CLINIC RESEARCH

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The Effect of Different Serum Potassium Levels on Progression of Chronic Kidney Disease

Farklı Serum Potasyum Düzeylerinin Kronik Böbrek Hastalığının İlerlemesi Üzerindeki Etkisi

ABSTRACT

Objective

Hyperkalemia is the most common electrolyte imbalance in chronic kidney disease (CKD). Research within the CKD population suggests a potential link between hyperkalemia, hypokalemia, fluctuations in serum potassium (sK+) levels, and CKD progression.This study aimed to clarify how different sK+ levels affect CKD progression.

Material and Methods

eGFR levels were assessed, identifying patients with decreased eGFR. A total of 1171 patients were included .sK+ levels were analyzed in groups, and a Binary Logistic Regression model was employed for GFR decrease prediction.

Results

The mean sK+ level was 4.6 ± 0.4 mmol/l. Hyperkalemia was observed in 26.1% of patients, with hypokalemia at only 0.6%. During the follow-up, eGFR levels exhibited a significant decrease. A negative correlation was observed between sK+ level and the final eGFR of patients. Specifically, sK+ levels ranging from 5.0 to 5.5 mmol/l and instances of hyperkalemia were linked with decreased eGFR, while sK+ levels at 3.5-4.0 mmol/l demonstrated a protective effect against eGFR decrease. Adjusting for albumin, calcium, urea levels, ACEi/ARB usage, β-AR blockers intake, and CCB administration in the regression model revealed that sK+ levels at 5.0-5.5 mmol/l and hyperkalemia independently contributed to eGFR decrease. Conversely, sK+ levels at 3.5-4.0 mmol/l emerged as a protective factor against eGFR decrease.

Conclusion

Our findings underscore the association of hyperkalemia and sK+ levels at 5.0-5.5 mmol/l with decreased eGFR among CKD patients. Conversely, maintaining sK+ levels at 3.5-4.0 mmol/l appears to mitigate the risk of eGFR decrease. Thus, vigilant sK+ monitoring is crucial in managing CKD effectively.

Key Words

Chronic Kidney Disease, Glomerular filtration rate, Potassium Level, Hyperkalemia, Hypokalemia

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ÖZ

Amaç

Hiperkalemi, kronik böbrek hastalığında (KBH) en yaygın elektrolit dengesizliğidir. KBH popülasyonu içinde yapılan araştırmalar, hiperkalemi, hipokalemi, serum potasyum (sK+) seviyelerindeki dalgalanmalar ve KBH progresyonu arasında olası bir bağlantı olduğunu öne sürmektedir.Bu çalışma, farklı sK+ seviyelerinin kronik böbrek hastalığı progresyonunu nasıl etkilediğini açıklığa kavuşturmayı amaçlamıştır.

Gereç ve Yöntemler

eGFR seviyeleri değerlendirilerek eGFR'si azalmış hastalar belirlendi. Toplamda 1171 hasta dahil edildi. sK+ seviyeleri gruplar halinde analiz edildi ve GFR azalmasını öngörmek için İkili Lojistik Regresyon modeli kullanıldı.

Bulgular

Ortalama sK+ seviyesi 4.6 ± 0.4 mmol/l idi. Hastaların %26.1'inde hiperkalemi, yalnızca %0.6'sında ise hipokalemi gözlendi. Takip süresince eGFR seviyelerinde önemli bir düşüş tespit edildi. sK+ seviyesi ile hastaların nihai eGFR'leri arasında negatif bir korelasyon ortaya çıktı. Özellikle, sK+ seviyeleri 5.0-5.5 mmol/l aralığında ve hiperkalemi durumları eGFR azalması ile ilişkili bulundu. Buna karşılık, sK+ seviyeleri 3.5-4.0 mmol/l aralığında olduğunda eGFR azalmasına karşı koruyucu bir etki gösterdi. Regresyon modeline albümin, kalsiyum, üre seviyeleri, ACEi/ARB kullanımı, β-AR bloker alımı ve CCB uygulaması dahil edilerek yapılan ayarlamalarda, sK+ seviyeleri 5.0-5.5 mmol/l ve hiperkaleminin bağımsız olarak eGFR azalmasına katkıda bulunduğu görüldü. Aksine, sK+ seviyeleri 3.5-4.0 mmol/l aralığında olduğunda eGFR azalmasına karşı koruyucu bir faktör olarak ortaya çıktı.

Sonuç

Bulgularımız, hiperkalemi ve 5,0-5,5 mmol/l arasındaki sK+ seviyelerinin KBH hastalarında azalan eGFR ile ilişkili olduğunu vurgulamaktadır. Öte yandan, sK+ seviyelerinin 3,5-4,0 mmol/l arasında tutulması, eGFR azalma riskini azaltmada önemli bir faktör gibi görünmektedir. Dolayısıyla, dikkatli sK+ izlemi, KBH'yi etkili bir şekilde yönetmede önemlidir.

