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Urinary Sodium-to-Potassium Ratio and Blood Pressure in CKD

Natalia Alencar de Pinho1,11, Jean Kaboré2,11, Maurice Laville3, Marie Metzger1, Céline Lange1,4, Christian Jacquelinet1,4, Christian Combe5, Denis Fouque3, Luc Frimat6,7, Carol Ayav7,8, Bruce M. Robinson9, Tilman Druke1, Ziad A. Massy1,10 and Bénédicte Stengel1; on behalf of the CKD-REIN Study Group12

1University Paris-Saclay, UVSQ, University Paris-Sud, Inserm, Clinical Epidemiology team, CESP, Villejuif, France; 2Institut de Recherche en Sciences de la Santé, CNRST, Ouagadougou, Burkina Faso, Centre Muraz, Bobo-Dioulasso, Burkina Faso; 3Centre Hospitalier Lyon Sud, Nephrology Department; Lyon University, INSERM U1060, CarMeN, Pierre-Bénite, France; 4Biomedicine Agency, Saint-Denis La Plaine, France; 5Centre Hospitalier Universitaire de Bordeaux, Service de Néphrologie Transplantation Dialyse Apherèse, Inserm U1026, Université Bordeaux Segalen, Bordeaux, France; 6CHRU de Nancy, Service de Néphrologie, Vandoeuvre-lès-Nancy, France; 7Université de Lorraine, APEMAC, Nancy, Lorraine, France; 8CHRU-Nancy, INSERM, CIC, Épidémiologie Clinique, Nancy, France; 9Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; and 10Ambroise Paré University Hospital, APHP, Department of Nephrology, Boulogne-Billancourt/Paris, France

Introduction: In the general population, urinary sodium-to-potassium (uNa/K) ratio associates more strongly with high blood pressure (BP) than either urinary sodium or potassium alone. Whether this is also the case among patients with chronic kidney disease (CKD) is unknown.

Methods: We studied the associations of spot urine sodium-to-creatinine (uNa/Cr), potassium-to-creatinine (uK/Cr), and uNa/K ratios with a single office BP reading in 1660 patients with moderate to severe CKD at inclusion in the CKD-REIN cohort.

Results: Patients’ median age was 68 (interquartile range [IQR], 59–76) years; most were men (65%), had moderate CKD (57%), and albuminuria (72%). Mean systolic and diastolic BP was 142/78 mm Hg. Spot uNa/Cr and uNa/K ratios were positively associated with systolic, mean arterial, and pulse pressures. The mean adjusted difference in systolic BP between the highest and the lowest quartile (Q4 vs. Q1) was 4.24 (95% confidence interval [CI], 1.53–6.96) mm Hg for uNa/Cr and 4.79 (95% CI, 2.18–7.39) mm Hg for uNa/K. Quartiles of spot uK/Cr were not associated with any BP index. The higher the quartile of uNa/K, the higher the prevalence ratio of uncontrolled (Q4 vs. Q1, 1.43; 95% CI, 1.19–1.72) or apparently treatment-resistant hypertension (Q4 vs. Q1, 1.35; 95% CI, 1.14–1.60). Findings were consistent in a subset of 803 individuals with 2 BP readings.

Conclusion: In patients with CKD, higher urinary sodium excretion is associated with higher BP, but unlike in general population, lower potassium excretion is not. Urinary Na/K does not add significant value in assessing high BP risk, except perhaps for hypertension control assessment.


KEYWORDS: blood pressure; chronic kidney disease; potassium; salt; sodium

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Arterial hypertension is the leading cause of cardiovascular morbidity and mortality in the world.1 In the general population, both high sodium intake and low potassium intake, assessed by urinary excretion analyses, associate with elevated BP levels2–9 and hypertension onset.10,11 The association of urinary sodium with BP follows a J-shaped curve, whereas the negative association with urinary potassium is linear, with steeper slopes in hypertensive than normotensive subjects.1 Meta-analyses of randomized clinical trials6,12 and cohort studies6,13 have unambiguously showed BP reduction in response to increased potassium intake in both healthy people and those with hypertension. In contrast, the magnitude of BP response to a reduction in sodium intake remains debated, as is the response in terms of cardiovascular and all-cause mortality.14–16 Studies in patients with CKD, whose BP is particularly difficult to control, are

Correspondence: Bénédicte Stengel, Clinical Epidemiology, Epidemiology Team, CESP INSERM 1018, 16 Avenue Paul Vaillant Couturier, 94807, Villejuif, France. E-mail: benedicte.stengel@inserm.fr

11NAdP and JK contributed equally.

