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Research Article

Hyperkalemia and Use of RAAS Inhibitors in Stage 3-5 Chronic Kidney Disease Non-Dialysis Patients: A Single-Center Experience

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Abstract

Objectives: Despite the risk of hyperkalemia, renin angiotensin aldosterone system inhibitors (RAASi) are widely used in chronic kidney disease (CKD) because of their positive effects on mortality. In this study, we aimed to investigate the frequency of hyperkalemia, the use of RAASi, and potassium binders in Stage 3-5 CKD non-dialysis patients.

Methods: In this cross-sectional study, non-dialysis patients with Stage 3-5 CKD were recruited and evaluated at two visits with a 3-month interval. The use of RAASi and potassium-lowering therapy of the patients were followed up. Presence of hyperkalemia at both visits was defined as persistent hyperkalemia.

Results: A total of 182 patients were included in the study. The mean serum potassium was 4.8±0.5 mmol/L, and the prevalence of hyperkalemia was 27.5%. Serum potassium level was similar between CKD groups. RAASi use was significantly higher in CKD Stages 3a and 3b than the other groups ($p<0.001$). Potassium binder use was highest in CKD Stage 5. Despite persistent hyperkalemia, most of the patients continued to use the RAASi. Potassium binder use was also high to tolerate hyperkalemia.

Conclusion: Our study reveals that RAASi continues to be used in daily practice even in cases of persistent hyperkalemia due to its positive effects.

Keywords: Chronic kidney disease, hyperkalemia, renin angiotensin aldosterone system inhibitors, potassium binder, persistent hyperkalemia.

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Hyperkalemia in chronic kidney disease (CKD) is associated with increased mortality.[1] CKD patients often have chronic metabolic acidosis and structural heart disease, making them more susceptible to malignant arrhythmias. Hyperkalemia is an independent risk factor for arrhythmia, hospitalization, and mortality.[2,3] Therefore, potassium, mostly stored intracellularly, is attempted to be maintained within a narrow range outside the cells. The kidneys play the most crucial role in potassium homeostasis.[4]

The prevalence of hyperkalemia varies widely in the literature, ranging from 1% to 50%. In individuals without any disease or medication use, the prevalence of hyperkalemia is less than 1%.[5-9] Clinical risks of hyperkalemia begin to increase when potassium levels exceed 5 mmol/L. The prevalence of hyperkalemia varies in studies depending on the reference values used for the hyperkalemia threshold.[1,10] In one study[9], the prevalence of patients with Stage 3-5 CKD and potassium ≥5.0 mmol/L was reported as 13.1%,

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while in another study conducted in patients with a mean estimated glomerular filtration rate (eGFR) of 14.6 ml/min/1.73 m^2, the prevalence of hyperkalemia was reported as 54.2% and 31.5% in groups with potassium >5 mmol/L and ≥5.5 mmol/L, respectively.[6]

Renin angiotensin aldosterone system inhibitors (RAASi) are widely used in CKD due to their effects on lowering blood pressure, reducing proteinuria, slowing CKD progression, improving cardiovascular outcome, and reducing mortality.[11-14] However, RAAS inhibitors increase the frequency and severity of hyperkalemia especially in CKD. It has been reported that the incidence of hyperkalemia increases in cases of heart failure and CKD (5% and 10%, respectively).[15]

In this study, we aimed to examine the relationship between the frequency of hyperkalemia and the use of RAAS inhibitors and potassium binders in Stage 3-5 CKD non-dialysis patients.

Methods

Study Design and Participants

This cross-sectional study was conducted between June 2019 and March 2020 at a tertiary care university hospital's nephrology outpatient clinic, involving patients with Stage 3-5 non-dialysis CKD. In a previous multicenter study, we investigated calcium-phosphorus metabolism. In this study, potassium metabolism was investigated in a subgroup of our previous study.[16] Patients were evaluated at two visits with a 3-month interval. Patients under 18 years of age, those with active solid organ and hematological malignancies, individuals receiving renal replacement therapy, those who develop acute kidney injury during follow-up, and those who were not evaluated in at least two visits with a 3-month interval were excluded from the study.

Data Collection

Data was obtained from patient files and the electronic database of the hospital. The following information was recorded for each patient: age, gender, primary cause of kidney disease (diabetic kidney disease, hypertensive nephropathy, glomerulonephritis, urinary tract abnormality), comorbid diseases (hypertension [HT], diabetes mellitus [DM], coronary artery disease [CAD], heart failure), eGFR, stage of kidney disease, serum potassium levels, presence of hyperkalemia, the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers, diuretics, potassium binders, and oral sodium bicarbonate.