Anahtar Kelimeler

Kronik Böbrek Hastalığı, Glomerüler Filtrasyon Hızı, Potasyum Seviyesi, Hiperkalemi, Hipokalemi

INTRODUCTION

Chronic kidney disease (CKD) is a prevalent and progressive condition associated with substantial morbidity and mortality rates globally. In Turkey, the mean prevalence is 15.7% (1). In the elderly population, the prevalence is significantly higher, ranging between 23.4% and 35.8% (2).CKD is known to increase mortality rates, lead to more frequent hospitalizations as the disease advances, and contribute to cardiovascular mortality (3).

The primary causes of CKD are diabetes mellitus (DM), hypertension (HT), and glomerulonephritis, which together account for a significant proportion of CKD cases (4). Although the pathophysiological pathways leading to CKD development vary depending on the etiology, nephron loss is a common consequence. This loss triggers remaining nephrons to compensate by increasing estimated glomerular filtration rate (eGFR), leading to sclerosis and further nephron loss, exacerbating CKD progression (5).
Serum potassium (sK+) regulation is crucial for maintaining homeostasis, with kidneys playing a pivotal role (6). As CKD progresses and eGFR decreases, kidney capacity to regulate sK+ levels diminishes. Therapeutic agents like angiotensin converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and diuretics commonly used in CKD management can further disrupt sK+ balance, resulting in hyperkalemia or hypokalemia, both associated with increased mortality risk among CKD patients (7, 8).

Recent studies highlight the complex impact of sK+ levels on CKD outcomes and mortality in CKD patients (9, 10). Notably, mortality risks vary even within "normal" sK+ range; lower mortality rates are observed in CKD patients with sK+ concentrations between 4.1 and 5.5 mEq/L, while higher mortality rates are linked to levels between 3.5 and 4 mEq/L, a range often deemed normal but associated with elevated risks (11). While existing literature extensively explores the relationship between sK+ levels and CKD morbidity and mortality, fewer studies investigate the effects in disease progression (9-13).
Thus, our study aims to fill this gap by investigating the influence of different sK+ levels on CKD progression.

MATERIAL and METHOD

Study characteristics

The study was conducted among patients attending the Nephrology Outpatient Clinic of our hospital from January 2012 to December 2016. During this period, a total of 4678 chronic kidney disease patients were screened. Among them, 3507 patients were excluded due tohaving fewer than three outpatient clinic visits, follow-up duration less than one year, missing data, development of acute kidney injury during follow-up, or requirement of renal replacement therapy. Thus, a sample of 1171 patients was selected for analysis.

Information on socio-demographic characteristics, duration of follow-up, laboratory parameters, comorbidities, and medication history, including the use of ACEIs, ARBs, and potassium-sparing diuretics impacting sK+ levels and CKD progression were retrospectively analyzed from patient records.

In our study, we utilized the CKD-EPI formula to classify patients, which is widely accepted as the most accurate method for estimating Glomerular Filtration Rate (eGFR) (14). The CKD-EPI formula is calculated as follows: GFR

= 175 × standardized Scr -1.154 × age -0.203 × 1.212 [if black] × 0.742 [if female] (GFR in mL/min/1.73 m2, Scr in mg/dL).

Transient hyperkalemia (a single sample) and hypokalemia can be attributed to various factors. Laboratory errors (hemolysis) and other technical factors were carefully considered during data analysis (15). Moreover, we accounted for potential potassium shifts from intracellular to extracellular compartments during sample collection, particularly in patients with uncontrolled hyperglycemia, such as those with diabetes mellitus, which could induce hyperkalemia (16). This aspect was carefully considered during data analysis.Specifically, samples nearest to the mean potassium value were selected to ensure the reliability of the results.

Patients were categorized based on their sK+ levels as follows: below 3.5 mmol/L (group 1), 3.5-3.9 mmol/L (group 2), 4-4.4 mmol/L (group 3), 4.5-4.9 mmol/L (group 4), 5-5.5 mmol/L (group 5), and above 5.5 mmol/L (group 6). Additionally, a separate classification was established for hypokalemia (<3.5 mmol/L), normokalemia (3.5-5.0 mmol/L), and hyperkalemia (>5.0 mmol/L).
Ethical approval for this study was obtained from the Non-Interventional Research Ethics Committee of Bezm-i Alem University Faculty of Medicine (Approval Date: 30.01.2018, Reference number: 3/18). The study was conducted in accordance withthe World Medical Association Declaration of Helsinki. All methods and procedures used in the study were performed in strict adherence to ethical standards.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM®, Chicago, USA). Descriptive statistics are summarized as numbers, percentages, means, standard deviations, and medians. The compliance of the variables with a normal distribution was examined using analytical methods (The Kolmogorov–Smirnov test). For normally distributed numerical variables, the T-test was used for comparisons between two groups, while the One-Way ANOVA test was employed for comparisons among three groups. Spearman and Pearson correlation tests were used in the correlation analysis. Non-normally distributed numerical variables were compared using the Mann-Whitney U test for two groups and the Kruskal Wallis Test for three or more groups. Nominal data were assessed using the Chi-square test for comparisons between two groups. Factors influencing eGFR decrease in patients with decreased eGFR were evaluated through Binary logistic regression analysis, with eGFR decrease as the dependent variable. Regression analysis was adjusted for albumin, calcium, urea, ACEis/ARBs, beta-adrenergic receptor blockers (β-AR blockers), calcium channel blockers (CCB), DM, and anemia to isolate the effect of sK+ levels on eGFR decrease. Results from regression analysis were reported as B (beta), OR (odds ratio), and CI (confidence interval). Statistical significance was set at $p < 0.05$ for all analyses in the study.

