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ORIGINAL ARTICLE

Prevalence and factors associated with hyperkalaemia in stable kidney transplant recipients

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ABSTRACT

Background. Hyperkalaemia is a frequent and potentially life-threatening condition in patients with chronic kidney disease (CKD). Even after successful kidney transplantation (KTx) , KTx recipients have mild to severe CKD. Moreover, they share comorbid conditions and frequently use medications that predispose to hyperkalaemia. This study aimed to examine the prevalence and factors associated with hyperkalaemia in this population.

Methods. Over a pre-specified period of 6 months (1 September 2019 to 31 March 2020), we recorded in cross-sectional fashion information on serum potassium (K^+) and relevant demographics, comorbidities, medications, laboratory and transplant-associated variables in clinically stable KTx recipients attending the Transplant Outpatient Clinic of our Department. Hyperkalaemia was classified as follows: serum K^+ level >5.0 mEq/L; and further as >5.0 mEq/L with concomitant use of sodium (Na^+) polystyrene sulphonate; serum K^+ ≥5.2 mEq/L ; serum K^+ ≥5.5 mEq/L. Univariate and multiple logistic regression analyses were used to identify factors associated with serum K^+ >5.0 mEq/L.

Results. The study population consisted of 582 stable KTx recipients, 369 (63.4%) males, aged 52.4 ± 13.5 years, with estimated glomerular filtration rate (eGFR) of 55.8 ± 20.1 mL/min/1.73 m^2 transplanted for >1 year. The prevalence of hyperkalaemia defined as K^+ >5.0 mEq/L; >5.0 mEq/L and use of Na^+ polystyrene sulphonate; K^+ ≥5.2; or K^+ ≥5.5 mEq/L, was: 22.7, 22.7, 14.4 and 4.1% (132, 132, 84 and 24 patients), respectively. In multivariate analysis, male gender [odds ratio (OR) = 2.020, 95% confidence interval (CI) 1.264–3.227] and use of renin–angiotensin–aldosterone system (RAAS) blockers (OR = 1.628, 95% CI 1.045–2.536) were independently associated with hyperkalaemia, while higher eGFR (OR = 0.967, 95% CI 0.955–0.979) and use of non-K^+-sparing diuretics (OR = 0.140, 95% CI 0.046–0.430) were associated with lower odds of the disorder.

Conclusions. The prevalence of mild hyperkalaemia in stable KTx recipients is relatively high but that of moderate or severe hyperkalaemia is low. Among a wide range of factors studied, only male gender and RAAS blockade were associated with increased odds of hyperkalaemia, while higher eGFR and diuretics were associated with decreased odds of hyperkalaemia.

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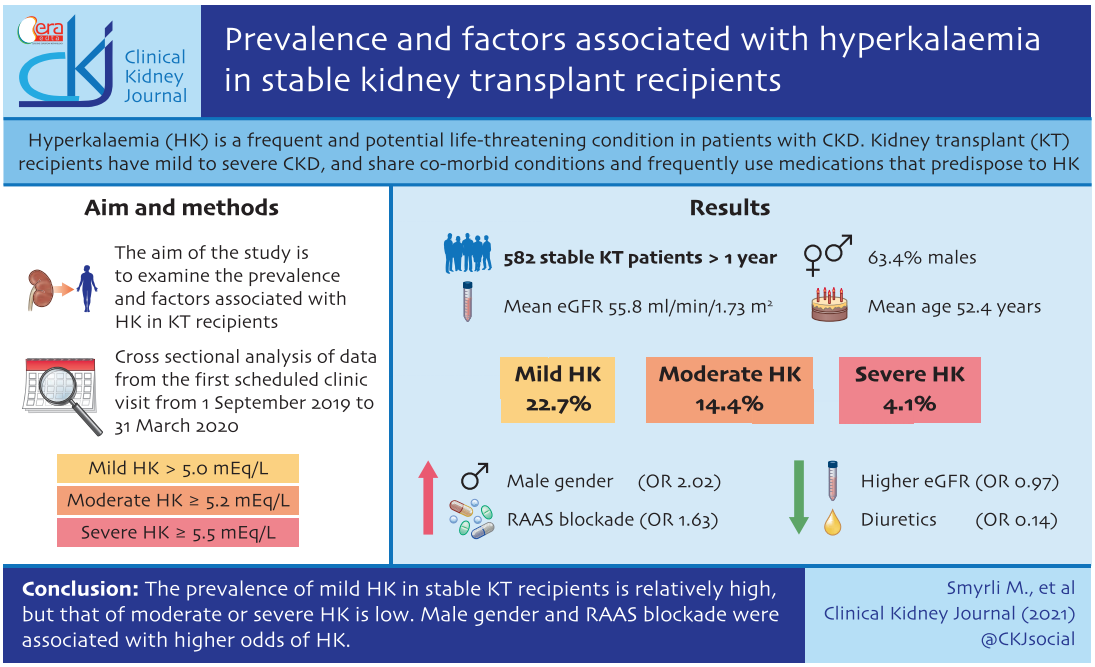
GRAPHICAL ABSTRACT



