Relationship between urinary potassium excretion, serum potassium levels and cardiac injury in non-dialysis chronic kidney disease: KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD)

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Abstract

Although the cardiovascular benefits of an increased urinary potassium excretion have been suggested, little is known about the potential cardiac association of urinary potassium excretion in patients with chronic kidney disease. In addition, whether the cardiac association of urinary potassium excretion was mediated by serum potassium levels has not been studied yet. We reviewed the data of 1633 patients from a large-scale multicentre prospective Korean study (2011–2016). Spot urinary potassium to creatinine ratio was used as a surrogate for urinary potassium excretion. Cardiac injury was defined as a high-sensitivity troponin T $\geq$ 14 ng/l. OR and 95 % (CI for cardiac injury were calculated using logistic regression analyses. Of 1633 patients, the mean spot urinary potassium to creatinine ratio was 49·5 (SD 22·6) mmol/g Cr and the overall prevalence of cardiac injury was 33·9 %. Although serum potassium levels were not associated with cardiac injury, per 10 mmol/g Cr increase in the spot urinary potassium to creatinine ratio was associated with decreased odds of cardiac injury: OR 0·917 (95 % CI 0·841, 0·998), $P = 0·047$) in multivariate logistic regression analysis. In mediation analysis, approximately 6·4 % of the relationship between spot urinary potassium to creatinine ratio and cardiac injury was mediated by serum potassium levels, which was not statistically significant ($P = 0·368$). Higher urinary potassium excretion was associated with lower odds of cardiac injury, which was not mediated by serum potassium levels.

Keywords: **Potassium: Troponin: Cardiac injury: Chronic kidney disease: Mediation**

It is known that the risk of hyperkalaemia is increased with the progression of chronic kidney disease (CKD)[1]. Of 3000–4000 mEq of total body potassium in a 70-kg person, only small amount ($\sim$ 2 %) is found in the extracellular space, and 98 % $\sim$ of exchangeable potassium is in intracellular space. Serum potassium levels are maintained within a narrow range by the inter-play of insulin, catecholamine, acid-base status and renal handling[2]. Hyperkalaemia causes the depolarisation of membrane potential but increases the potassium channel conductance, resulting in tall T waves, P wave loss and QRS wave widening[3]. Hence, several clinicians are familiar with reducing the potassium intake in patients with CKD. In the non-CKD population, however, a high dietary potassium intake has been suggested to have beneficial effects. As the dietary potassium

increased, systolic and diastolic blood pressure decreased[4]. A decreased potassium intake was associated with an increased all-cause mortality[5]. Although controversial[6,7], a decreased potassium intake in the CKD population was also associated with an increased risk of CKD progression[8].

CKD patients are at a high risk for developing cardiovascular (CV) events[9,10,11]. Therefore, the early detection of CV risk factors is of utmost importance to improve the clinical outcomes. A decreased potassium intake was associated with an increased risk of CV events in the general population[5] and increased potassium intake was associated with a decreased risk of CV events and CKD progression in type 2 diabetes patients[12]. However, the potential effect of dietary potassium on CV risk has rarely been studied in the CKD population till recently. As a novel CV risk, high-sensitivity troponin T (hs-TnT), the first highly sensitive assay for cardiac troponins, has been associated with current and future CV events[13,14], even if only slightly elevated[15,16].

Therefore, the relationship between dietary potassium and serum hs-TnT in the CKD population will expand our knowledge of the potential cardiac effect of dietary potassium in the CKD population. Because approximately 70–80 % of the dietary potassium intake is excreted into the urine[17], urinary potassium excretion has been used as a surrogate for dietary potassium intake[5–8]. In the current study, we first analysed the relationship between urinary potassium excretion and serum hs-TnT levels. Subsequently, we explored whether the relationship between urinary potassium excretion and serum hs-TnT is mediated by serum levels of potassium, using the data from a large number of adults who were enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD).

Materials and methods

Participants

The KNOW-CKD is a multicentre, prospective cohort study in Korea with a study population of 2238 patients with non-dialysis CKD stages 1–5 who were enrolled between 2011 and 2016. The detailed design and methods of the KNOW-CKD were previously published (NCT01630486 at http://www.clinicaltrials.gov)[18]. Of the 2238 cohort subjects, 605 individuals were excluded, including 103 individuals with missing serum potassium values, 112 individuals missing spot urinary potassium to creatinine ratio, eight individuals with missing serum hs-TnT and 382 individuals with missing other covariates including total CO_2 information. Therefore, this study included a total of 1633 patients (online Supplementary Fig. S1).

Ethics statement

The protocol of the KNOW-CKD adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) at each participating hospital, including Seoul National University Hospital (IRB number: 1104-089-359), Yonsei University Severance Hospital (IRB number: 4-2011-0163), Kangbuk Samsung Medical Center (IRB

number: 2011-01-076), Seoul St. Mary's Hospital (IRB number: KC11OIMI0441), Gil Hospital (IRB number: GIRBA2553), Nowon Eulji Medical Center (IRB number: 201105-01), Chonnam National University Hospital (IRB number: CNUH-2011-092) and Busan Paik Hospital (IRB number: 11-091). Written informed consent was obtained from all subjects. All data were fully anonymised before we accessed them.