RESULTS

Socio-demographic and clinical data

The median age of the patients in this study was 66 years, with 45.9% (n=537) being male. The mean serum sK+ level was 4.6 ± 0.4 mmol/l, and the median duration of follow-up was 938 days. Table I provides additional socio-demographic, clinical and laboratory characteristics of the patient cohort.

While the majority of patients exhibited normal sK+ levels (73.3%), 26.1% were diagnosed with hyperkalemia, and only 0.6% had hypokalemia. Upon admission, the creatinine level averaged 2.0 ± 0.9 mg/dl, which increased to 2.5 ± 1.6 mg/dl at the last follow-up, signifying a significant increase over the follow-up period (p<0.001). Using the CKD-EPI formula, the eGFR at admission was 35.9 ± 15.5 mL/min/1.73 m2, compared to 31.2 ± 17.3 mL/min/1.73 m2 at the last assessment. eGFR levels showed a significant decrease during patient follow-up (p<0.001).

Correlation between eGFR and sK+ level

Upon categorizing sK+ levels as normokalemia, hypokalemia, or hyperkalemia and examining their correlation with eGFR, significant differences were observed only in the last eGFR values among the groups. Specifically, patients with normokalemia exhibited higher last eGFR values compared to those with hyperkalemia (p=0.010). In post-hoc analyses, the initial eGFR value was higher in group 3 than in group 1 (p=0.037). No significant differences were observed among the other groups. The final eGFR value was higher in group 3 than in group 6, and in group 4 than in group 6. No significant differences were observed among the other groups (p=0.008). Table II provides a summary of the patients sK+ levels and corresponding groups, along with the distribution of eGFR values based on K+ levels.

Correlation between eGFR and other factors

Patients taking ACEis/ARBs demonstrated significantly higher initial eGFR (p<0.001) and last eGFR (p<0.001) compared to non-users. Conversely, patients using CCB, β-AR blockers, and allopurinol showed lower last eGFR values compared to non-users. Additionally, patients with DM or anemia had lower last eGFR values compared to those without these conditions, while other comorbidities showed no significant association with eGFR. Table III-provides an overview of eGFR levels and their correlations with various factors.

eGFR decrease and associated factors

The median difference between initial and last eGFR among patients was 4.3 mL/min/1.73 m2. Notably, 32.6% (n=382) of patients experienced an increase in eGFR, while 66.4% (n=777) showed a decrease, and 1% (n=12) showed no change in eGFR. Patients with increased eGFR

Table I. Socio-demographic, clinical and laboratory characteristics of the patient cohort.

*Data were expressed as mean±sd for numerical variables with normal distribution, median (IQR) for numerical variables without normal distribution, and n(%) for categorical variables.

Abbreviations: DM; Diabetes mellitus, HT; Hypertension, CHF; Congestive heart failure, CAD; Coronary artery disease, ACE; angiotensin converting enzyme, ARB; angiotensin receptor blocker, β-AR blockers;beta-adrenergic receptor blockers, CCB; calcium channel blockers