Definitions

Chronic kidney disease was defined according to the National Kidney Foundation's guidelines.[17] Patients with eGFR <60 ml/min/1.73 m^2 for more than three months were considered CKD.[18] Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[19] The average of eGFR values obtained from two clinical visits with a 3-month interval was calculated using the following formula, and patients were grouped according to the CKD stages (stage 3, eGFR of >30 to 60 ml/min/1.73 m^2; stage 4, eGFR >15 to 30 ml/min/1.73 m^2; and stage 5, eGFR ≤15 ml/min/1.73 m^2).[18,19] Hyperkalemia was defined as serum potassium levels greater than the upper value of the laboratory reference limit (>5.1 mmol/L).[1] Presence of hyperkalemia at both visits was defined as persistent hyperkalemia. Normal potassium levels at both visits were defined as normokalemia.

Statistical Analysis

Descriptive statistics were expressed as mean, standard deviation (SD) for the continuous data, and as count and proportion for the categorical data. Categorical data were analyzed using the chi-square or Fisher's exact tests. The normality of the continuous variables was calculated using the Shapiro-Wilk test. The independent samples t-test or Mann-Whitney U test were used to determine any significant differences between the groups. Statistical analyses were performed using the IBM SPSS for Windows v.22 software (SPSS Inc., Chicago, IL, USA). Values of $p<0.05$ were considered significant.

Results

Baseline Characteristics of the Study Population

A total of 182 patients were included in our study. Baseline demographic, clinical, and laboratory data of the patients are presented in Table 1. The mean age was 65.9±13.2 years, and 47.3% of the patients were male. Diabetic kidney disease was the most common cause of chronic kidney disease (33.5%). The most common comorbid condition was HT, followed by DM, CAD, and HF (79.1%, 55%, 18.6%, 14.3% respectively). When patients were grouped according to CKD stages, it was observed that a significant portion of the patients were in CKD stages 3a and 3b (45.1% and 32.4% respectively). The mean serum potassium was 4.8±0.5 mmol/L, and the prevalence of hyperkalemia was 27.5%.

Comparison of Groups According to CKD Stages

The demographic, clinical, and laboratory data of the patients according to their CKD stages are presented in Table 2. Among the groups, age, gender, prevalence of DM,

Table 1. Baseline demographic, clinical, and laboratory data of the patients

Variables	n=182
Age, years	65.9±13.2
Male, (%)	86 (47.3)
Primary kidney disease, (%)	
Diabetic kidney disease	61 (33.5)
Unknown	49 (26.9)
Hypertensive nephropathy	29 (15.9)
Glomerulonephritis	17 (9.4)
Urinary tract abnormalities	14 (7.7)
Miscellaneous	12 (6.6)
Comorbid disease, (%)	
Hypertension	144 (79.1)
Diabetes mellitus	100 (55.0)
Coronary artery disease	34 (18.6)
Heart Failure	26 (14.3)
e-GFR, ml/min/1.73 m^2	40.7±13.0
Stage of kidney disease, (%)	
Stage 3a	82 (45.1)
Stage 3b	59 (32.4)
Stage 4	35 (19.2)
Stage 5 ND	6 (3.3)
Potassium, mmol/L	4.8±0.5
Hyperkalemia, (%)	50 (27.5)

Data are expressed as mean±SD for quantitative parameters; e-GFR: estimated glomerular filtration rate, ND: non-dialysis.

hyperkalemia, beta-blocker use, and diuretic use were similar. eGFR showed significant variation according to CKD stages (p<0.001). Potassium levels were significantly lower in Stage 3a patients compared to Stage 3b and Stage 4 patients (p=0.029). The prevalence of hyperkalemia did not significantly differ among the groups, but it was most prominent in Stage 4, followed by Stage 3b and Stage 5.

As eGFR decreased, a decrease in the use of ACEIs/ARBs was observed; CKD Stage 3a and 3b patients were using ACEIs/ARBs significantly more than Stage 4 and 5 patients (p<0.001). Regarding the potassium binder use, there was a significant difference between the groups. It was observed that potassium binder use was more common in CKD Stage 5. The use of oral sodium bicarbonate was more common as the GFR decreased (p<0.001).

Hyperkalemia, Potassium Binder and RAASi Use

The frequency of hyperkalemia was 27.5% at the first visit and 38.5% at the second visit (Fig. 1). The frequency of persistent hyperkalemia was 17.1%. Potassium binder and RAASi use were evaluated in cases of hyperkalemia and normokalemia (Table 3). Potassium binder use was significantly higher in patients with hyperkalemia at the first visit compared to normokalemia (28.0%, 13.6%, respectively, p=0.023). The use of RAASi was similar in both groups at the first visit. The use of potassium binder and RAASi was similar in hyperkalemic patients at the second visit. The use of potassium binder was significantly higher in patients with persistence hyperkalemia than in patients with normokalemia (54.8%, 9.7%, p<0.001, respectively), while the use of RAASi was similar.