Exposure: estimated dietary potassium intake

Random urine samples were collected after overnight fasting. Urine potassium was measured using the ion-selective electrode method. Additionally, urine creatinine was measured using the Jaffe method in the central laboratory (Lab Genomics).

We assumed that the 24-h urine potassium excretion matched with the dietary potassium intake. However, taking full urine 24 h a day is too burdensome for patients. In this regard, spot urinary potassium to creatinine ratio has been proposed as a good surrogate for 24 h urinary potassium excretion[19–21]. Exposure of this study was spot urinary potassium to creatinine ratio (mmol/g Cr), which was calculated from urine potassium (mmol/l)/urine creatinine (mg/dl) × 100.

Outcome: cardiac injury

The serum hs-TnT levels were measured in the central laboratory with a highly sensitive electro-chemiluminescence immuno-assay using an Elecsys 2010 analyser (Roche Diagnostics GmbH), which has an analytical measurement range of 3–10 000 ng/l. Cardiac injury was defined as hs-TnT ≥ 14 ng/l, the 99th percentile of a normal reference population[13] and a level proved to be associated with major adverse events[15,16]. We also performed a sensitivity analysis for cardiac injury, defined as a CKD-specific hs-TnT cut-off of ≥ 126 ng/l[22].

Other measurements and definitions

Clinical data, including detailed demographic information and baseline laboratory results, were extracted using an electronic data management system (PhactaX). After 5 min of seated rest, the blood pressure was measured using an electronic sphyg-momanometer. The BMI was calculated as the weight (kg) per square metre of height (m^2). In the central laboratory, serum creatinine was measured using an isotope dilution MS-traceable method, wherein the level of intact parathyroid hormone was measured using a Cobas e411 analyser (Roche Diagnostics GmbH), the level of 25-hydroxyvitamin D was measured using the ADIVIA Centaur XP analyser (Siemens Healthcare Diagnostics) and urine albumin was measured using the immunoturbidimetry. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[23]. CKD and its stages were defined using the Kidney Disease Improving Global Outcomes 2012 guidelines[24]. Blood specimens were collected after overnight fasting. The following laboratory variables were measured at the laboratory of each participating centre: values of Hb, leucocytes, blood urea nitrogen, albumin, HDL-cholesterol, TAG, albumin, fasting glucose, serum potassium, Ca, phosphorus and total CO_2.

Previous CV disease was defined as a physician diagnosis of coronary artery disease, cerebrovascular disease or peripheral vascular disease at the time of enrolment. The renin-angiotensin system inhibitors are angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers. The Charlson co-morbidity index (CCI) was assessed using the method described previously[25].

Statistical analysis

In this analysis, there were no missing values. The distributions of the continuous variables were evaluated using histograms and Q–Q plots. It was observed that two variables, CCI and urine albumin-to-creatinine ratio, were not normally distributed. Normally distributed continuous variables have been expressed as mean values and standard deviations, non-normally distributed continuous variables as median and interquartile range and categorical variables as percentage. The differences were analysed using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis test for non-normally distributed continuous variables and χ^2 test for categorical variables. The P_{trend} was analysed by linear regression for normally distributed continuous variables, Jonckheere–Terpstra test for non-normally distributed continuous variables and the Cochran–Armitage trend test for categorical variables. The OR and 95 % CI for cardiac injury were calculated using logistic regression analyses. In multivariate analyses, covariates were chosen based on clinical relevance (smoking status and renin-angiotensin system inhibitors) and statistical relevance (age, sex, causes of CKD, anti-platelet drugs, anti-lipid drugs, previous CV disease, CCI, BMI, systolic and diastolic blood pressure, fasting glucose, HDL-cholesterol, TAG, serum potassium, Ca, phosphorus, total CO_2, 25-hydroxyvitamin D, intact parathyroid hormone, albumin, Hb, leucocyte, blood urea nitrogen, eGFR and urine albumin-to-creatinine ratio) with cardiac injury.

The locally weighted scatterplot smoothing (LOWESS) regression curve on a scatter plot was used to assess the potential non-linear relationship. To identify the potential mediators between exposure and outcome, a causal mediation analysis was performed using 2000 simulations with a 'mediation' package[26]. A P value of <0·05 was considered statistically significant. All analyses were performed using R software Version 3.6.2 (R Foundation for Statistical Computing released 2019).

Results

Of 1633 patients, the mean age was 53·6 (SD 12·4) years and 61·7 % were men. The causes of CKD were diabetic nephropathy in 26·6 % of patients, hypertensive nephropathy in 19·8 %, glomerulonephritis in 29·8 % and other causes in 23·8 %. The mean eGFR was 52·9 (SD 31·0) ml/min/1·73 m² and median urine albumin-to-creatinine ratio was 347·7 (interquartile range 81·4–1049·3) mg/g Cr. The mean serum potassium and spot urinary potassium to creatinine ratio were 4·6 (SD 0·6) mEq/l and 49·5 (SD 22·6) mmol/g Cr, respectively. The distribution of serum hs-TnT was left-skewed with a median 10 (interquartile range 6–17) ng/l (Fig. 1(a)). The overall prevalence of cardiac injury was 33·9%, which increased with the progression of CKD stages (Fig. 1(b)).