Keywords: diuretics, glomerular filtration rate, hyperkalaemia, kidney transplantation, renin–angiotensin–aldosterone system blockers

INTRODUCTION

Hyperkalaemia is one of the most frequent electrolyte disorders in clinical practice. Severe hyperkalaemia is a potentially life-threatening condition due to the risk of cardiac conduction abnormalities leading to arrhythmias and sudden death [1, 2]. Hyperkalaemia is relatively rare in the general population but it is considered as an established complication of both acute kidney injury and chronic kidney disease (CKD), especially when estimated glomerular filtration rate (eGFR) is $<60\,mL/min/1.73\,m^2$ [3–5]. Although low renal function is a cause for potassium (K^+) elevation *per se*, in patients with impaired renal function hyperkalaemia is even more aggravated by superimposed factors, such as diabetes mellitus (DM), hyporeninaemic hypoaldosteronism, advanced heart failure (HF) and high dietary K^+ intake, but most importantly, by the use of medications that increase serum K^+. These medications include mainly renin–angiotensin–aldosterone system inhibitors and β-blockers, which are essential for the treatment of common comorbid conditions, such as hypertension, proteinuric nephropathy and HF [6–9]. Several lines of evidence suggest that hyperkalaemia is a major factor leading to the use of submaximal doses or discontinuation of RAAS inhibitors (RAASis) and β-blockade in clinical practice [10]. To this end, in recent years two new K^+-lowering agents were shown to effectively and safely reduce K^+ levels and are expected to enable more appropriate use of cardioprotective agents [11].

Kidney transplantation (KTx) is the treatment of choice for patients with end-stage renal disease (ESRD), as it is associated with at least 2-fold higher life expectancy and improved quality of life compared with renal replacement therapy. Despite a substantial improvement in renal function, the vast majority of transplanted patients do not reach a normal GFR. Further, they still have a higher burden of comorbid conditions and higher risk of cardiovascular morbidity and mortality compared with the general population [12, 13]. Factors like post-transplant DM (PTDM), increased appetite leading to high K^+ intake and need for use of cardioprotective medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers and aldosterone receptor antagonists, combined with the use of immunosuppressive agents, such as cyclosporine and tacrolimus, are all factors that can interfere with K^+ homoeostasis, also in KTx recipients [14, 15].

Despite the fact that the KTx recipients share many common factors contributing to hyperkalaemia with patients with pre-dialysis CKD, studies investigating the impact of hyperkalaemia in KTx are scarce and small, while relatively larger studies have been conducted in order to assign more specific questions. For example, a retrospective study evaluated the relationship between the use of cyclosporine and tacrolimus with hyponatraemia and hyperkalaemia in 125 KTx recipients [16], a cross-sectional study examined the prevalence and the causes of renal tubular acidosis (RTA) in the late transplantation period [17], while the largest study in the field evaluated the impact of ACEIs and ARBs on the incidence of hyperkalaemia [18]. Therefore, we aimed to assess in a cross-sectional fashion the prevalence and potential determinants of hyperkalaemia

among a wide set of demographic, clinical and laboratory characteristics in a population of KTx recipients followed in a KTx Clinic of a tertiary University Hospital.

MATERIALS AND METHODS

Study design and patients

This is a cross-sectional study in stable KTx recipients who were under regular follow-up in the Transplantation Outpatient Clinic of Laiko General Hospital, Athens, Greece. This Nephrology and Renal Transplantation Clinic is the largest transplantation centre in Greece, performing up to 80–90 KTxs annually.

KTx recipients are regularly attending the outpatient clinic at intervals ranging from 1 week to 6 months. At every visit, a complete routine haematological and biochemical laboratory work up, including serum K^+, as well as target trough levels of immunosuppressive medications, is performed. All immunosuppressive and concomitant medications, patients' weight and blood pressure (BP) are also monitored and recorded at every visit.

For the purpose of this study, we collected data at a single time point (i.e. at the first scheduled visit during a pre-specified period of 6 months from 1 September 2019 to 31 March 2020) for all clinically stable KTx recipients, regularly attending the outpatient transplant clinic, who had completed at least 1 year from surgery and had complete information for the main variables of interest. The study protocol was approved by the Institutional Review Board of the Laiko General Hospital.