	n (%)	Mean ± SD	Median(IQR)	Min-max
Age (years)			66 (16)	19-85
Duration of follow-up (days)	**(n=1171)**		938 (834)	366-2297
Gender				
Male	537 (45.9)			
Female	634 (54.1)			
DM	421 (36.0)			
HT	387 (33.0)			
Anemia	386 (33.0)			
CHF	54 (4.6)			
CAD	45 (3.8)			
Nephrotic syndrome	9 (0.8)			
Nephritic syndrome	4 (0.3)			
ACEis/ARBs	413 (35.3)			
Diuretics	469 (40.1)			
Thiazides	111 (9.5)			
Loop diuretics	296 (25.3)			
sK+-sparing diuretics	122 (10.4)			
β-AR blockers	362 (30.9)			
CCB	565 (48.2)			
N-dihydropyridines	143 (12.2)			
Dihydropyridines	486 (41.5)			
Allopurinol	281 (21.0)			
Potassium (mmol/L)	**(n=1171)**	4.6 ± 0.4		3.3-6.1
Albumin (g/dl)	**(n=1162)**	4.0 ± 0.4		1.9-4.9
CRP (mg/l)	**(n=1030)**		0.7 (1.5)	0-26.3
Erythrocytes (10^3/μL)	**(n=1142)**		1.3 (2.9)	0-663
Phosphorus (mg/dl)	**(n=1153)**	3.8 ± 0.7		1.9-7.9
HbA1C (%)	**(n=804)**	6.5 ± 1.1		3.9-11.0
Calcium (mg/dl)	**(n=1167)**	9.1 ± 0.5		6.0-11.4
Magnesium (mg/dl)	**(n=649)**	1.9 ± 0.3		1.0-3.5
Sodium (mmol/L)	**(n=1170)**	138 ± 2		124-147
Total protein (g/dl)	**(n=1153)**	1.0 ± 0.9		1.0-15.0
Protein/creatinine in spot urine	**(n=833)**		0.7 (1.6)	0-60
Urea (mg/dl)	**(n=1171)**		76.8 (52.3)	25.8-252.1
Uric acid (mg/dl)	**(n=1165)**		7.4 (2.0)	2.5-13.9

Table II. The sK+ levels and groups of the patients and eGFR distribution by sK+ levels

*One_way ANOVA analysis

	N (%)	Initial eGFR (CKD-EPI)	Last eGFR (CKD-EPI)	eMean GFR (CKD-EPI)
Hypokalemia	7 (0.6)	30.6 ± 11.6	26.4 ± 9.9	26.6 ± 7.2
Normokalemia	858 (73.3)	36.0 ± 16.0	32.1 ± 17.7	31.9 ± 16.2
Hyperkalemia	306 (26.1)	35.5 ± 14.0	28.7 ± 16.1	30.1 ± 14.1
p		0,576	**0,010**	0,152
Group 1 <3.50 mmol/L	7 (0.6)	30.6 ± 11.6	26.4 ± 9.9	26.6 ± 7.2
Group 2 3.50-3.99 mmol/L	60 (5.1)	30.6 ± 16.7	29.1 ± 19.3	27.0 ± 17.0
Group 3 4.00-4.49 mmol/L	287 (24.5)	36.5 ± 16.4	33.4 ± 18.0	32.7 ± 16.7
Group 4 4.50-4.99 mmol/L	511 (43.6)	36.4 ± 15.7	31.8 ± 17.3	32.1 ± 15.7
Group 5 5.00-5.50 mmol/L	261 (22.3)	36.1 ± 13.9	29.5 ± 16.4	30.8 ± 14.2
Group 6 >5.5 mmol/L	45 (3.8)	32.0 ± 14.1	24.6 ± 13.8	26.2 ± 12.7
p		**0,037**	**0,008**	**0,016**

