients (22). This might explain the finding that the prescription of SGLT2 inhibitors in mild hyperkalemic patients was significantly higher than that in those with moderate/severe hyperkalemia.

The most common ambulatory pharmacologic treatment changes for hyperkalemia include discontinuation or dose decrease of RAASi, initiation or dose increase of K^{+-} wasting diuretics, or initiation of K^{+-} binding medications such as SPS. The selection of ambulatory intervention varies widely among professionals, the progression of CKD, and the availability of the treatments (13). Hyperkalemia frequently restricts the use of RAASi and can cause a dose reduction or discontinuation of medication, thereby diminishing its possible benefits. Consequently, hyperkalemia poses a significant concern for clinicians, especially in the context of ACEi and ARB usage (24). In a study conducted by Delgado-Jiménez et al. (25), hyperkalemia was cited as the cause for not prescribing or failing to achieve the target dose of mineralocorticoid receptor antagonists (MRAs) in 34.8% and 12.5% of patients, respectively. The impact of hyperkalemia on the prescription or achieving the target dose with ACEi, ARBs, and angiotensin-neprilysin inhibitors was notably lower than that with MRAs (25). In a retrospective cohort study by Hundemer et al. (26) recruiting older adults who developed hyperkalemia, the most frequently employed strategy in response to hyperkalemia was discontinuation of RAASi, accounting for 74% of 11,317 patients who received a pharmacologic intervention. This was followed by reducing the RAASi dosage (15%), increasing the diuretic dosage (7%), prescribing a new diuretic (3%), and using SPS (1%) (26). Consistent with the literature, we found that 39.42% of hyperkalemic patients did not reach a target dose, and hyperkalemia was the reason for not reaching the target dose of RAASi in 12.41% who had moderate/severe hyperkalemia. Moreover, 6.57% of hyperkalemic patients discontinued ACEi/ARB treatment, and 3.65% were prescribed a decreased dose of ACEi/ARBs, all of whom had moderate/severe hyperkalemia. 19.71% of hyperkalemic patients received SPS, which is a safe and tolerable gastrointestinal K^+ binder that enables the long-term control of hyperkalemia, perhaps facilitating the optimization of RAASi medication, and probably altering the existing CKD situation.

The best method for managing RAASi-related hyperkalemia in outpatient settings is still under debate. When it comes to choosing which intervention to employ, the specialists and clinics differ greatly from one another. In patients on RAAS inhibitors, the concurrent use of loop or thiazide diuretics has been linked to a lower incidence of hyperkalemia (22). The addition of diuretics to the treatment regimen to mitigate the risk of hyperkalemia may also enhance the effectiveness of RAAS blockade. Thiazides, in particular, have been found to reduce albuminuria by 42% when combined with RAAS blockade in short-term studies (lasting 4 weeks) (18), and they are recommended for improving the antihypertensive effectiveness of RAAS blockers (27). However, the ability of thiazides to lower K^+ levels may be limited in patients with lower e-GFR values, although serum K^+ levels in these patients may still respond to loop diuretics. It is important to note that K^{+-} sparing diuretics such as triamterene, amiloride, and those targeting the mineralocorticoid receptor can increase the risk of hyperkalemia (28). Hundemer et al. (26) also pointed out that among elderly patients (with an average age of 79 years), the most common intervention was the discontinuation of RAAS inhibitors (74%). Nevertheless, 10% of patients received new or increased doses of diuretics (26). This finding aligns with our results, where the proportion of hyperkalemic patients who were prescribed new or increased doses of diuretics was 11.43%.

Study Limitations

There are indeed several limitations to our study. First, it is essential to acknowledge that this study is retrospective and observational in nature. As a result, we could only find correlations between the study treatments and outcome measures-not causes and effects. We used a single definition of hyperkalemia and grouped a limited number of patients by severity, although the results were consistent across these groups.

Second, the outcome measures in our study were confined to a 180-day timeframe. This temporal limitation might restrict our capacity to establish correlations between outpatient interventions for RAAS inhibitor-associated hyperkalemia and long-term outcomes, which could differ from the short-term outcomes observed in this study. For instance, the long-term effects of RAAS inhibitor discontinuation on diseases such as proteinuric CKD and congestive heart failure, where RAAS inhibitors are recognized for slowing disease progression, might necessitate a longer timeframe to become fully clear.

Third, because our study concentrated on the influence of hyperkalemia severity on ambulatory interventions, patients who were acutely ill or had experienced acute kidney injury at the time of the hyperkalemia episode were excluded, as well as patients hospitalized within 30 days of the initial hyperkalemia diagnosis.

Additionally, it is worth noting that newer K^{+-} binding agents such as patiromer and zirconium cyclosilicate were not included in our study because they were not widely available in our clinic or country during the timeframe of our research. These agents provide an alternative approach for the management of outpatient hyperkalemia.

These limitations should be considered when interpreting the findings and implications of our study.

Conclusion

In conclusion, among 471 patients with CKD, hyperkalemia was detected in 29.1% of the patients, mild in 21.7%, moderate in 6.2%, and severe in 1.3%. Among non-adherence to RAASi treatment, RAASi discontinuation was the pharmacologic intervention in 27.45% of patients with mild hyperkalemia and in 74.29% of patients with moderate/severe hyperkalemia. The main reason for not reaching the target dose of RAASi was hyperkalemia in 48.57% of patients with moderate/severe hyperkalemia. These findings suggest that serum K^+ concentration may be correlated with major adverse clinical outcomes and affect the type of pharmacological intervention in patients with CKD. It should be considered that hyperkalemia may cause ACEi-ARB discontinuation, and halting to reach the target dose, and close monitoring of hyperkalemic patients in clinics is advisable. Confirming the short- and long-term effects of several treatment options for RAASi-related hyperkalemia requires several prospective investigations. Further randomized controlled trials are necessary to determine the ideal blood K^+ levels for patients with CKD.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee of Non-invasive Clinical Research (approval number: 311, date: 14.10.2022).

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