12Members of the CKD-REIN Study Group are listed in the Appendix.

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scarce.17 Short-term randomized trials in patients with moderate to severe CKD have shown that clinically relevant BP reductions follow dietary sodium restriction.18,19 In observational studies, high sodium intake based on 24-hour urinary sodium excretion has been associated with increased systolic BP at CKD stages 3–4,20,21 but not at stages 1–2,22 whereas findings from studies that reported association of potassium intake with BP led to contradictory conclusions.23–25 As far as the effects of sodium and potassium intake on renal outcomes are concerned, most reports indicate that high sodium intake is associated with more rapid CKD progression,24,26 whereas potassium intake remains a matter of debate.24,27,28

Interaction between sodium and potassium appears to be a key component of BP regulation.29 The sodium-to-potassium ratio has therefore been suggested as a stronger predictor of BP than either sodium or potassium excretion alone.30–32 However, the method for assessing the intake of sodium and potassium is critical. The reliability of estimates from food questionnaires is poor, especially compared with repeated 24-hour urine collection.31 However, 24-hour urine sampling is difficult to obtain in cohort studies and not necessarily reliable in terms of completeness.33,34 Spot urine-based assessments have been proposed as a more practical alternative, based on urinary sodium-to-creatinine (uNa/Cr) or sodium-to-potassium (uNa/K) ratios.9,31,35,36 Whether spot uNa/K is more informative than spot uNa/Cr or uK/Cr alone for assessing the impact on BP and hypertension control in patients with CKD has not yet been investigated. We therefore tested the hypothesis that uNa/K excretion is a stronger predictor of BP level and hypertension control status than either urinary sodium or potassium excretion alone in patients with moderate or severe CKD, using spot urine samples.

METHODS

Study Participants

CKD-REIN is an ongoing prospective cohort study conducted in 40 French hospitals that provide outpatient nephrology care, nationally representative geographically and for legal status (public, private nonprofit, and private for-profit). A total of 3033 adults with a proven CKD diagnosis and an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m², neither dialyzed nor transplanted, were included from 2013 through 2016. Full information about participant selection and study design is available elsewhere.37 The French Institute of Health and Medical Research (Inserm) Institutional Review Board (IRB00003888) approved the study protocol, and all participants signed informed consents.

Clinical and Laboratory Measurements

Patient data forms were completed by trained clinical research associates with information from patient interviews and medical records. We collected detailed medical history, including cardiovascular comorbidities and risk factors. Patients were classified with diabetes if mentioned in medical records, if they used glucose-lowering medication, or if they had HbA1c ≥7%. They were classified with dyslipidemia if stated in medical records or if they used lipid-lowering medications. Information on medication use, including antihypertensive agents, was obtained from drug prescriptions for the 3 months before the baseline interview. Height and weight were measured by nephrologists (or outpatient nurses) during a routine visit at study inclusion, and body mass index (BMI) was calculated. All patients were prescribed a set of standard blood and urine tests (recommended by French Health Authority for routine CKD care), to be performed at their usual laboratory at study entry. GFR was estimated from serum creatinine with the CKD-Epidemiology Collaboration equation38 and albuminuria (or equivalent) was classified according to the Kidney Disease Improving Global Outcomes 2012 guideline stages.39

BP Measurements and Definition of Hypertension Status

BP was measured by nephrologists or outpatient nurses during a routine visit at study inclusion, according to each clinic’s routine practices. According to the study protocol, they were asked to measure BP twice, in sitting position, after a 5-minute rest. No BP reading was available for 78 (2.5%) participants, who were excluded from the study. Only 803 (48.4%) had a second BP reading. We used a single BP measurement for the main analyses and considered the following indices: systolic and diastolic BPs, mean arterial pressure (2×diastolic + systolic BP)/3, and pulse pressure (systolic – diastolic BP). Arterial hypertension was defined as a medical history of hypertension or anti-hypertensive medication use. Participants were classified according to hypertensive status as follows: no hypertension; controlled hypertension, if systolic BP <140 mm Hg and diastolic BP <90 mm Hg while taking up to 3 antihypertensive drug classes; uncontrolled hypertension, if systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg while taking up to 3 antihypertensive drug classes (diuretics excluded); or apparently treatment-resistant hypertension, if systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg while taking 3 antihypertensive drug classes (including a diuretic), or if taking more than 3 antihypertensive drug classes independently of BP level.
Assessment of Urinary Sodium and Potassium Excretion