The clinical characteristics according to the quartile of spot urinary potassium to creatinine ratio are depicted in Table 1. With the increase of quartile of spot urinary potassium to creatinine ratio, age increased, but proportions of men and current smoking decreased. Previous CV disease, usage of renin-angiotensin system inhibitors, anti-platelet drugs, lipid lowering drugs and CCI were not associated with quartiles of spot urinary potassium to creatinine ratio. Proportion of diabetic nephropathy as a cause of CKD linearly decreased with the increase of spot urinary potassium to creatinine ratio quartile. With an increase in the spot urinary potassium to creatinine ratio quartile, the eGFR increased; however, urine albumin-to-creatinine ratio decreased. As the spot urinary potassium to creatinine ratio quartile increased, serum levels of Ca and total CO_2 increased, but the values of intact parathyroid hormone, leucocyte and blood urea nitrogen decreased.
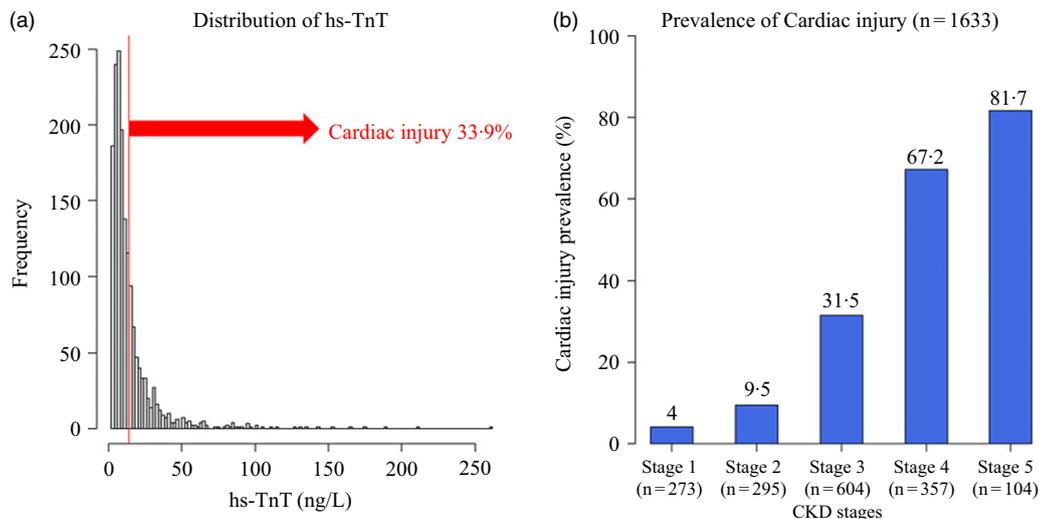

Fig. 1. Distribution of hs-TnT and the prevalence of cardiac injury. hs-TnT, high-sensitivity troponin T; SCI, subclinical cardiac injury; CKD, chronic kidney disease.

Table 1. Baseline characteristics according to the quartile of estimated dietary potassium intake
(Mean values and standard deviations; numbers and percentages; medians and interquartile ranges)