Table III. eGFR and associated factors

		Initial eGFR	Last eGFR	Mean eGFR
Gender Female		33.5 ± 14.2	29.1 ± 16.6	29.2 ± 14.6
Male		38.6 ± 16.5	33.7 ± 17.9	34.0 ± 16.4
	p	**<0.001**	**<0.001**	**<0.001**
ACEis/ARBs	(+)	40.6 ± 15.6	33.7 ± 18.0	34.9 ± 16.2
	(-)	33.3 ± 14.8	29.9 ± 16.8	29.5 ± 15.0
	p	**<0.001**	**<0.001**	**<0.001**
CCB	(+)	32.3 ± 14.8	26.7 ± 17.0	27.0 ± 15.0
	(-)	39.2 ± 15.4	35.4 ± 16.6	35.5 ± 15.1
	p	**<0.001**	**<0.001**	**<0.001**
Thiazides	(+)	39.7 ± 15.0	32.2 ± 17.4	33.4 ± 15.4
	(-)	35.5 ± 15.5	31.1 ± 17.3	31.2 ± 15.6
	p	**0,005**	0,550	0,156
Loop diuretics	(+)	35.5 ± 15.1	31.2 ± 17.3	30.8 ± 15.2
	(-)	36.0 ± 15.7	31.2 ± 17.3	31.6 ± 15.8
	p	0,621	0,949	0,441
sK+ sparing	(+)	36.1 ± 13.7	30.7 ± 15.7	30.2 ± 13.4
	(-)	35.8 ± 15.7	31.3 ± 17.5	31.6 ± 15.9
	p	0,884	0,755	0,379
β-AR blockers	(+)	32.0 ± 14.8	25.9 ± 17.1	26.6 ± 15.1
	(-)	37.6 ± 15.5	33.6 ± 16.9	33.6 ± 15.4
	p	**<0.001**	**<0.001**	**<0.001**
Allopurinol	(+)	33.2 ± 14.1	27.7 ± 15.5	28.2 ± 13.5
	(-)	36.7 ± 15.8	32.3 ± 17.7	32.4 ± 16.1
	p	**0.001**	**<0.001**	**<0.001**
HT	(+)	35.6 ± 15.2	30.8 ± 17.8	30.6 ± 15.8
	(-)	36.0 ± 15.7	31.4 ± 17.1	31.8 ± 15.5
	p	0,686	0,530	0,191
DM	(+)	35.4 ± 14.6	28.9 ± 15.3	29.6 ± 13.9
	(-)	36.2 ± 16.0	32.5 ± 18.2	32.4 ± 16.4
	p	0,397	**<0.001**	**0,003**
Anemia	(+)	34.9 ± 14.4	29.7 ± 16.1	29.7 ± 14.5
	(-)	36.3 ± 16.0	31.9 ± 17.9	32.2 ± 16.1
	p	0,141	**0,042**	**0,010**
CHF	(+)	36.4 ± 13.8	29.3 ± 14.8	29.4 ± 14.0
	(-)	35.8 ± 15.6	31.3 ± 17.5	31.5 ± 15.7
	p	0,809	0,401	0,326
CAD	(+)	35.6 ± 13.8	29.3 ± 15.0	29.8 ± 14.2
	(-)	35.9 ± 15.6	31.3 ± 17.4	31.5 ± 15.7
	p	0,925	0,459	0,476
Nephrotic syndrome	(+)	31.4 ± 18.4	29.8 ± 21.5	25.1 ± 15.6
	(-)	35.9 ± 15.5	31.2 ± 17.3	31.5 ± 15.6
	p	0,390	0,802	0,226
Nephritic syndrome	(+)	46.7 ± 28.1	50.3 ± 28.0	39.2 ± 24.6
	(-)	35.8 ± 15.5	31.1 ± 17.3	31.4 ± 15.6
	p	0,164	0,266	0,317

Abbreviations:DM; Diabetes Mellitus, HT; Hypertension, CHF; Congestive heart failure, CAD; Coronary artery disease, ACEis; Angiotensin converting enzyme inhibitors, ARB; angiotensin receptor blockers;β-AR blockers;beta-adrenergic receptor blockers, CCB; calcium channel blockers

Table IV. Analysis of sK+ levels in patients with and without a eGFR decline during the follow-up period and comparison of other patients

	With a eGFR decrease N=777	Without a eGFR decrease N=394	p
Age, med (IQR)	67 (15)	66 (17)	0.245[a]
Duration of follow-up, med (IQR)	1004 (843)	827 (716)	**<0.001** [a]
sK+, mean ± sd	4.69 ± 0.44	4.60 ± 0.45	**0.002**[b]
Group 1, n (%)	4 (0.5)	3 (0.8)	0.605[c]
Group 2, n (%)	32 (4.1)	28 (7.1)	**0.028** [c]
Group 3, n (%)	188 (24.2)	99 (25.1)	0.726 [c]
Group 4, n (%)	332 (42.7)	179 (45.4)	0.378 [c]
Group 5, n (%)	190 (24.5)	71 (18.0)	**0.012** [c]
Group 6, n (%)	31 (4.0)	14 (3.6)	0.714 [b]
Albumin, mean ± sd	3.9 ± 0.4	4.0 ± 0.4	**0.002** [b]
CRP med (IQR)	0.7 (1.5)	0.7 (1.6)	0.880 [a]
Erythrocytes med (IQR)	1.4 (2.9)	1.1 (2.9)	0.127 [a]
P mean ± sd	3.9 ± 0.7	3.6 ± 0.6	**<0.001** [b]
HbA1C mean ± sd	6.5 ± 1.1	6.5 ± 1.2	0.349 [b]
Calcium mean ± sd	9.1 ± 0.5	9.3 ± 0.5	**<0.001** [b]
Mg mean ± sd	1.98 ± 0.32	1.92 ± 0.32	**0.018** [b]
Sodium mean ± sd	138 ± 2	138 ± 2	0.423 [b]
Urea med (IQR)	85.5 (55.1)	63.8 (35.7)	**<0.001** [a]
Uric acid med (IQR)	7.5 (1.9)	7.3 (2)	**0.021** [a]
Female, n (%)	422 (54.3)	212 (53.8)	0.870[c]
Male, n (%)	355 (45.7)	182 (46.2)	0.870 [c]
ACEs/ARBs, n (%)	292 (37.6)	121 (30.7)	**0.020** [c]
CCB, n (%)	394 (50.7)	171 (43.4)	**0.018** [c]
Thiazides, n (%)	79 (10.2)	32 (8.1)	0.259 [c]
Loop diuretics, n (%)	198 (25.5)	98 (24.9)	0.821[c]
K-sparing diuretics, n (%)	80 (10.3)	42 (10.7)	0.847[c]
β-AR blockers, n (%)	259 (33.3)	103 (26.1)	**0.012** [c]
Allopurinol, n (%)	196 (25.2)	85 (21.6)	0.167 [c]
HT, n (%)	257 (33.1)	130 (33)	0.978 [c]
DM, n (%)	303 (39)	118 (29.9)	**0.002** [c]
Anemia, n (%)	272 (35)	114 (28.9)	**0.037** [c]
CHF, n (%)	54 (4.6)	18 (4.6)	0.960 [c]
CAD, n (%)	28 (3.6)	17 (4.3)	0.550 [c]
Nephrotic syndrome, n (%)	6 (0.8)	3 (0.8)	0.984 [c]
Nephritic syndrome, n (%)	2 (0.3)	2 (0.5)	0.488 [c]