Table 2. Baseline demographic, laboratory and treatment data according to CKD stages.

Variables	Stage 3a (n=82)	Stage 3b (n=59)	Stage 4 (n=35)	Stage 5 ND (n=6)	p
Age, years	65.4±10.2	66.9±15.7	67.1±14.3	57.5±16.1	0.097
Male gender, (%)	35 (42.7)	29 (49.2)	18 (51.4)	4 (66.7)	0.588
Diabetes mellitus, (%)	42 (51.2)	36 (61.0)	19 (54.3)	3 (50.0)	0.786
e-GFR, ml/min/1.73 m^2	52.1±4.8	38.3±5.1	22.7±4.4	13.5±17.8	<0.001
Potassium, mmol/L	4.7±0.4	4.9±0.5	4.9±0.5	4.5±0.8	0.029[a,b]
Hyperkalemia, (%)	15 (18.3)	20 (33.9)	13 (37.1)	2 (33.3)	0.092
ACEi/ARB use, (%)	63 (76.8)	46 (78.0)	15 (42.9)	2 (33.3)	<0.001[b,c,d,e]
Beta-blocker use, (%)	36 (43.9)	30 (50.8)	13 (37.1)	2 (33.3)	0.563
Diuretic use, (%)	38 (46.3)	21 (35.6)	15 (42.9)	4 (66.7)	0.381
Potassium binder use, (%)	10 (12.2)	10 (16.9)	8 (22.9)	4 (66.7)	0.006[c,e,f]
Oral sodium bicarbonate use, (%)	1 (1.2)	3 (5.1)	8 (22.9)	6 (100.0)	<0.001[b,c,d,e,f]

Data are expressed as mean±SD for quantitative parameters. Significant p values are written in bold; ND: non-dialysis, e-GFR: estimated glomerular filtration rate, ACEi: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. [a]significant between Stage 3a and 3b, [b]significant between Stage 3a and 4, [c] significant between Stage 3a and 5 ND, [d]significant between Stage 3b and 4, [e]significant between Stage 3b and 5 ND, [f]significant between Stage 4 and 5 ND.

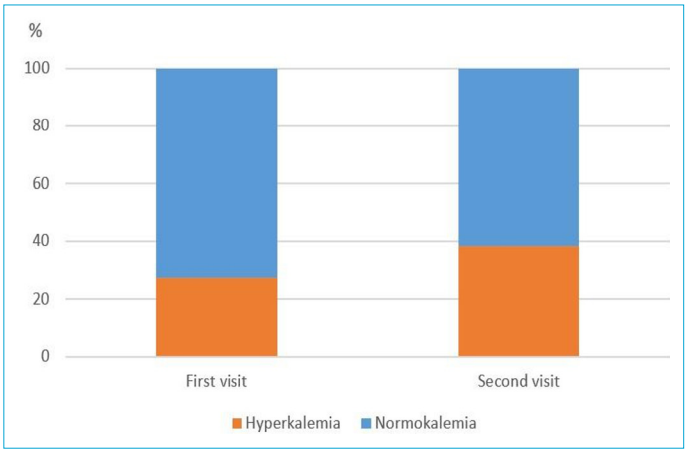

Figure 1. Incidence of hyperkalemia in first and second visit.

Discussion

The kidneys play a major role in potassium homeostasis.[4] Hyperkalemia is significant due to its association with increased mortality in patients with CKD.[2] The prevalence of hyperkalemia in the literature varies greatly depending on the characteristics of the selected patient population. However, consistently, about half of hyperkalemia cases are diagnosed with CKD, and the frequency of hyperkalemia increases with worsening kidney function.[20] The frequency of hyperkalemia varies depending on the different threshold values defined in the studies. Additionally, apart from patient-specific factors such as older age, male gender, presence of comorbid diseases such as diabetes mellitus and heart failure, as well as the use of RAASi, are associated with an increased prevalence of hyperkalemia.[8,9,21]

In our study, the prevalence of hyperkalemia was 27.5% in CKD 3-5 non-dialysis patients. According to CKD stages, the prevalence of hyperkalemia increased after Stage 3a, but it was similar among other groups. Notably, the threshold for the increase in the frequency of hyperkalemia was eGFR<45 ml/min/1.73 m^2. In Stage 5, the prevalence of hyperkalemia was 33.3% and this is generally consistent with the literature. The defined threshold for hyperkalemia significantly affects hyperkalemia prevalence. In one study, the prevalence of patients with potassium >5.5 mmol/L in Stage 5 CKD patients was 40%[20], and in another study, the prevalence of patients with potassium >5 mmol/L and ≥5.5 in the same group was 54.2% and 31.5%, respectively.[6]