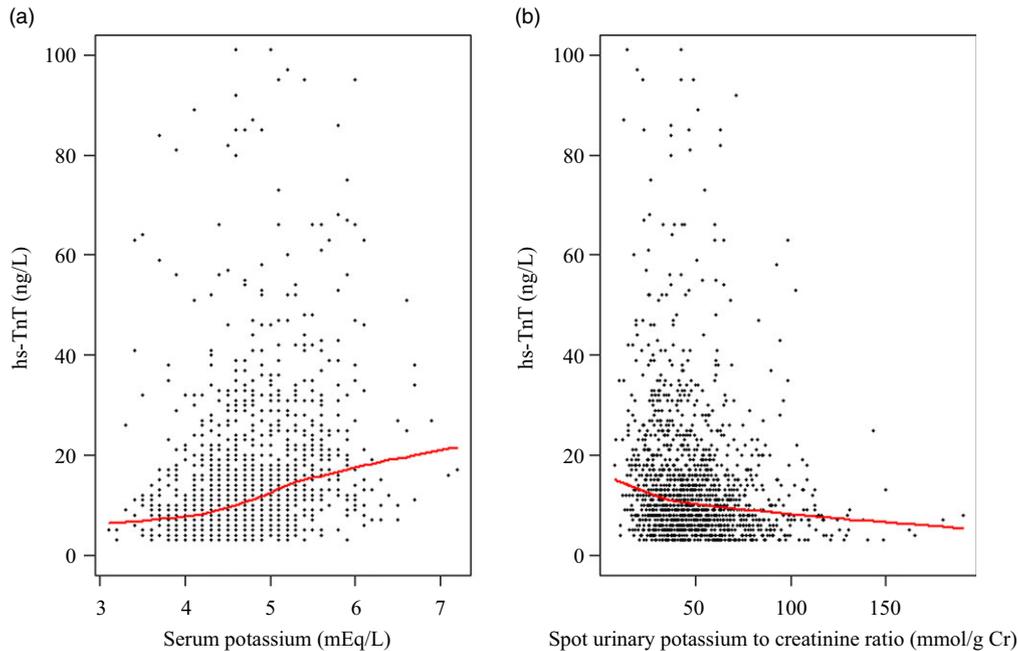|	Quartile of spot urinary potassium to creatinine ratio (mmol/g Cr)									
	1Q: 7·7–33·8 (n 408)		2Q: 33·8–45·4 (n 407)		3Q: 45·4–60·6 (n 409)		4Q: 60·6–190·4 (n 409)		P	P_{trend}
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age (years)	50·3	13·8	53·4	12·0*	55·3	11·2*	55·3	11·8*	<0·001	<0·001
	n	%	n	%	n	%	n	%		
Male sex	323	79·2	293	72·0	234	57·2*,†	158	38·6*,†,‡	<0·001	<0·001
Current smoking	85	20·8	88	21·6	50	12·2*,†	34	8·3*,†	<0·001	<0·001
Cause of CKD										
DMN	132	32·4	102	25·1	93	22·7*	108	26·4	0·015	0·039
HTN	79	19·4	90	22·1	85	20·8	69	16·9	0·274	0·317
GN	128	31·4	120	29·5	123	30·1	115	28·1	0·784	0·364
Others	69	16·9	95	23·3	108	26·4*	117	28·6*	0·001	<0·001
Previous CV disease	70	17·2	65	16·0	77	18·8	62	15·2	0·526	0·704
RAS inhibitor	359	88·0	347	85·3	359	87·8	242	83·6	0·209	0·165
Anti-platelet drugs	122	29·9	122	30·0	118	28·9	111	27·1	0·791	0·348
Lipid lowering drugs	211	51·7	228	56·0	219	53·5	215	52·6	0·636	0·994
	Median	IQR	Median	IQR	Median	IQR	Median	IQR		
CCI	3·0	2·0–5·0	3·0	2·0–5·0	3·0	2·0–5·0	3·0	1·0–5·0	0·384	0·156
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Systolic BP (mmHg)	126·5	15·8	128·5	15·4	127·8	15·5	127·4	15·5	0·318	0·557
Diastolic BP (mmHg)	75·7	11·0	77·6	11·1	77·6	11·3	76·3	10·3	0·028	0·409
BMI (kg/m²)	24·7	3·5	24·6	3·5	24·6	3·3	24·5	3·5	0·835	0·372
Fasting glucose (mmol/l)	6·2	2·3	6·1	2·0	6·0	2·0	6·1	2·0	0·754	0·626
TAG (mmol/l)	1·9	1·2	1·8	1·1	1·8	1·2	1·7	1·0	0·085	0·015
HDL-cholesterol (mmol/l)	1·2	0·4	1·3	0·4	1·3	0·4*	1·4	0·4*,†	<0·001	<0·001
Serum K (mmol/l)	4·7	0·6	4·6	0·6	4·6	0·6	4·6	0·6	0·461	0·267
Total CO_2 (mmol/l)	24·7	4·0	25·5	3·4*	26·2	3·2*†	26·5	3·4*†	<0·001	<0·001
Ca (mmol/l)	2·28	0·15	2·29	0·13	2·29	0·12	2·30	0·12	0·018	0·004
Phosphorus (mmol/l)	1·21	0·25	1·18	0·23	1·18	0·20	1·21	0·20	0·054	0·771
25OH Vit.D (nmol/l)	42·7	17·3	44·7	18·3	44·2	20·5	45·1	20·5	0·300	0·117
Intact PTH (ng/l)	82·6	78·2	76·8	84·7	67·8	54·6	63·9	80·8*	0·002	<0·001
Albumin (g/l)	41·9	4·2	41·7	4·6	41·6	4·5	42·5	4·2	0·019	0·105
Hb (g/dl)	12·8	2·2	13·0	2·1	12·9	2·0	12·7	1·9	0·321	0·353
Leucocyte (×10³/µl)	6·9	2·1	6·8	1·9	6·5	1·8*	6·2	1·8*,†	<0·001	<0·001
BUN (mmol/l)	11·7	6·7	10·7	5·9	9·6	5·1*	8·7	4·6*,†	<0·001	<0·001
Serum Cr (µmol/l)	198·7	122·1	174·5	108·3*	152·8	89·3*	124·2	73·0*,†,‡	<0·001	<0·001
eGFR (ml/min/1·73 m²)	45·6	30·1	49·2	29·0	53·3	29·5*	63·5	32·5*,†,‡	<0·001	<0·001
	Median	IQR	Median	IQR	Median	IQR	Median	IQR		
UACR (mg/g Cr)	383·0	105·4–1182·4	349·6	91·1–1165·3	344·7	72·0–1038·9	301·8	51·6–881·8	0·044	0·018

CKD, chronic kidney disease; GN, glomerulonephritis; CV, cardiovascular; RAS, RAS, renin-angiotensin system; CCI, Charlson co-morbidity index; BP, blood pressure; Cr, creatinine; eGFR, estimated glomerular filtration rate; 25-OH Vit.D, 25-hydroxyvitamin D; PTH, parathyroid hormone; BUN, blood urea nitrogen; UACR, urine albumin-to-creatinine ratio.
In post-hoc analysis with Bonferroni correction, *, † and ‡ indicate $P < 0.01$ when compared with 1Q–3Q, respectively.
Values are expressed as mean values and standard deviations for normally distributed continuous variables, median (interquartile range) in non-normally distributed variables and n (percentage) for categorical variables.
The differences were analysed using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis test for non-normally distributed continuous variables and χ^2 test for categorical variables.
P_{trend} was analysed by linear regression for normally distributed continuous variables, the Jonckheere–Terpstra test for non-normally distributed continuous variables and the Cochran–Armitage trend test for categorical variables.