Urinary sodium, potassium, and creatinine excretion was assessed either through second-void urine samples or through 24-hour urine collection, according to each clinic’s routine practices. These assessments were performed within 3 months before or after the inclusion visit (date of BP assessment). For the spot urine measurements, exclusion of outliers outside the concentration ranges of 4 to 260 mmol/l, 3 to 102 mmol/l, and 0.1 to 3 g/l for sodium, potassium, and creatinine, respectively, left 1660 participants with valid values. A subgroup of 852 participants had values of sodium, potassium, and creatinine excretion measured in both spot and 24-hour urine samples.

Statistical Analyses

Categorical variables are presented as percentages, and continuous variables as means ± SDs or medians (IQR), depending on the normality of their distribution, assessed graphically with QQ-plots. The percentage of missing data was less than 5% for most variables, except for the second BP reading (51.6%). In the main analysis, we used a single BP reading as outcome and performed multiple imputation for study covariates. Analyses through the complete datasets were combined according to Rubin and Schenker’s rules. Median (IQR) spot uNa/K, uK/Cr, and uNa/Cr ratios were described according to age, sex, eGFR, and BMI and compared with the Mann-Whitney test. Crude and adjusted associations of BP indices, with each of the 3 ratios modeled by 4-knot restricted cubic splines, were compared with the Mann-Whitney test. Crude and adjusted prevalence ratios of hypertension were estimated. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

The characteristics of the 1660 patients included are presented in Table 1. Most were aged 65 years or older, were men (65%), and had eGFR less than 45 (81%) and moderately or severely increased albuminuria (72%). Mean systolic and diastolic BPs were, respectively, 142 mm Hg and 78 mm Hg. Approximately 90% of the patients had a medical history of arterial hypertension, and only 30% had controlled BP. Older patients and women had higher uNa/Cr and uK/Cr than, respectively, younger patients and men (Figure 1). Obese patients had higher uNa/Cr and uNa/K than nonobese patients, as did patients with lower versus higher education level. None of the ratios varied with eGFR level.

Associations of Spot Urine Sodium and Potassium Ratios With BP and Hypertension Control Status

In the crude analysis, spot uNa/Cr and uNa/K were significantly associated with systolic, mean arterial, and pulse pressures but not with diastolic pressure (Supplementary Table S2). Mean systolic BP was 138 mm Hg and 146 mm Hg for the lowest and highest quartiles of spot uNa/Cr, respectively, and 139 mm Hg and 145 mm Hg for those of spot uNa/K. Spot uK/Cr was not associated with any of the BP indices. After restricted cubic spline modeling and adjustment for potential confounders, spot uNa/Cr and uNa/K remained positively associated with systolic, mean arterial, and pulse pressures (Figure 2; Supplementary Table S3). The mean difference in systolic BP between the highest and the lowest quartile of both spot uNa/Cr and uNa/K was approximately 4 to 5 mm Hg. Estimated interactions with age, gender, eGFR, BMI, and the prescription of diuretics or RAS inhibitors other sensitivity analyses: one using the mean of 2 values in the subsample of 803 patients with 2 BP readings (complete case analysis), and another in all 1660 patients with imputed second readings as needed. Multiple imputation of 100 datasets were made with the fully conditional specification method. Covariates included in the imputation model for BP are shown in Supplementary Table S1, according to whether 1 or 2 BP readings were available. The fraction of missing information was 0.21 and 0.45 for the second systolic and diastolic BP values, respectively.

Two-sided significance tests were used, and P values < 0.05 were considered significant. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC).
were not statistically significant (all $P > 0.10$, data not shown).

Patients in the higher quartiles of uNa/K were more likely to have uncontrolled (adjusted prevalence ratio Q4 vs. Q1, 1.43; 95% CI, 1.19–1.72) or apparently treatment-resistant hypertension (adjusted prevalence ratio Q4 vs Q1, 1.35; 95% CI, 1.14–1.60) than controlled hypertension (Figure 3; Supplementary Table S4). Association of hypertension status with uNa/Cr ratio was weaker than with uNa/K ratio.