a Mann-Whitney U test
b Student T test
c Chi-square analysis

Table V. The analysis of factors affecting eGFR reduction

Factor	B	p	OR	95% CI
sK+ Group 2	-0,662	**0,025**	0,516	0,289-0,920
sK+ Group 5	0,357	**0,030**	1,429	1,035-1,974
Albumin	0,359	0,070	1,432	0,971-2,112
Calcium	-0,494	**0,002**	0,610	0,449-0,829
Urea	0,014	**<0.001**	1,014	1,010-1,019
ACEis/ARBs	0,495	**0,001**	1,640	1,241-2,168
β-AR blockers	0,127	0,404	1,135	0,843-1,529
CCB	-0,038	0,787	0,963	0,730-1,269
DM	0,197	0,164	1,217	0,923-1,606
Anemia	0,180	0,206	1,197	0,906-1,582

* Binary Logistic Regression analysis
** B; beta, OR; odds ratio, CI; confidence interval

had a median increase of 6.1 mL/min/1.73 m2, whereas those with decreased eGFR showed a median decrease in eGFR had higher potassium levels (p=0.002).
Regarding sK+ groups, patients with stable eGFR were more prevalent in group 2 (p=0.028), while those with decreased eGFR were more common in group 5 (p=0.012). Additionally, in patients with decreased GFR, the frequency of normokalemia was lower (p=0.028), while the frequency of hyperkalemia was higher (p=0.012).

Comparing patients with and without decreased GFR, it was observed that those with decreased GFR had a longer follow-up duration (p<0.001) and higher levels of sK+, phosphorus, magnesium, urea, and uric acid, along with lower levels of albumin and calcium. Additionally, the use of ACEis/ARBs, CCB, β-AR blockers, DM, and anemia was more prevalent among patients with decreased eGFR. Table IV provides a summary of the analysis of sK+ levels among patients with and without eGFR decrease during the follow-up period, along with comparisons of other factors.

Regression analysis of factors associated with eGFR decrease

In the multivariate analyses, sK+ groups 5 and 2, along with albumin, phosphorus, calcium, urea, uric acid, the use of CCB, β-AR blockers, and ACEis/ARBs, anemia, and DM were included in the regression analysis. Due to multicollinearity with other independent variables, uric acid and phosphorus were excluded. The regression model demonstrated good fit(X2=107.992, p<0.001).

Regression analysis showed that being in sK+ group 2 decreased the risk of eGFR decrease by 0.516-fold (p=0.025), while being in group 5 increased it by 1.429-fold (p=0.030). The risk of eGFR decrease was 1.640 times higher in patients using ACEis/ARBs (p=0.001), whereas the use of β-AR blockers and CCB, DM, and anemia did not show a significant effect on eGFR decreas. The summary of factors affecting eGFR decrease is presented in Table V. Then, the regression model created by classifying sK+ levels as normokalaemia, hypokalemia and hyperkalemia, it was preferred to include only hyperkalemia because normokalemia was not associated with a decrease in eGFR and a correlation was observed between hypokalemia and hyperkalemia. It was observed that the regression model created was significant (X2 = 102.767, p < 0.001).In the regression analysis, it was observed that hyperkalemia increased the likelihood of eGFR decline by 1.446 times, hypoalbuminemia by 1.508 times, elevated urea levels by 1.014 times, and ACEis/ARBs usage by 1.666 times, while high calcium levels decreased it by 0.606 times. The use of β-AR blockers, CCB, presence of DM, and anemia did not have a significant effect on eGFR decrease. When adjusted for albumin, calcium, urea, ACEi/ARB, β-AR blockers, CCB, DM and anemia, factors shown to be associated with eGFR decrease, it was observed that Group 2 and Group 5 levels were independently determinants of eGFR decrease (p=0.035, p=0.036, respectively). Similarly, when sK+ level was included in the analysis as hyperkalemia, it was found to be an independent determinant of eGFR decrease when adjusted for other factors (p=0.022).