(a) (b)

Fig. 2. Relationship between serum potassium, spot urinary potassium to creatinine ratio and hs-TnT. The red line in the scatter plot indicated the LOWESS regression curve. Values of hs-TnT > 100 ng/l were truncated. hs-TnT, high-sensitivity troponin T.

Relationship between spot urinary potassium to creatinine ratio and cardiac injury

We explored the relationship between serum potassium, spot urinary potassium to creatinine ratio and serum hs-TnT levels (Fig. 2). With the increase in serum potassium and spot urinary potassium to creatinine ratio, the serum hs-TnT levels steadily increased and decreased, respectively. To identify the potential confounding association of eGFR, we analysed the relationship between eGFR and serum potassium, spot urinary potassium to creatinine ratio and hs-TnT levels (online Supplementary Fig. S2) and found that an increased eGFR was associated with decreased serum levels of potassium and hs-TnT but increased spot urinary potassium to creatinine ratio. To adjust for confounders, we performed multivariate logistic regression analyses (Table 2) and found only spot urinary potassium to creatinine ratio was independently associated with cardiac injury in fully adjusted model: OR 0·917 and 95 % CI (0·841, 0·998) ($P = 0.047$). After excluding 789 patients for whom 24-h urine potassium excretion results were unavailable, 844 patients remained for the sensitivity analysis. Similarly, serum potassium levels were not associated with cardiac injury, but 24-h urinary potassium excretion showed decreased odds for cardiac injury: OR 0·833 and 95 % CI (0·744, 0·930) ($P = 0.001$). On the other hand, serum potassium and spot urinary potassium to creatinine ratio were not associated with cardiac injury defined with a CKD-specific hs-TnT cut-off (online Supplementary Table S1).

Mediation and subgroup analysis

To identify the potential mediating association of serum potassium levels with the relationship between spot urinary potassium to creatinine ratio and cardiac injury, we performed a mediation analysis (Fig. 3). It was observed that approximately 6·4 % of the association of the spot urinary potassium to creatinine ratio with cardiac injury was mediated by serum potassium levels, which was not statistically significant ($P = 0.368$). We found significant modification between spot urinary potassium to creatinine ratio by age ($P_{interaction} = 0.015$), eGFR ($P_{interaction} = 0.021$) and CCI ($P_{interaction} = 0.002$) (Table 3). Increased spot urinary potassium to creatinine ratio was associated with cardiac injury only in age < 55 years, eGFR ≥ 46 ml/min/1·73 m^2 and CCI < 4.

Discussion

Among clinicians, it is a regular practice to reduce the potassium intake in CKD patients. Additionally, several CKD patients are educated to avoid high-potassium foods. In this study, we can also identify the habitual patterns that patients with good kidney function consumed more potassium, while patients with poor kidney function avoided potassium intake (online Supplementary Fig. S2-B). However, until recently, there have been no official recommendations to limit the potassium intake in patients with CKD. Specific codes of conduct have not been suggested even in the KDIGO 2012 guideline with respect to the consumption of potassium in CKD patients[27]. In the meantime, several studies have consistently suggested the harm of a low potassium diet and potential CV benefits of a high-potassium diet[4,5,8,12]. Nonetheless, there have been no studies to evaluate the relationship between urinary potassium excretion and cardiac injury in CKD patients. In addition, whether the relationship between urinary potassium excretion and cardiac injury is mediated by serum potassium levels has never been studied.

Cardiac troponins are structural proteins of the heart. Traditionally, the elevation of cardiac troponins means myocardial

Table 2. Relationship between serum potassium level, urinary potassium excretion and cardiac injury (Odds ratios and 95 % confidence intervals)

	Univariate			Model 1*			Model 2†			Model 3‡		
	OR	95 % CI	P	OR	95 % CI	P	OR	95 % CI	P	OR	95 % CI	P
Total (n 1633)												
Serum potassium (mmol/l)	3·822	3·132, 4·693	<0·001	2·088	1·643, 2·662	<0·001	1·303	0·991, 1·715	0·058	0·917	0·680, 1·236	0·571
Spot urinary potassium to creatinine ratio (10 mmol/g Cr)	0·845	0·801, 0·889	<0·001	0·816	0·758, 0·877	<0·001	0·869	0·802, 0·939	<0·001	0·917	0·841, 0·998	0·047
Sensitivity (n 844)												
Serum potassium (mmol/l)	3·251	2·485, 4·299	<0·001	2·017	1·461, 2·804	<0·001	1·346	0·927, 1·962	0·119	0·937	0·622, 1·411	0·756
24-h urinary potassium excretion (10 mEq/d)	0·853	0·793, 0·915	<0·001	0·789	0·717, 0·866	<0·001	0·825	0·745, 0·912	<0·001	0·833	0·744, 0·930	0·001