Sensitivity Analysis

The sensitivity analysis on the type of urinary measurement included 852 participants who had both spot and 24-hour urine measurements at baseline. Median 24-hour uNa in this population was 128 mmol (IQR, 97–170 mmol) per day, equivalent to salt intake of 7.3 g per day. Only 21% of these participants had an estimated sodium intake of less than 90 mmol per day (5 g of salt per day), as recommended by Kidney Disease Improving Global Outcomes guidelines. Median 24-hour uK was 58 mmol (IQR, 42–72 mmol) per day. Associations between 24-hour urine measurements and systolic BP were consistent with those based on spot urine in terms of direction (Table 2; Supplementary Table S5). Effect estimates tended to be stronger with spot urine than with 24-hour urine markers. The sensitivity analyses according to the mean of 2 systolic BP readings provided similar associations whether based on complete cases or multiple imputation as those from the main analysis (Supplementary Table S5).

DISCUSSION

The main finding of this study was that urinary sodium, but not potassium, was positively associated with systolic, mean arterial, and pulse pressures in patients with moderate to severe CKD. The uNa/K ratio was similarly associated with these BP indices and also significantly associated with uncontrolled and apparently treatment-resistant hypertension. Diastolic BP was associated with uNa/Cr, but effect size was modest.
These findings show that the association of sodium and potassium intake with BP in patients with CKD is different from that observed in the general population. The study also suggests the suitability of spot urinary measurements for epidemiological studies in patients with CKD.

Some observational studies have found a positive association between BP and urinary sodium excretion studies in the general population, whereas others have reported either no or only a weak association. One of the largest observational studies in this context, by Mente et al., showed a J-curve shaped relation between BP and sodium intake, with a nadir at 2 to 3 g/d (90–130 mmol/d). In that study, the effect size of the association of systolic and diastolic BP with increasing sodium excretion (per 1 g/d increment) was weak in normotensive people (1.30 mm Hg for systolic and 0.58 mm Hg for diastolic pressure). It was somewhat greater, but still relatively small, in those with hypertension (2.49 mm Hg for systolic and 0.91 mm Hg for diastolic pressure). Importantly, Mente et al. observed a clinically relevant association with systolic BP only among persons whose sodium intake exceeded 5 g/d (220 mmol/d). This finding was confirmed in a recent analysis based on the UK Biobank data. In our study, the median estimated sodium intake in participants with available 24-hour urine collection was 128 mmol/d (7.3 g of salt), similar to that observed in the French general population (122 mmol/d) but above the Kidney Disease Improving Global Outcomes recommendation of <90 mmol/d for patients with CKD.

Compared with other studies of patients with similar levels of kidney function, our findings confirm the positive relation between sodium intake and systolic, but not diastolic, BP. In contrast, Koo et al. did not observe an association between systolic BP and 24-hour urinary sodium excretion in Korean patients, mainly with CKD stages 1 to 3. It is likely that this association is more readily apparent in severe than in mild to moderate stages of CKD because of the increase in salt sensitivity with CKD progression. Nevertheless, other factors certainly play a role, including baseline BP, age, race, comorbidities, and genetic background.
Our findings about urinary potassium excretion and BP contrast with those made in general populations and in hypertensive patients, as an inverse association of potassium intake (based on urine measurements) with BP levels has been reported in most of them.\textsuperscript{3,6,9,12} In patients with CKD, one study has reported that participants with higher urinary potassium excretion were more likely to have lower systolic BP,\textsuperscript{24} whereas others did not find this association,\textsuperscript{23,25} as ours did not. Why then would the relation between potassium intake and BP differ in patients with CKD? Many factors might explain the absence of an association between BP and urinary potassium in CKD. First, potassium homeostasis in CKD requires endocrine and ion transport adaptations to their distribution, different from distribution in the physiological state. In addition, extrarenal mechanisms of potassium elimination, in particular the gastrointestinal route, could become increasingly important as kidney function declines.\textsuperscript{45} Sandle \textit{et al.}\textsuperscript{46} observed an increase in rectal K+ secretion in patients with CKD, probably reflecting stimulation of an active K+ secretory process of uncertain mechanism. Even though serum aldosterone was normal in their patients with CKD, others have attributed this increase to secondary hyperaldosteronism.\textsuperscript{47} Second, the normal association between potassium intake and BP is almost certainly confounded by antihypertensive treatments, particularly the effects of renin-angiotensin-aldosterone system inhibitors and diuretics.\textsuperscript{48} More than 75\% of our CKD study population were receiving renin-angiotensin-aldosterone system inhibitors, and half of them diuretics. Diabetes and old age represent further independent factors contributing to the disturbance of potassium homeostasis in CKD.\textsuperscript{49} Third, dietary counseling for patients with CKD and prescription of oral potassium-binding drugs may help reduce, respectively, potassium intake and intestinal absorption.