Although RAAS inhibitors commonly cause hyperkalemia, they are widely used in CKD because of their effects on lowering blood pressure, reducing proteinuria, slowing CKD progression, improving cardiovascular outcomes and reducing mortality.[11-14] It has been reported that the incidence of hyperkalemia due to RAASi is <2% when used for HT without additional risk factors, approximately 5% in dual blockade, and 5% and 10% in the presence of heart failure and CKD, respectively.[15] In our study, patients in Stage 3a and 3b were found to use RAASi significantly more than the other groups. A recent study showing that RAASi did not exhibit their classical renoprotective effects in advanced CKD patients with an average eGFR of 18 ml/min/1.73 m^2 is significant.[22] Our study indicates a decrease in RAASi usage in patients with Stage 4 and 5 CKD. As kidney disease progresses, the increase in the frequency of hyperkalemia can be seen as the reason for this condition. The fact that the frequency of hyperkalemia did not increase as expected in Stage 5 can be explained by the use of potassium binder and oral sodium bicarbonate, which significantly increased compared to other stages. In addition, the decrease in the use of RAASI in the same group may have caused a decrease in the frequency of hyperkalemia. In daily practice, it is frequently observed that the concern of hyperkalemia leads to a decrease in the use of RAASi.

Due to the renoprotective and cardioprotective effects, it is recommended to use RAASi by taking appropriate precautions in patients with hyperkalemia.[23] It is recommended that RAASi use be continued in patients with a serum potassium level <5.5 mmol/L, a patient-based treatment decision should be planned in patients with a serum potassium level between 5.5-6.0 mmol/L, and discontinued in patients with a serum potassium level >6.0 mmol/L.[23] Although a low-potassium diet has traditionally been recommended for the treatment of hyperkalemia, the evidence is weak.[1] Oral potassium binder calcium polystyrene sulfonate is widely used in our country. In case of serum bicarbonate

Table 3. The use of potassium binder and RAASi in cases of hyperkalemia and normokalemia

	First visit n=182	p	Second visit n=182	p	Persistence n=182	p
Potassium level						
Above normal/potassium binder use, (%)	50 (27.5)/14 (28.0)	0.023	70 (38.5)/13 (24.3)	0.060	31 (17.1)/17 (54.8)	<0.001
Normal/potassium binder use, (%)	132 (72.5)/18 (13.6)		112 (61.5)/13 (11.6)		93 (51.1)/9 (9.7)	
Above normal/RAASi use, (%)	50 (27.5)/36 (72.0)	0.618	70 (38.5)/51 (72.8)	0.611	31 (17.1)/20 (64.5)	0.083
Normal/RAASi use, (%)	132 (72.5)/90 (68.2)		112 (61.5)/70 (62.5)		93 (51.1)/58 (62.4)	

level < 22 mmol/L, the use of oral sodium bicarbonate is also recommended for the treatment of hyperkalemia.[17] A remarkable finding in our study; In the first and second visits, approximately 70% of the patients with hyperkalemia were using RAASi, and a significant portion (64.5%) of the patients with persistent hyperkalemia continued to be treated with RAASi. In our study, the continued use of RAASi despite persistent hyperkalemia and the use of potassium binders in these patients are consistent with current recommendations.

There are some limitations in our study. Firstly, this study is a cross-sectional study and patients who applied in a certain period were included in the study. This has led to different numbers of patients between groups and may limit the results to reflect the general population. Secondly, although data on oral bicarbonate use of patients are available, information regarding serum bicarbonate levels are lacking.

In conclusion, hyperkalemia is frequently seen in CKD patients and exacerbates as kidney function decreases. Current recommendations are in favor of insisting on the use of RAASi with diet and treatment modifications in patients using the RAASi. Our study reveals that RAASi continues to be used in persistent hyperkalemia cases and this situation is tried to be tolerated with potassium binders. The lack of studies on therapeutic inertia, which can be defined as not initiating appropriate therapy in the presence of hyperkalemia in CKD patients, is striking. It would be beneficial for future studies to focus on this issue.

Disclosures

Ethics Committee Approval: The study was approved by the local ethics committee (approval number: 83045809) and conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – C.K.; Design – C.K.; Supervision – C.K.; Materials – C.K., S.G.O.; Data collection &/or processing – C.K., S.G.O.; Analysis and/or interpretation – C.K.; Literature search – C.K.; Writing – C.K.; Critical review – C.K.

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