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Proteinuria Modifies the Relationship Between Urinary Sodium Excretion and Adverse Kidney Outcomes: Findings From KNOW-CKD

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Introduction: High sodium intake is associated with increased proteinuria. Herein, we investigated whether proteinuria could modify the association between urinary sodium excretion and adverse kidney outcomes in patients with chronic kidney disease (CKD).

Methods: In this prospective observational cohort study, we included 967 participants with CKD stages G1 to G5 between 2011 and 2016, who measured 24-hour urinary sodium and protein excretion at baseline. The main predictors were urinary sodium and protein excretion levels. The primary outcome was CKD progression, which was defined as a ≥50% decline in the estimated glomerular filtration rate (eGFR) or the onset of kidney replacement therapy.

Results: During a median follow-up period of 4.1 years, the primary outcome events occurred in 287 participants (29.7%). There was a significant interaction between proteinuria and sodium excretion for the primary outcome ($P = 0.006$). In patients with proteinuria of <0.5 g/d, sodium excretion was not associated with the primary outcome. However, in patients with proteinuria of ≥0.5 g/d, a 1.0 g/d increase in sodium excretion was associated with a 29% higher risk of adverse kidney outcomes. Moreover, in patients with proteinuria of ≥0.5 g/d, the hazard ratios (HRs) (95% confidence intervals[CIs]) for sodium excretion of <3.4 and ≥3.4 g/d were 2.32 (1.50–3.58) and 5.71 (3.58–9.11), respectively, compared with HRs for patients with proteinuria of <0.5 g/d and sodium excretion of <3.4 g/d. In sensitivity analysis with 2 averaged values of sodium and protein excretion at baseline and third year, the results were similar.

Conclusion: Higher urinary sodium excretion was more strongly associated with an increased risk of adverse kidney outcomes in patients with higher proteinuria levels.

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Chronic kidney disease (CKD) is a serious public health problem, and according to the Global Burden of Disease Study 2017, the global prevalence (approximately 697.5 million cases) was 9.1%.[1] CKD is associated with an increased risk of hospitalization, cardiovascular events, and death. Moreover, the risk of adverse outcomes is higher in patients with more advanced CKD.[2] Therefore, correction of modifiable risk factors is important to delay CKD progression.

In addition to pharmaceutical interventions, lifestyle modifications are considered an important therapeutic strategy for managing CKD. In particular, salt restriction has been emphasized because of its harmful effects on kidney health. High salt intake is highly related to

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hypertension[3–5] and can suppress the response to renin-angiotensin-aldosterone system (RAAS) blockers, resulting in inadequately controlled blood pressure (BP) in patients with hypertension.[6,7] It also damages blood vessel walls through oxidative stress and inflammatory reactions.[8] Furthermore, high salt consumption causes fluid retention, thereby increasing BP and making it challenging to control BP.[9,10] In patients with CKD, excessive sodium intake is associated with increased urinary protein excretion.[11,12] Notably, salt restriction can enhance the proteinuria lowering effect of RAAS blockers.[13,14] Given such unfavorable effects of sodium, recent guidelines recommend limiting dietary sodium intake to <2.3 g (equivalent to salt intake of <5.0 g) per day in patients with CKD.[15,16]

Although there have been growing concerns regarding high sodium intake, studies on the relationship between urinary sodium excretion and CKD progression have shown conflicting results.[17] Recent studies by our cohort investigators and a Japanese study group showed that high urinary sodium excretion was associated with a significantly increased risk of CKD progression.[18,19] However, other studies showed no relationship between urinary sodium excretion and kidney function decline.[20–22] Notably, recent randomized controlled trials (RCTs) with salt restriction showed some positive results regarding BP control and changes in proteinuria; however, these studies were limited by small sample sizes and short-term observations.[23,24]

Given that studies with dietary interventions are challenged by many difficulties, mostly because of attrition and compliance issues, long-term studies with strict adherence to dietary prescriptions are not feasible.[25] Therefore, findings from prospective observation of long-term cohort studies can provide valuable information about the association between sodium intake and clinical outcomes. Given that high salt intake is significantly correlated with proteinuria and both salt and proteinuria adversely affect kidney function,[11,12,26] we wonder if the clinical implication of urinary sodium excretion with respect to CKD progression might differ depending on proteinuria level. Therefore, we addressed this issue using 24-hour urine collection, a gold standard measurement for urinary sodium, and protein excretion.