Data collection

All study data for each subject were recorded during the scheduled visit on the relevant patient charts and were transferred to a purpose-built electronic data-collecting sheet. We collected routine data on demographics [gender, age at the time of transplantation as well as age at the date of the examination, height and weight for the calculation of body mass index (BMI)]; cause of ESRD; previous dialysis vintage; comorbidities (hypertension, diabetes, coronary heart disease, stroke, HF, liver disease, chronic obstructive pulmonary disease and peripheral artery disease); and routine haematological and biochemical parameters [K^+, sodium (Na^+), urea, creatinine, etc.], for each participant. We also recorded information related to KTx such as ABO incompatibility between donor and recipient, human leukocyte antigen (HLA) sensitization, donor age, age difference between donor and recipient, presence of PTDM, graft origin (deceased or living) and trough levels of calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors (mTORis). We recorded the current immunosuppressive regimens consisting of CNIs (tacrolimus, and less often cyclosporine), antimetabolites, mTORis and corticosteroids. Additionally, we collected information on concomitant medications, including those that interfere with K^+ regulation, such as ACEIs, ARBs, renin inhibitors, aldosterone blockers (spironolactone and eplerenone), β-blockers, thiazide diuretics, loop diuretics, non-steroidal anti-inflammatory drugs or cyclooxygenase inhibitors, oral hypoglycaemic agents and insulin, heparin, trimethoprim, pentamidine, digoxin, resin K+ exchangers and Na^+ bicarbonate.

Definitions

For reasons of relevance to common clinical practice and in accordance with previous studies, hyperkalaemia was classified as follows: serum K^+ level >5.0 mEq/L and further as: serum K^+ >5.0 mEq/L with concomitant use of Na^+ polystyrene sulphonate; serum K^+ ≥5.2 mEq/L; and serum K^+ ≥5.5 mEq/L. Hypokalaemia was defined as serum K^+ <3.5 mEq/L. In addition to the above hyperkalaemia thresholds, we examined the percentage of patients with serum K^+ levels <3.5, ≥3.5 to ≤5.0, >5.0 to <5.5 and ≥5.5 mEq/L. eGFR was calculated with the use of the CKD Epidemiology Collaboration equation [19].

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences version 23 (SPSS Inc., Chicago, IL, USA). The normality of distribution for quantitative variables was examined using the Kolmogorov–Smirnov test. Continuous variables are expressed as mean ± standard deviation or median (interquartile range) according to normality of the distribution; categorical variables are presented as absolute and relevant frequencies. Comparisons for quantitative parameters with the Student's *t*-test or the Mann–Whitney test and for qualitative parameters were performed with the chi-square or the Fisher's exact tests. Univariate and multivariable logistic regression analyses were performed in the total study population to evaluate the effect of various parameters possibly interfering with K^+ homoeostasis with the threshold for the definition of hyperkalaemia set at >5.0 mEq/L. Variables were tested for interactions and included in the multivariable model if $P < 0.2$ in univariate analysis. Odds ratios (ORs) are reported with 95% confidence intervals (CIs). Probability values of $P < 0.05$ (two-tailed) were considered statistically significant in all comparisons.

RESULTS

Demographic and clinical characteristics

Of a total of 668 patients that had a scheduled appointment during the pre-specified period, 58 patients were excluded as they had less than a year from KTx surgery during their regular appointment; another 23 patients were excluded as they missed their clinic appointments during the pre-specified follow-up period, while 3 patients restarted dialysis and 2 more patients died before their clinic visit (Figure 1). Thus, the final study population consisted of 582 patients, the clinical and demographic characteristcs of whom are shown in Table 1. From the total cohort, 369 patients were males (63.4%), the

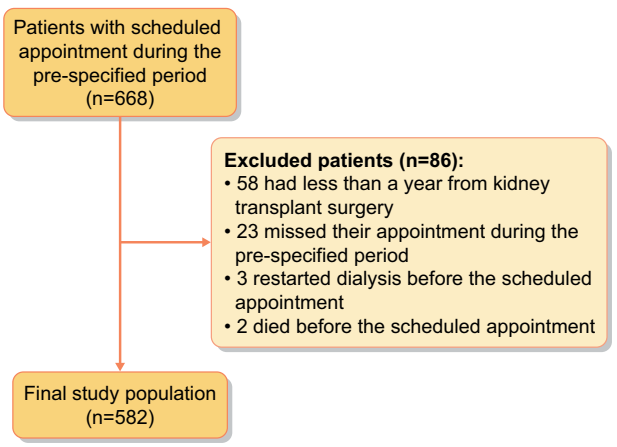


FIGURE 1: Study flow chart.

Table 1. Demographic, clinical and routine biochemical characteristics of the total study cohort and patients with and without elevated serum K^+ levels