* In model 1, the covariates were age, sex, smoking status, causes of chronic kidney disease, administration of renin-angiotensin system inhibitors, anti-platelet drugs, anti-lipid drugs, previous CVD, age-adjusted Charlson co-morbidity index, BMI, systolic and diastolic blood pressure, fasting glucose, HDL-cholesterol and TAG levels.
† In model 2, the covariates were variables of model 1 with Ca, phosphorus, 25-hydroxy vitamin D, intact parathyroid hormone, albumin, Hb and leucocytes.
‡ In model 3, the covariates were variables of model 2 with blood urea nitrogen, estimated glomerular filtration rate, total CO_2 and urine albumin-to-creatinine ratio. OR and 95 % CI for cardiac injury were calculated using logistic regression.

cell death[14]. However, as the assays of troponin became more sensitive, much lower levels of troponin can be determined, and the elevation of troponins in those once-undetectable ranges now reflects not only myocardial death but also the injury of structures and functions of the heart[13]. Among others, hs-TnT was the first highly sensitive assay for cardiac troponin, and the most validated, and 14 ng/l for hs-TnT has been suggested to be a good cut-off for cardiac injury[13], not only as the 99th percentile of a normal reference population but also the value that can predict future CV events and mortality[15,16]. In this study, the overall prevalence of cardiac injury in stable non-dialysis CKD patients was 33·9 %, which was concordant with the known findings that CKD patients are a high-risk group for CV events[9–11]. The prevalence of cardiac injury increased with the increase of CKD stages, and approximately 82·0 % of CKD stage 5 patients had cardiac injury. Therefore, the factors associated with cardiac injury need to be studied further.

In this study, we found that the serum potassium levels were not associated with cardiac injury, after adjusting for the markers of kidney function and damage. We propose two possible explanations for these results. First, the risk of arrhythmia is profoundly increased only when serum potassium is in extreme range, such as < 3·0 mEq/l or ≥ 7·0 mEq/l[3,28]. However, the serum potassium levels in this population were too stable. The range of serum potassium was between 3·1 mEq/l and 7·2 mEq/l, and only two patients showed serum potassium ≥ 7·0 mEq/l in this population. Second, the pathophysiology of dyskalaemia-related arrhythmia was mostly changing the excitation and relaxation of membrane potential, not the structural proteins[3]. Since troponins are structural proteins, the serum levels of potassium may not be associated with the serum levels of hs-TnT.

Unlike serum potassium levels, higher urinary potassium excretion was associated with lower odds of cardiac injury, even after adjusting for markers of kidney function and damage. The relationship between urinary potassium excretion and cardiac injury was independent of serum potassium levels. We confirmed that the relationship between the urinary potassium excretion and cardiac injury was not mediated by serum potassium levels in mediation analysis. We postulated that the beneficial association of a urinary potassium excretion with cardiac injury may be derived from the intimate relationship between the high-potassium diet and healthy food patterns[29]. Or, high fruit and vegetables diets that are high in potassium are also high in dietary bicarbonate equivalents. In this study, patients with higher spot urinary potassium to creatinine ratio quartile showed higher levels of total CO_2, suggesting certain high-potassium diets might reduce serum potassium levels to a certain degree by treating metabolic acidosis[30]. Therefore, whether the potential beneficial renal and cardiac effects of a high-potassium diet[4,5,8,12] were from potassium per se need to be tested in future interventional studies.

In a sensitivity analysis, both serum potassium levels and urinary potassium excretion were not associated with cardiac injury defined as a CKD-specific hs-TnT cut-off of ≥ 126 ng/l, even in univariate analysis (online Supplementary Table S1). This may be because patients with hs-TnT ≥ 126 ng/l are highly related to myocardial infarction, myocarditis and congestive
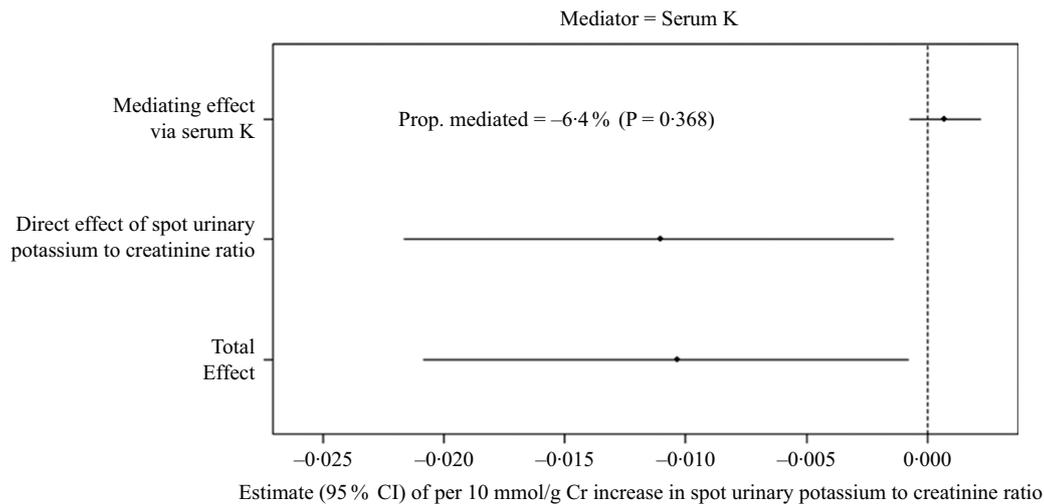
Fig. 3. Mediation analysis for the relationship between spot urinary potassium to creatinine ratio and cardiac injury. The exposure was spot urinary potassium to creatinine ratio, the mediator was serum potassium and the outcome was cardiac injury. The relationship between exposure and outcome was calculated with multivariate logistic regression analysis, and that between exposure and mediator was calculated with multivariate linear regression analysis. Prop. mediated, proportion mediated.