DISCUSSION

The kidneys play a crucial role in balancing sK+ levels. Abnormal sK+ levels observed in patients with decreased renal function highlight the significance of the kidneys in maintaining sK+ balance (6).Both hyperkalemia and hypokalemia can occur in patients with CKD and end-stage kidney disease (17). Hyperkalemia has been previously linked to increased mortality in patients undergoing kidney replacement therapy (KRT) (18). Similarly, hypokalemia has been proposed to be associated with mortality. It is reported to contribute to mortality not only due to the electrophysiological effects of sK+ but also due to its correlation with poor nutritional status (19).

sK+ levels have been primarily studied in end-stage renal failure, with limited exploration in patients across different stages of chronic kidney disease or those not undergoing KRT. In a study conducted by Einhorn et al. in 2009, it was noted that hyperkalemia was more common in patients with CKD compared to those without CKD, based on a cohort of over 70,000 CKD patients. However, the number of studies evaluating the relationship between different sK+ levels and non-KRT CKD patients is quite limited. Thus, in our study, we investigated the relationship between different sK+ levels and eGFR in CKD patients, excluding those with end-stage renal disease (10).

One notable finding of our study was that patients with decreasing eGFR during follow-up had higher sK+ levels. Additionally, in regression analysis, it was observed that sK+ levels between 3.50-3.99 mmol/L were protective against eGFR decrease in CKD patients, while sK+ levels between 5.00-5.50 mmol/L were determinants of GFR decrease. Similarly, the presence of hyperkalemia was associated with a 1.446-fold increase in eGFR decrease. Hypokalemia, however, was not associated with eGFR decrease. This study contributes to the limited literature on the role of different sK+ levels in eGFR decrease among non-KRT CKD patients.

Previous studies support our findings, particularly regarding high sK+ levels. For instance,Takaichi et al.'s 2008 study involving 9,196 non-KRT CKD patients found a decrease in eGFR associated with sK+ levels above 5 mEq/l(20). Similarly, Hsieh et al.'s 2011 study on 531 stage 3-5 CKD patients noted a tendency of sK+ levels to increase with advancing CKD stage (21). These studies reported that as the stage of CKD increased, there was a tendency for sK+ levels to rise. These findings support the notion that higher sK+ levels are associated with a decrease in GFR. The nephrons in the kidneys play a crucial role in sK+ balance. As renal function decrease, sK+ excretion from the nephrons increases in an attempt to maintain balance. However, in cases of severe kidney damage, this balance is disrupted. Elevated sK+ levels stimulate aldosterone secretion, leading to increased sK+ excretion. However, with progressive kidney damage, inadequate nephron numbers result in insufficient sK+ excretion, leading to elevated sK+ levels (22).

The studies conducted by Nakhoul et al.'sin 2015, involving approximately 36,000 patients with a eGFR below 60 ml/min/1.73m² and Tanaka K et al.'s 2021 study in 1330 non-KRT CDK patients both reported that sK+ levels above 5.0 mmol/l were associated with decreased eGFR, similar to our results (12, 23). However, unlike our study, sK+ levels below 3.5 mmol/l were also associated with decreased GFR (12, 23).Actually, persistent hypokalemia, also known as hypokalemic nephropathy, is a well-recognized condition associated with decreased kidney function (24). Persistent hypokalemia can lead to renal fibrosis through mechanisms such as renal inflammation and activation of the renin-angiotensin-aldosterone system. Renal inflammation contributes to increased inflammatory processes in kidney tissue and progression of damage. Similarly, activation of the renin-angiotensin-aldosterone system regulates blood pressure and fluid-electrolyte balance in the kidneys, impacting their structure and functionality (25). In our study, no association was found with low potassium levels. Among the included patients, potassium levels were below 3.5 mmol/L in only 7 individuals, so this relationship may not have been determined.

In the study by Korgaonkar et al., 820 CKD patients were followed for an average of 2.6 years. The analysis revealed that hypokalemia (<4.0 mmol/L), after adjusting for other factors, was a predictor of end-stage renal failure and mortality, while hyperkalemia (>5.5 mmol/L) was not (11). The disparity between studies could be attributed to differences such as the lack of assessment of mortality and end-stage renal failure in our study, as well as the use of different potassium levels (<3.5 mmol/l &<4 mmol/l).

In a large prospective European multicenter study by Rooij ENM et al. in 2023, a U-shaped relationship was found between sK+ levels and the combined outcome of death or initiation of KRT among over 1,700 patients aged ≥65 with CKD stages 4-5.The study with an 8-year follow-up period, the sK+ level associated with the lowest risk of death or initiation of kidney KRT was approximately 4.9 mmol/L. Compared to this level, low (≤3.5 mmol/L) and high (>6.0 mmol/L) sK+ concentrations carried a 1.6-fold and 2.2-fold higher risk for death or KRT initiation, respectively, after multivariable adjustment(26).A subanalysis of a meta-analysis included over 42,000 CKD patients with a mean age of 70 and a mean eGFR of 42 mL/min/1.73 m². In this analysis, it was found that sK+ levels between 4.0 and 4.5 mmol/L were associated with the lowest risk of both all-cause mortality and initiation of KRT(27).In our study, maintaining sK+ levels within the range of 3.5-4.0 mmol/l was shown to be protective against eGFR decrease.