Parameter	Total population	K^+ ≤5.0 mEq/L	K^+ >5.0 mEq/L	P-value[a]
N (%)	582	450 (77.3)	132 (22.7)	–
Age at baseline, years	52.4 ± 13.5	52.5 ± 13.5	51.9 ± 13.6	0.669
Male gender, *n* (%)	369 (63.4)	273 (60.7)	96 (72.7)	**0.011**
Height, m	1.69 ± 0.11	1.69 ± 0.11	1.70 ± 0.12	0.602
Weight, kg	73.4 ± 15.1	73.4 ± 15.2	73.2 ± 15.0	0.894
BMI, kg/m^2	25.4 ± 3.7	25.4 ± 3.9	25.1 ± 3.2	0.424
Dialysis vintage, years	4.7 ± 4.1	4.7 ± 4.1	4.9 ± 4.2	0.638
ESRD primary cause, *n* (%)				
Glomerulopathy	170 (29.2)	134 (29.8)	36 (27.3)	0.770
Diabetes	19 (3.3)	13 (2.9)	6 (4.5)	
Hypertension	40 (6.9)	30 (6.7)	10 (7.6)	
Inherited	138 (23.7)	112 (24.9)	26 (19.7)	
Obstructive diseases	52 (8.9)	40 (8.9)	12 (9.1)	
Other	21 (3.6)	16 (3.6)	5 (3.8)	
Unknown	142 (24.4)	105 (23.3)	37 (28.0)	
Comorbidities, *n* (%)				
Hypertension	362 (62.2)	280 (62.2)	82 (62.1)	0.983
DM	13 (2.2)	8 (1.8)	5 (3.8)	0.183
Dyslipidaemia	128 (22.0)	99 (22.0)	29 (22.0)	0.994
CAD	43 (7.4)	36 (8.0)	7 (5.3)	0.298
Stroke	11 (1.9)	9 (2.0)	2 (1.5)	0.719
HF with reduced EF	12 (2.1)	7 (1.6)	5 (3.8)	0.155
COPD	12 (2.1)	8 (1.8)	4 (3.0)	0.483
Peripheral vascular disease	11 (1.9)	8 (1.8)	3 (2.3)	0.719
Office SBP, mmHg	125.0 ± 13.1	124.9 ± 13.3	125.5 ± 12.4	0.604
Office DBP, mmHg	76.6 ± 7.0	76.5 ± 6.9	76.7 ± 7.2	0.726
WBC, cells/mL	7520 [3023]	7460 [3065]	7585 [2790]	0.797
PLT, cells/mL	221 000 [76 500]	221 000 [75 250]	219 000 [79 500]	0.719
Hb, g/dL	13.0 ± 1.7	13.1 ± 1.7	12.8 ± 1.8	0.121
Urea, mg/dL	61.4 ± 28.8	57.9 ± 27.3	73.2 ± 30.6	0.185
Creatinine, mg/dL	1.47 ± 0.53	1.40 ± 0.50	1.70 ± 0.59	**<0.001**
eGFR, mL/min/1.73 m^2	55.8 ± 20.1	58.0 ± 20.1	48.3 ± 18.1	**<0.001**
K^+, mEq/L	4.63 ± 0.48	4.44 ± 0.35	5.27 ± 0.020	0.133
Na^+, mEq/L	140.5 ± 2.9	140.6 ± 3.0	140.2 ± 2.7	**<0.001**
Calcium, mg/dL	9.5 ± 0.6	9.5 ± 0.6	9.7 ± 0.6	0.149
Phosphate, mg/dL	3.2 ± 0.7	3.2 ± 0.7	3.2 ± 0.6	**0.007**
Uric acid, mg/dL	6.6 ± 1.3	6.5 ± 1.3	7.0 ± 1.4	0.390
Glucose, mg/dL	99.4 ± 21.4	98.8 ± 21.1	101.6 ± 22.5	**<0.001**
Total cholesterol, mg/dL	193 [47]	194 [48]	186 [47]	**0.038**
Triglycerides, mg/dL	134 [79]	134 [79]	133 [78]	0.637
LDL, mg/dL	105 [41]	106 [45]	100 [34]	0.112
HDL, mg/dL	57 [17]	57 [17]	56 [19]	**0.038**
iPTH, pg/mL	91 [77]	89 [77]	95 [84]	0.476

[a]P-value for comparisons between K^+ groups. Normally distributed variables are presented as mean ± standard deviation, non-normally distributed variables as median [interquartile range] and categorical variables as absolute frequency (proportion). Probability values of P<0.05 were considered statistically significant in all comparisons are in bold.

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; LDL, low-density lipoprotein; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone; WBC, white blood cells; PLT, platelet; Hb, haemoglobin.

mean age was 52.4 ± 13.5 years, mean eGFR 55.8 ± 20.1 mL/min/1.73 m^2 and dialysis vintage before KTx 4.7 ± 4.1 years.

Prevalence of hyperkalaemia

The mean K^+ level in our patient cohort was 4.63 ± 0.48 mEq/L. The prevalence of hyperkalaemia defined as serum K^+ >5.0 mEq/L in the overall population was 22.7% (132 out of total 582 patients). Only four patients were on Na^+ polystyrene sulphonate, all of whom had serum K^+ >5.0 mEq/L; thus the prevalence of hyperkalaemia, defined as K^+ >5.0 mEq/L and concomittant use of Na^+ polystyrene sulphonate, was again 22.7%. The prevalence of hyperkalaemia defined as K^+ ≥5.2 mEq/L and ≥5.5 mEq/L was 14.4% (84 patients) and 4.1% (24 patients), respectively. No patient had serum K^+ levels ≥6.0 mEq/L.