Table 3. Subgroup analysis for the relationship between spot urinary potassium to creatinine ratio and cardiac injury, according to the status of confounders (Odds ratios and 95 % confidence intervals)

Subgroup		Adjusted OR	95 % CI	P	P_{int}
Age ≥ 55 years	No (n 806)	0·776	0·644, 0·925	0·006	0·015
	Yes (n 827)	0·971	0·875, 1·076	0·576	
Male sex	No (n 625)	0·935	0·815, 1·066	0·325	0·245
	Yes (n 1008)	0·901	0·798, 1·015	0·087	
eGFR ≥ 46 ml/min/1·73 m^2	No (n 816)	0·972	0·877, 1·079	0·596	0·021
	Yes (n 817)	0·739	0·611, 0·883	0·001	
Serum K ≥ 4·5 mEq/l	No (n 691)	0·872	0·718, 1·047	0·153	0·877
	Yes (n 942)	0·933	0·843, 1·031	0·176	
CCI ≥ 4	No (n 601)	0·427	0·243, 0·679	0·001	0·002
	Yes (n 1032)	0·974	0·89, 1·065	0·561	
UACR ≥ 348 mg/g Cr	No (n 816)	0·93	0·814, 1·057	0·275	0·923
	Yes (n 817)	0·923	0·819, 1·037	0·181	
Leucocyte ≥ 6·3 (×10^3/μl)	No (n 815)	0·967	0·855, 1·09	0·594	0·852
	Yes (n 818)	0·853	0·748, 0·969	0·016	

eGFR, estimated glomerular filtration rate; CCI, Charlson co-morbidity index; UACR, urine albumin-to-creatinine ratio; P_{int}, P for interaction.
Subgroup was categorised based on median value.
Adjusted OR and 95 % CI per 10 mmol/g Cr increase of spot urinary potassium to creatinine ratio were calculated using multivariate logistic regression analysis, entering into age, sex, smoking status, causes of chronic kidney disease, administration of renin-angiotensin system inhibitors, anti-platelet drugs and anti-lipid drugs, previous CVD, CCI, BMI, systolic and diastolic blood pressure, fasting glucose, HDL-cholesterol, TAG, Ca, phosphorus, total CO_2, 25-hydroxy vitamin D, intact parathyroid hormone, albumin, Hb, leucocyte, blood urea nitrogen, eGFR, total CO_2 and UACR as covariates.
When covariates were chosen as subgroup, they were excluded from the model.

heart failure[13], which are much more serious conditions than cardiac injury and are overwhelmingly influenced by other factors rather than potassium intake.

This study has several strengths. First, this was the first study to simultaneously evaluate the potential inter-relationship between serum potassium, urinary potassium excretion and cardiac injury in patients with large-scale non-dialysis CKD. Second, there have been no studies on whether the potential beneficial association of high-potassium intake was from potassium per se or not. Although inconclusive, our study results may provoke research interests and lead to subsequent studies in this field. Finally, the study was based on a globally recognised CKD cohort (KNOW-CKD)[31,32]. The multicentre setting minimised selection and centre-specific bias. In addition, the wide range of baseline kidney function and inclusion of various causes of CKD may augment the reliability of our study results.

However, this study also has some limitations. First, this was a cross-sectional study. Therefore, a causal relationship cannot be ascertained using the study results. Second, only half of the cohort participants had 24-h urine potassium excretion. Therefore, the primary exposure of the study was a surrogate, not measured values. However, since we used the most validated surrogate for urinary potassium excretion[19–21], and the study purpose was hypothesis generation, not confirming a causal relationship, this limitation might be acceptable. Third, the single ethnicity of the patients in this study limits our ability to generalise our results.

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In conclusion, higher urinary potassium excretion was associated with lower odds of cardiac injury. However, the potential cardiac association of higher urinary potassium excretion was not mediated by serum potassium levels. Future studies need to be conducted to confirm the results of this study.