When comparing patients with decreased and non-decreased eGFR, it was observed that in patients with decreased eGFR, the follow-up period was longer (p<0.001), P level was higher (p<0.001), Mg level was higher (p=0.018), urea (p<0.001), and uric acid (p=0.021) were higher, while albumin level (p=0.002) and calcium level (p<0.001) were lower. In patients with decreased eGFR, the presence of ACEis/ARBs (p=0.020), CCB (p=0.018), β-AR blockersuse (p=0.012), DM (p=0.002), and anemia (p=0.037) was more common. Regression analysis revealed that, except for potassium levels, the decrease in calcium levels, elevated urea, and ACEis/ARBs usage were determinants of decreased GFR.

Blood pressure and proteinuria control are crucial in preventing eGFR decrease in CKD, leading to common use of ACEis/ARBs in early CKD stages. Large trials

(SHARP and BEACON) have shown benefits of ACEis/ARBs in early CKD (28, 29).Similarly, it is known that CCB reduce proteinuria, decrease mortality, and have positive effects on blood pressure in patients with CKD (30). In CKD patients, although ACEIs/ARBs are the first-line treatment, activation of the sympathetic nervous system worsens renal dysfunction. As a result, β-AR blockers are also incorporated into the treatment regimen.

In our study, the incidence of absolute hypokalemia was 0.6%, while hypokalemia occurred in 5.7% of cases. Hyperkalemia was observed in 26.1% of patients, with an absolute hyperkalemia frequency of 3.8%. These findings align with previous reports in the literature. For instance, a population-based study by Thomsen et al. conducted in Denmark in 2017 reported a hyperkalemia prevalence of 28% among 157,766 newly diagnosed CKD patients (31). This study also noted an increasing frequency of hyperkalemia with advancing CKD stages. Similarly, Nakhoul et al. in 2015 found hypokalemia and hyperkalemia incidences of 3% and 11%, respectively, in stage III and stage IV CKD patients (12). The reported prevalence of hyperkalemia in CKD patients varies widely in the literature, ranging from 8% to 73%. This variability depends on factors such as the study population, defined thresholds for hyperkalemia (>5 mmol/L &>5.5 mmol/L), included CKD stages (stages I-V), and duration of patient follow-up (32).

However, our study has several limitations. More than 30% of our patients had a history of DM. In patients with Type 4 Renal tubular acidosis due to DM or chronic CDK, metabolic acidosis can lead to hyperkalemia (33). The lack of data on metabolic acidosis rates and bicarbonate treatment is one of the limitations of our study. Additionally, the use of the creatinine-based estimated GFR calculation method, the CKD-EPI formula, presents another limitation. Many medications commonly used in CKD patients, such as H2 receptor antagonists and fibrates, can influence serum creatinine levels. Similarly, conditions like sarcopenia can also affect creatinine levels, potentially reducing the accuracy of the results (34).

Furthermore, the inability to definitively determine the direction of the relationship between hyperkalemia and kidney function is another limitation. Although hyperkalemia has been associated with impaired kidney function, it remains unclear whether hyperkalemia causes kidney dysfunction or is a consequence of it (10). This causality uncertainty is another limitation of our study.

These limitations could be addressed in future research by increasing the sample size, adopting prospective study designs, and extending the follow-up period.

CONCLUSION

CKD often progresses to more advanced stages and ultimately leads to kidney failure in a significant number of patients.The risk of mortality increases markedly with the development of cardiovascular comorbidities in kidney failure. Accurately predicting disease progression is crucial to enable timely interventions. Based on our findings, it is recommended to anticipate progression in patients with sK+ levels between 5.00-5.50 mmol/L or those presenting with hyperkalemia.Proactive measures should be taken to mitigate the risks associated with progression in these individuals.

Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Bezm-i Alem University Faculty of Medicine Ethics Committee (Approval Date: 30.01.2018, Reference number: 3/18).

Informed Consent

All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Author Contributions

Concept – İ.G., Ö.C.E.; Design – İ.G.; Supervision – Ö.C.E.; Resources – İ.G.; Materials – İ.G.; Data Collection and/or Processing – İ.G.; Analysis and/ or Interpretation – İ.G., Ö.C.E.; Literature Search – İ.G., Ö.C.E.; Writing Manuscript – İ.G.; Critical Review – İ.G., Ö.C.E.

Conflict of Interest

The authors have no conflict of interest to declare.

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