The distribution of serum K^+ levels in the population studied is shown in Figure 2. Overall, only two patients (0.3%) had K^+ levels <3.5 mEq/L. Another 77.0% had normal K^+ levels (≥3.5 to ≤5.0 mEq/L), whereas 18.6 and 4.1% had serum K^+ levels >5.0 to <5.5 mEq/L and ≥5.5 mEq/L, respectively.

Factors associated with hyperkalaemia

In univariate comparisons (Table 1), individuals with serum K^+ >5.0 mEq/L were more often males, compared with those with

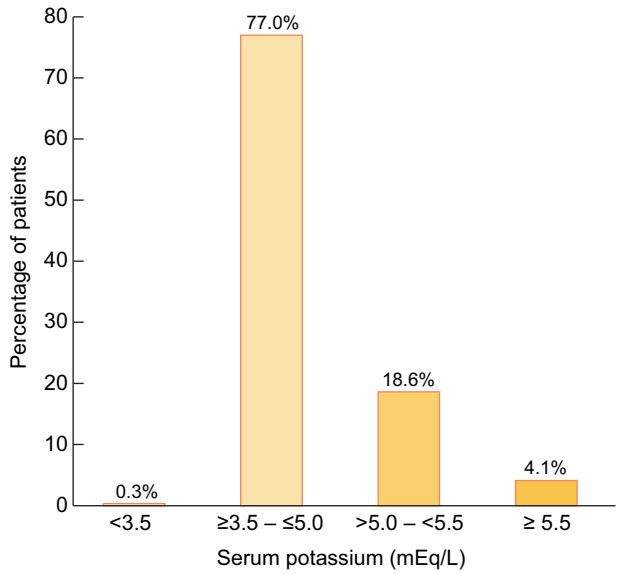


FIGURE 2: Distribution of serum K^+ levels in the study population.

K^+ ≤5.0 mEq/L (77.2% versus 60.7%, P = 0.011). The two groups did not differ significantly with respect to age, BMI, dialysis vintage, burden of comorbidities and primary cause of kidney disease. Systolic and diastolic BP (SBP and DBP) levels were also comparable between groups. However, as shown in Table 1, a number of differences between groups were noted in routine biochemistry parameters, with patients with high K^+ having significantly higher levels of serum creatinine and lower eGFR (48.3 ± 18.1 mL/min/1.73 m^2 versus 58.0 ± 20.1 ml/min/1.73 m^2, P < 0.001) than those with normal K^+. In addition, there were subtle but significant differences in serum Na^+, phosphate and glucose (101.6 ± 22.5 mg/dL versus 98.8 ± 21.1 mg/dL, P < 0.001).

Table 2 presents information on the use of medications, including those interfering with K^+ homoeostasis. The use of ACEIs (27.3% versus 18.2%, P = 0.023) was more common and that of ARBs (11.4% versus 6.7%, P = 0.076) marginally more common among patients with high K^+. In contrast, the use of thiazide and loop diuretics was less common (3.0% versus 10.9%, P = 0.006). As discussed above, only four patients, all in the high K^+ group, were using Na^+ polystyrene sulphonate. The proportion of patients using β-blockers, insulin oral hypoglycaemic agents, heparin, Na^+ bicarbonate and β2-agonists did not differ between groups. Of note, none of the study subjects was receiving a renin inhibitor, torsemide, non-steroidal anti-inflammatory drugs or pentamidine at the time of the study.

With regards to transplantation-related factors (Table 3), there were no differences between the two groups either in means of donor and recipient age or donor–recipient age difference, or in the time since transplantation. Similarly, renal allograft origin (deceased or living), ABO incompatibility, HLA sensitization and development of PTDM were similar between the groups. In addition, immunosuppressive drugs such as steroids, cyclosporine, tacrolimus and mycophenolate mofetil, as well as levels of both CNIs, did not differ between groups. Considering immunosuppressive drugs, the only difference observed was that patients with elevated K^+ levels were less likely to receive mTORis compared with those with serum K^+ ≤5.0 mEq/L (3.8% versus 11.1%, P = 0.011).

Additionally, we performed multiple logistic regression analysis including serum K^+ >5.0 mEq/L as the dependent variable and several demographic, clinical and laboratory factors that were previously identified from univariate analyses as independent variables. As shown in Table 4, in multivariate analysis age, BMI, comorbidities, cause of ESRD and dialysis vintage, and most of the drugs examined were not associated with higher odds of hyperkalaemia. This was also the case for transplantation-related factors, such as donor and recipient age, time since transplantation, immunological risk and immunosuppresive therapy. Thus, the only variables that were independently associated with higher odds of hyperkalaemia in multivariate analysis were male gender (adjusted OR = 2.020, 95% CI 1.264–3.227) and use of RAASis (including ACEIs, ARBs and aldosterone blockers) (adjusted OR = 1.628, 95% CI 1.045–2.536), while higher eGFR (adjusted OR = 0.967, 95% CI 0.955–0.979) and non-K^+-sparing diuretic use were associated with lower odds of hyperkalaemia (OR = 0.140, 95% CI 0.046–0.430).