Acknowledgements

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114523002064

References

1. Drawz PE, Babineau DC & Rahman M (2012) Metabolic complications in elderly adults with chronic kidney disease. *J Am Geriatr Soc* **60**, 310–315.
2. Palmer BF & Clegg DJ (2019) Physiology and pathophysiology of potassium homeostasis: core curriculum 2019. *Am J Kidney Dis* **74**, 682–695.
3. Weiss JN, Qu Z & Shivkumar K (2017) Electrophysiology of hypokalemia and hyperkalemia. *Circ Arrhythm Electrophysiol* **10**, e004667.
4. Binia A, Jaeger J, Hu Y, et al. (2015) Daily potassium intake and sodium-to-potassium ratio in the reduction of blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens* **33**, 1509–1520.
5. O'Donnell M, Mente A, Rangarajan S, et al. (2014) Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med* **371**, 612–623.
6. Leonberg-Yoo AK, Tighiouart H, Levey AS, et al. (2017) Urine potassium excretion, kidney failure, and mortality in CKD. *Am J Kidney Dis* **69**, 341–349.
7. He J, Mills KT, Appel LJ, et al. (2016) Urinary sodium and potassium excretion and CKD progression. *J Am Soc Nephrol* **27**, 1202–1212.
8. Kim HW, Park JT, Yoo TH, et al. (2019) Urinary potassium excretion and progression of CKD. *Clin J Am Soc Nephrol* **14**, 330–340.
9. Kiuchi MG & Mion D Jr (2016) Chronic kidney disease and risk factors responsible for sudden cardiac death: a whiff of hope? *Kidney Res Clin Pract* **35**, 3–9.
10. Ahmed KA & Al-Attab WM (2017) Prognostic performance of combined use of high-sensitivity troponin T and creatine kinase MB isoenzyme in high cardiovascular risk patients with end-stage renal disease. *Kidney Res Clin Pract* **36**, 358–367.
11. Cha RH, Kang SW, Park CW, et al. (2017) Sustained uremic toxin control improves renal and cardiovascular outcomes in patients with advanced renal dysfunction: post-hoc analysis of the Kremezin study against renal disease progression in Korea. *Kidney Res Clin Pract* **36**, 68–78.
12. Araki S, Haneda M, Koya D, et al. (2015) Urinary potassium excretion and renal and cardiovascular complications in patients with type 2 diabetes and normal renal function. *Clin J Am Soc Nephrol* **10**, 2152–2158.
13. Twerenbold R, Jaffe A, Reichlin T, et al. (2012) High-sensitive troponin T measurements: what do we gain and what are the challenges? *Eur Heart J* **33**, 579–586.
14. Thygesen K, Alpert JS, White HD, et al. (2007) Universal definition of myocardial infarction. *Circulation* **116**, 2634–2653.
15. Everett BM, Brooks MM, Vlachos HE, et al. (2015) Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med* **373**, 610–620.
16. Ndrepepa G, Colleran R, Braun S, et al. (2016) High-sensitivity troponin t and mortality after elective percutaneous coronary intervention. *J Am Coll Cardiol* **68**, 2259–2268.
17. Holbrook JT, Patterson KY, Bodner JE, et al. (1984) Sodium and potassium intake and balance in adults consuming self-selected diets. *Am J Clin Nutr* **40**, 786–793.
18. Oh KH, Park SK, Park HC, et al. (2014) KNOW-CKD (KoreaN cohort study for outcome in patients with chronic kidney disease): design and methods. *BMC Nephrol* **15**, 1471–2369.
19. Tanaka T, Okamura T, Miura K, et al. (2002) A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. *J Hum Hypertens* **16**, 97–103.
20. Kawasaki T, Itoh K, Uezono K, et al. (1993) A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. *Clin Exp Pharmacol Physiol* **20**, 7–14.
21. Mente A, O'Donnell MJ, Dagenais G, et al. (2014) Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. *J Hypertens* **32**, 1005–1014.
22. Bansal N, Zelnick LR, Ballantyne CM, et al. (2022) Upper reference limits for high-sensitivity cardiac troponin T and N-terminal fragment of the prohormone brain natriuretic peptide in patients with CKD. *Am J Kidney Dis* **79**, 383–392.
23. Levey AS, Stevens LA, Schmid CH, et al. (2009) A new equation to estimate glomerular filtration rate. *Ann Intern Med* **150**, 604–612.
24. Stevens PE, Levin A & Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members (2013) Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* **158**, 825–830.
25. Charlson M, Szatrowski TP, Peterson J, et al. (1994) Validation of a combined comorbidity index. *J Clin Epidemiol* **47**, 1245–1251.
26. Tingley T, Yamamoto T, Hirose K, et al. (2014) mediation: R package for causal mediation analysis. *J Stat Softw* **59**, 1–38.
27. Kidney Disease Improving Global Outcome Work group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Chapter 3: management of progression and complications of CKD. *Kidney Int Suppl* **3**, 73–90.

28. Pezhouman A, Singh N, Song Z, *et al.* (2015) Molecular basis of hypokalemia-induced ventricular fibrillation. *Circulation* **132**, 1528–1537.

29. Clase CM, Carrero JJ, Ellison DH, *et al.* (2020) Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int* **97**, 42–61.

30. Goraya N, Simoni J, Jo CH, *et al.* (2013) A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. *Clin J Am Soc Nephrol* **8**, 371–381.

31. Orlandi PF, Huang J, Fukagawa M, *et al.* (2019) A collaborative, individual-level analysis compared longitudinal outcomes across the international network of chronic kidney disease (iNETCKD) cohorts. *Kidney Int* **96**, 1217–1233.

32. Alencar de Pinho N, Levin A, Fukagawa M, *et al.* (2019) Considerable international variation exists in blood pressure control and antihypertensive prescription patterns in chronic kidney disease. *Kidney Int* **96**, 983–994.