A large body of evidence supports an interdependence between sodium and potassium in the pathogenesis of hypertension and suggests that the sodium-to-potassium ratio might be more relevant in...
determining BP than the assessment of each of them separately. In particular, meta-analyses of randomized clinical trials have shown either a more marked reduction in BP in response to an increase in potassium intake than a reduction in sodium intake or else an independent association between a reduction in 24-hour $uNa/K$ and a decrease in systolic BP after adjustment for potassium supplementation in meta-regression.

Moreover, $uNa/K$, assessed by 24-hour urine measurement, has been reported to be superior to urinary sodium or potassium alone in predicting cardiovascular endpoints. In our study, spot $uNa/K$ was not more informative than $uNa/Cr$ in terms of systolic and pulse pressure levels, although it was slightly more informative than $uNa/Cr$ as regards the efficacy of hypertension control. Further investigation is needed to clarify the clinical value of such findings.

To our knowledge, this study is the first to investigate the relation of spot urine sodium and potassium measurements to BP and hypertension control status in patients with CKD. Sensitivity analysis in our study suggests that spot urine assessment may be suitable for assessing sodium intake in epidemiological studies in CKD, which is important given the burden and potential issues associated with 24-hour urine collection. Furthermore, spot urine indices were modeled by using restricted cubic splines, which allowed clear appreciation of their nonlinearity. Finally, we were able to adjust the analyses for many potential confounders, including evidence of atherosclerotic disease and use of antihypertensive drugs.

This study has several limitations. First, we used single spot urine collection as a surrogate for daily sodium and potassium intake, which may reduce the strength of their association with BP. However, although this method may represent individual nutrient intake poorly, it is probably valid in cohort studies with large sample size. Second, reduced creatinine excretion with kidney function decline may have resulted in overestimation of $uNa/Cr$ and $uK/Cr$ ratios, and potential confounding in their association with BP. Nevertheless, this overestimation, similar for
Table 2. Sensitivity analyses: adjusted* variations in systolic blood pressure (in mm Hg) by quartiles of spot urine sodium-to-creatinine, potassium-to-creatinine, and sodium-to-potassium ratios and according to the type of urine measurements and the type of analysis considering the mean of 2 blood pressure readings

<table>
<thead>
<tr>
<th>Urine measurements</th>
<th>Mean of 2 blood pressure readings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spot urine</td>
</tr>
<tr>
<td>uNa/Cr (mmol/g)</td>
<td></td>
</tr>
<tr>
<td>Q1 &lt; 69.6</td>
<td>146</td>
</tr>
<tr>
<td>Q2 [69.6–102.3]</td>
<td>231</td>
</tr>
<tr>
<td>Q3 [102.3–142.7]</td>
<td>255</td>
</tr>
<tr>
<td>Q4 ≥142.7</td>
<td>220</td>
</tr>
</tbody>
</table>

| uK/Cr (mmol/g)     |           |          |               |                    |
| Q1 < 38.0          | 188       | Ref      | 191           | Ref               |
| Q2 [38.0–46.9]     | 213       | 0.38 (–2.26 to 3.02) | 198 | –0.44 (–1.98 to 1.11) | 214 | 0.20 (–2.09 to 2.50) | 415 | 0.89 (–0.74 to 2.52) |
| Q3 [46.9–61.1]     | 233       | –0.47 (–3.39 to 2.46) | 232 | –1.79 (–4.05 to 0.46) | 209 | 1.14 (–1.55 to 3.83) | 414 | 0.59 (–1.31 to 2.48) |
| Q4 ≥61.1           | 218       | –1.92 (–5.85 to 2.02) | 231 | –3.34 (–7.07 to 0.40) | 181 | 1.46 (–2.30 to 5.22) | 422 | –0.38 (–3.03 to 2.26) |