DISCUSSION

This study was designed to examine the prevalence of hyperkalaemia in KTx recipients and to evaluate possible associations with factors that may contribute to its occurrence. The prevalence of hyperkalaemia in the current population examined at the >5.0 mEq/L threshold was ∼23%, while only 4.1% had K^+ levels ≥5.5 mEq/L. These results suggest that mild hyperkalaemia is common but moderate to severe hyperkalaemia uncommon in stable KTx recipients. Among a wide range of demographic, clinical and laboratory characteristics examined, only a small set of factors were independently associated with hyperkalaemia. Male gender and use of RAASis were associated with higher odds, while higher eGFR and thiazide or loop diuretic use were associated with lower odds of the disorder. None of the factors associated with the process and medications for transplantation affected the occurrence of hyperkalaemia.

In KTx recipients, there is a paucity of studies evaluating the overall prevalence and the determinants of hyperkalaemia. Most studies in the field examine specific issues, or patients during the early post-transplant period. Experimental models have shown that both CNIs increase K^+ levels by inhibiting the Na^+/K^+/ATPase in the luminal K^+ channels; moreover, an over activation of the $Na^+/K^+/2Cl$ co-transporter of the distal tubule by tacrolimus but not by cyclosporine has been described [20]. Higgins retrospectively studied 125 KTx recipients during the early (first 90 days after transplantation) transplantation period comparing the impact of the two CNIs on Na^+ and K^+ levels. Serum K^+ levels were significantly higher in recipients receiving tacrolimus compared with those receiving cyclosporine and this effect was even more prominent among those with concomitant hyponatraemia [16]. Given the fact that in the modern immunosuppressive era tacrolimus has almost uniformly replaced cyclosporine with >90% of KTx recipients being discharged on Tac-based immunosuppression nowadays, head-to-head comparison studies between the two CNIs on specific side effects are almost absent [21].

Another study evaluated the impact of various trough levels of tacrolimus during the very early (2 weeks) post-transplant period in a cohort of 816 KTx recipients. Primary outcomes included delayed graft function and length of stay and secondary outcomes hyperkalaemia and biopsy-proven acute rejection. Though tacrolimus levels were high (>10 ng/mL) in three of the four groups investigated, there was no difference in the rates of hyperkalaemia (which were 24, 27 and 26%, respectively) between groups. Of note, the threshold for hyperkalaemia in this study was set at 6.0 mEq/L [22]. During the late (>12 months

Table 2. Use of common medications, including those that could interfere with K^+ regulation in patients with and without elevated serum K^+ levels

Parameter	$K^+ \leq 5.0$ mEq/L	$K^+ > 5.0$ mEq/L	P-value
N (%)	450 (77.3)	132 (22.7)	–
ACEIs	82 (18.2)	36 (27.3)	**0.023**
ARB	30 (6.7)	15 (11.4)	0.076
CCBs	163 (36.2)	40 (30.3)	0.210
β-blockers	154 (34.2)	40 (30.3)	0.401
Thiazide or loop diuretics	49 (10.9)	4 (3.0)	**0.006**
K^+-sparing diuretics	6 (1.3)	0 (0.0)	0.345
α-blockers	31 (6.9)	16 (12.1)	0.052
Centrally active	17 (3.8)	6 (4.5)	0.691
Oral hypoglycaemic agents	26 (5.8)	5 (3.8)	0.371
Insulin	17 (3.8)	9 (6.8)	0.137
Cinacalcet	83 (18.4)	24 (18.2)	0.945
Vitamin D analogues	128 (28.4)	42 (31.8)	0.454
EPO	26 (5.8)	10 (7.6)	0.451
Heparin	3 (0.7)	2 (1.5)	0.318
Trimethoprim	8 (1.8)	3 (2.3)	0.719
Digoxin	1 (0.2)	0 (0.0)	1.000
Na^+ polystyrene sulphonate	0 (0.0)	4 (3.0)	**0.003**
Statins	94 (20.9)	24 (18.2)	0.496
Na^+ bicarbonate	9 (6.8)	23 (4.0)	0.055
β2-agonists	2 (1.5)	3 (0.5)	0.130
Clopidogrel	1 (0.8)	14 (2.4)	0.209
Aspirin	48 (10.7)	12 (9.1)	0.601
NOACs	23 (5.1)	7 (5.3)	0.930

Probability values of $P<0.05$ were considered statistically significant in all comparisons are in bold. Data are presented as *n* (%). CCBs, calcium channel blockers; EPO, erythropoietin; NOACs, novel oral anticoagulants.

Table 3. Factors related to KTx in patients with and without elevated serum K^+ levels

Parameter	Total population	$K^+ \leq 5.0$ mEq/L	$K^+ > 5.0$ mEq/L	P-value
Age when transplanted, years	44.8 ± 13.4	45.1 ± 13.5	43.9 ± 12.9	0.377
Years since transplantation, years	5.2 [9.1]	5.3 [8.7]	4.6 [10.8]	0.644
Donors age, years	52.5 ± 14.2	52.4 ± 14.2	53.2 ± 14.3	0.557
Difference between donors' and recipients' ages, years	7.9 [26.3]	7.0 [26.7]	9.9 [25.4]	0.217
Deceased origin, *n* (%)	166 (28.5)	128 (28.4)	38 (28.8)	0.939
Sensitization, *n* (%)	29 (5.0)	24 (5.3)	5 (3.8)	0.473
ABO incompatibility, *n* (%)	14 (2.4)	11 (2.4)	3 (2.3)	0.910
PTDM, *n* (%)	44 (9.8)	14 (10.6)	58 (10.0)	0.780
Steroids, *n* (%)	539 (92.6)	420 (93.3)	119 (90.2)	0.219
Tacrolimus, *n* (%)	483 (83.0)	376 (83.6)	107 (81.1)	0.502
Cyclosporine, *n* (%)	53 (9.1)	36 (8.0)	17 (12.9)	0.087
Mycophenolate mofetil, *n* (%)	556 (95.5)	428 (95.1)	128 (97.0)	0.363
mTORis, *n* (%)	55 (9.5)	50 (11.1)	5 (3.8)	**0.011**
Tacrolimus levels, ng/mL	6.2 [1.6]	6.2 [1.7]	6.3 [1.7]	0.111
Cyclosporine C0 levels, ng/mL	159.6 ± 60.9	156.5 ± 56.3	165.2 ± 69.6	0.592
Cyclosporine C2 levels, ng/mL	521.6 ± 171.9	499.9 ± 172.8	561.0 ± 167.1	0.183
mTORis levels, ng/mL, *n* (%)	5.5 ± 1.1	5.5 ± 1.2	5.5 ± 0.7	0.977

Probability values of $P<0.05$ were considered statistically significant in all comparisons are in bold. Normally distributed variables are presented as mean ± standard deviation, non-normally distributed variables as median [interquartile range] and categorical variables as absolute frequency (proportion).

after transplantation) post-transplant period one cross-sectional study examined the prevalence and risk factors for RTA in a cohort of 576 stable KTx recipients with well-preserved renal function. RTA was found in 76 out of 576 patients (13%). Hyperkalaemia was present in a total of 32 patients, 11 with distal RTA subtype Ib (hyperkalaemic) and 21 with subtype IV distal RTA. Interestingly, this study also showed higher association of tacrolimus-based compared with cyclosporine-based immunosuppression with the development of RTA [17]. Finally, Mitterbauer *et al.* conducted a cohort study in 2041 KTx recipients that did not assess hyperkalaemia prevalence, but longitudinally compared serum K^+ levels between subjects with versus without ACEI/ARB therapy using a mixed-effects general linear model. The overall adjusted estimated serum K^+ difference between recipients with versus without ACEI/ARB therapy was 0.08 mmol/L ($P < 0.001$), while diuretics were associated with a

Table 4. Univariate and multivariate analysis of factors possibly associated with serum K^+ >5.0 mEq/L in the total study population

	Univariate analysis			Multivariate analysis		
Parameter	Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Age, years	0.997	0.983–1.011	0.668			
Male gender	1.729	1.128–2.650	0.012	2.020	1.264–3.227	**0.003**
BMI, kg/m^2	0.979	0.929–1.031	0.423			
Dialysis vintage, years	1.011	0.966–1.058	0.638			
Hypertension	0.996	0.667–1.485	0.983			
DM	2.175	0.699–6.765	0.179	3.438	0.943–12.531	0.061
Dyslipidaemia	0.998	0.625–1.595	0.994			
CAD	0.644	0.280–1.483	0.301			
HF with reduced EF	2.492	0.778–7.984	0.124	3.283	0.876–12.305	0.078
COPD	1.727	0.512–5.826	0.379			
eGFR (mL/min/1.73 m^2 increase)	0.973	0.963–0.984	<0.001	0.967	0.955–0.979	**<0.001**
Years since transplantation, years	1.012	0.985–1.039	0.391			
Sensitization	0.699	0.261–1.869	0.475			
CNIs	1.430	0.650–3.145	0.374			
Steroids	0.654	0.331–1.293	0.222			
Mycophenolate mofetil	1.645	0.557–4.861	0.368			
Oral hypoglycaemic agents	0.642	0.242–1.706	0.374			
Insulin	1.864	0.811–4.284	0.143	1.227	0.481–3.132	0.668
RAASi	1.735	1.152–2.615	0.008	1.628	1.045–2.536	**0.031**
Diuretics	0.256	0.091–0.722	0.010	0.140	0.046–0.430	**0.001**
β-blockers	0.836	0.550–1.271	0.401			
Heparin	2.292	0.379–13.865	0.366			
Na^+ bicarbonate	2.279	0.963–5.390	0.061	1.475	0.588–3.702	0.408
β2-agonists	6.908	0.621–76.785	0.116	8.325	0.414–167.237	0.166

Probability values of P<0.05 were considered statistically significant in all comparisons are in bold. CAD, coronary artery disease; COP D, chronic obstructive pulmonary disease; EF, ejection fraction.