| uNa/K              |           |          |               |                    |
| Q1 < 1.5           | 167       | Ref      | 150           | Ref               |
| Q2 [1.5–2.2]       | 241       | 3.10 (0.17 to 6.04) | 239 | 2.88 (–0.75 to 6.11) | 220 | 1.77 (–0.80 to 4.34) | 417 | 1.77 (0.07 to 3.48) |
| Q3 [2.2–3.1]       | 232       | 4.38 (1.26 to 7.51) | 251 | 2.61 (–0.99 to 6.22) | 213 | 2.72 (–0.09 to 5.52) | 415 | 3.11 (1.21 to 5.00) |
| Q4 ≥3.1            | 212       | 4.84 (1.01 to 8.67) | 212 | 3.97 (–0.08 to 8.02) | 190 | 3.73 (0.16 to 7.31) | 415 | 3.98 (1.43 to 6.54) |

DBP, diastolic blood pressure; MAP, mean arterial blood pressure; PP, pulse pressure; Ref, reference; uK/Cr, urine potassium-to-creatinine ratio; uNa/Cr, urine sodium-to-creatinine ratio; uNa/K, urine sodium-to-potassium ratio.

*Model adjusted for age, gender, education level, estimated glomerular filtration rate, albuminuria category, history of diabetes, heart failure, dyslipidemia, body mass index, and number of antihypertensive drug classes.

both ratios, would not explain the specific associations of BP with sodium, but not potassium urinary excretion, and the risk of confounding was handled by adjusting for eGFR. Third, we used office BP, which may not always comply with standard procedures for accurate measurement, and thus is prone to white-coat effect and overestimates. Urinary sodium and potassium excretion are not related to the type of BP measurements; however, this should not have biased the observed associations. Fourth, data were missing for a number of second BP readings, and some covariates. Multiple imputation analysis was performed to allow the use of all data available and showed consistent results with the main analysis. Fifth, because our cohort mainly included Caucasian patients, these findings may not be generalizable to other ethnicities with different dietary intake patterns and genetic factors. Finally, the observational nature of the study does not allow any causal interpretation, and further investigation is needed to assess whether the cross-sectional associations observed in this study hold up longitudinally.

In conclusion, our study shows that high urinary sodium excretion, and hence high oral sodium intake, is associated with high BP in patients with moderate or severe CKD. In contrast, we failed to find an association with urinary potassium excretion. The uNa/K ratio thus does not appear to add anything to the study of the association between these electrolytes and BP, except perhaps that with uncontrolled hypertension. We suggest that spot urine samples are useful in assessing sodium intake in epidemiological studies in CKD. Further investigation is needed to address whether spot urine assessment can improve prediction of outcomes in CKD.

APPENDIX

List of Members of the CKD-REIN Study Group


DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We acknowledge the CKD-REIN study coordination staff for their efforts in setting up the CKD-REIN cohort: Elodie Spery, Sophie Renault, Reine Ketchemin, and all the clinical research associates. We thank Jo Ann Cahn for editing the English version. The French Institute of Health and Medical Research (Inserm) Institutional Review Board approved the study protocol, and all participants signed informed consents.

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Part of this study was presented as a poster during the American Society of Nephrology’s Kidney Week 2018 in San Diego, CA, USA, in October 23–28, 2018.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Patient characteristics according to their number of blood pressure readings.

Table S2. Mean (SD) systolic and diastolic blood pressure, mean arterial pressure, and pulse pressure according to quartiles of spot urine (A) sodium-to-creatinine, (B) potassium-to-creatinine, and (C) sodium-to-potassium ratios.

Table S3. Crude and adjusted variations in systolic and diastolic blood pressure, mean arterial pressure, and pulse pressure by quartiles of spot urine (A) sodium-to-creatinine, (B) potassium-to-creatinine, and (C) sodium-to-potassium ratios.

Table S4. Crude and adjusted odds ratios of hypertension status by quartiles of spot urine (A) sodium-to-creatinine, (B) potassium-to-creatinine, and (C) sodium-to-potassium ratios.

Table S5. Sensitivity analyses: crude variations in systolic blood pressure (in mm Hg) by quartiles of spot urine (A) sodium-to-creatinine, (B) potassium-to-creatinine, and (C) sodium-to-potassium ratios and according to the type of urine measurements and the type of analysis considering the mean of 2 blood pressure readings.

Strobe Statement.

Centers participating in the CKD-REIN Study.

REFERENCES