0.11 mmol/L ($P < 0.001$) lower K^+ and each GFR decrease by 10 mL/min led to an increase of 0.04 mmol/L ($P < 0.001$) [18].

The prevalence of hyperkalaemia in pre-dialysis CKD patients has been examined more thoroughly. In a cross-sectional analysis of electronic medical records involving 1216 individuals with eGFR values of 30–60, 15–30 and <15 mL/min/1.73 m^2, the prevalence of serum K^+ >5.0 mEq/L rose from ~10% to 18% and 22%, respectively [23]. In a cohort study of 1038 patients with CKD, the prevalence of hyperkalaemia (serum K^+ >5.0 mmol/L or intake of ion exchange resin) was at 17% for the total population, increasing from 2% to 42% as eGFR decreased from >60 to <20 mL/min/1.73 m^2; in multivariate analysis, male gender and use of RAASis were independently associated with hyperkalaemia [24]. In a study of 238 outpatients followed in a low-clearance clinic with a mean eGFR of 14.5 ± 4.8 mL/min/1.73 m^2, a prevalence of hyperkalaemia of 53.8, 31.5 and 8.5% for serum K^+ levels of >5.0, >5.5 and >6.0 mEq/L, respectively, was reported, while an eGFR <15 mL/min/1.73 m^2 was independently associated with hyperkalaemia [4]. In a population of 360 CKD patients with an average eGFR at 43 mL/min/1.73 m^2, hyperkalaemia (serum K^+ >5.0 mmol/L or intake of ion exchange resin) was at 21.7%, while CKD Stage 4, smoking and ACEI use were all associated with increased odds of hyperkalaemia [8]. Another study of about 13 500 patients with eGFR <60 mL/min/1.73 m^2, concluded that for every 5 mL/min/1.73 m^2 drop in eGFR, patients had a 26% higher risk for hyperkalaemia (defined as K^+ >5.5 mEq/L) [25]. Our findings suggest a prevalence of hyperkalaemia slightly higher than most of the abovementioned studies, i.e. 22.7% at the >5.0 mEq/L threshold for a population with an average eGFR at 56 mL/min/1.73 m^2; however, the occurrence of moderate hyperkalaemia (≥5.5 mEq/L) was low. In addition, our findings in multivariate analysis are largely consistent with the previous results, showing that male gender and RAASis were associated with higher odds, and preserved eGFR with lower odds of hyperkalaemia, respectively.

To the best of our knowledge, this is the first cross-sectional study assessing the prevalence and determinants of hyperkalaemia in a large cohort of stable KTx recipients at the long-term post-transplantation period. The study was carefully designed in order to assess a wide range of demographic, laboratory and biochemical factors that could affect K^+ levels. Furthermore, it evaluated simultaneously all medications known to affect K^+ regulation and several factors relevant to KTx that may also interfere. However, this is a cross-sectional analysis, thus we could not establish cause and effect associations between hyperkalaemia and the factors examined. The cross-sectional design also did not allow us to assess whether previous medical decisions (i.e. discontinuation of ACEIs or ARBs, switch in immunosuppression, prescription of diuretics or Na^+ bicarbonate administration) aiming to change serum K^+ levels had preceded the current investigation; in any case, the study aimed to capture the actual reality of everyday clinical practice. Finally, our study was carried out in a single centre; though we believe our sample is representative of the average KTx recipient of a European transplant centre, it is not clear whether our observations could be generalizable to other KTx populations with largely different dietary habits, or treatment strategies.

In conclusion, this study shows that hyperkalaemia is rather frequent in stable KTx recipients. However, moderate and severe hyperkalaemia are rather rare, a fact likely related to the well-preserved renal function in the vast majority of patients. Among a large set of demographic, clinical and laboratory factors examined, the parameters independently associated with

hyperkalaemia in this population were largely similar to those in patients with CKD, i.e. male gender and RAASis were associated with higher odds, while preserved eGFR and common diuretics (thiazide and loop diuretics) with lower odds of hyperkalaemia, while there was no impact of any immunosuppressive agent on serum K^+ levels. Longitudinal studies are warranted to evaluate the possible influence of hyperkalaemia on the choice of and the adherence to recommended medications, such as RAASis, and its association with morbidity and mortality in this patient population.

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AUTHORS' CONTRIBUTIONS

Study conception and design were carried out by P.A.S., I.N.B. and S.M.; data acquisition was done by M.S. and M.K.; statistical analysis was performed by C.L.; data interpretation was carried out by M.S. and P.A.S.; manuscript drafting was done by M.S., P.A.S. and S.M.; supervision and mentorship were provided by I.N.B. and S.M. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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