METHODS

Study Participants

The Korean Cohort Study for Outcome in Patients with CKD is a prospective nationwide cohort study. Patients aged between 20 and 75 years with CKD stages G1 to G5 who had not undergone kidney replacement therapy were enrolled in the study. Participants from the Korean Cohort Study for Outcome in Patients with CKD study voluntarily provided informed consent and were recruited from 9 university-affiliated tertiary care hospitals throughout Korea between 2011 and 2016. The protocol summary was registered at ClinicalTrials.gov (NCT01630486). In total, 2238 participants were included in the Korean Cohort Study for Outcome in Patients with CKD cohort. We excluded 31 participants who were lost to follow-up after their first visit and 5 participants with inadequate 24-hour urine volume (<500 ml). In addition, participancts without baseline demographic data including body mass index ($n = 2$), systolic BP ($n = 2$) and participants without baseline hemoglobin ($n = 2$), albumin ($n = 9$), phosphate ($n = 2$), or total cholesterol ($n = 5$) data were excluded. Moreover, participants without 24-hour urine data for protein ($n = 293$), sodium ($n = 39$), and potassium ($n = 875$) at baseline were excluded. We further excluded 6 participants with extreme urine sodium excretion (24-hour urine <20 mEq/d or >1000 mEq/d). Finally, 967 patients were included in the study (Figure 1).

Data Collection and Measurements

Baseline demographic data and medical history, including age, sex, education, economic status, smoking status, alcohol consumption, primary renal disease, history of hypertension, and diabetes, Charlson comorbidity index, and medication use were documented at enrollment. Anthropometric data, including height and body weight (BW), were recorded. BP measurements were performed during clinic visits after 5 minutes of rest, in a sitting position using an electronic sphygmomanometer. Dietary protein intake (DPI) was measured at baseline and was defined as the estimated DPI/BW (g/d/kg BW). Estimated DPI was calculated using the following formula: $6.25 \times$ (24-hour urinary urea [mg/d]/1000 + $0.03 \times$ BW [kg]) + (24-hour urinary protein [mg/d]/1000). The recommended level was a DPI of ≥ 0.8 g/d/kg BW.[27,28]

Blood samples were obtained after overnight fasting for laboratory measurements, including hemoglobin, creatinine, albumin, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and electrolytes. We evaluated urinary sodium and protein excretion using 24-hour urine collected at baseline. All participants were instructed to discard the first urine of the day and collect urine over the following 24 hours in standard containers. The total volume collected was measured. The 24-hour urine samples were repeatedly collected at the third year. Serum creatinine was measured using an isotope-dilution mass spectrometry–traceable method,

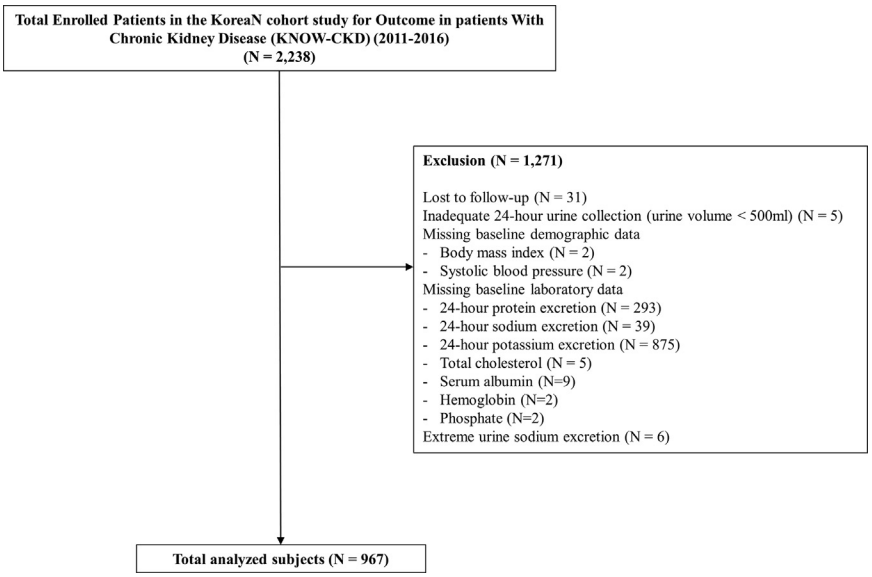

Figure 1. Flow diagram of the study cohort. KNOW-CKD, Korean Cohort Study for Outcome in Patients with CKD.

and the estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation.

Main Predictors

The main predictors of this study were the baseline 24-hour urinary sodium and protein excretion levels. Severe proteinuria was defined as a daily protein excretion of ≥0.5 g/d. We further assessed exposure measures using the average of 24-hour urinary sodium and protein excretion at baseline and the third year (Supplementary Figure S1). Measured 24-hour urinary sodium excretion was used to estimate the daily salt intake based on the assumption that >90% of all salt ingested was excreted through urine.[29,30] Significant urinary sodium excretion was defined as the participant's median sodium excretion of 3.4 g/d. The participants were divided into the following 4 groups based on the median concentrations of proteinuria of 0.5 g/d and sodium excretion of 3.4 g/d: low protein and low sodium excretion (group 1), low protein and high sodium excretion (group 2), high protein and low sodium excretion (group 3), and high protein and high sodium excretion (group 4).

Study Outcomes

The primary outcome of our study was the CKD progression, which was defined as a ≥50% decline in eGFR or the development of CKD G5 requiring kidney replacement therapy. Survival time was defined as the time from enrollment to the date of the primary outcome event occurrence. Patients who were lost to follow-up were censored at the time of their last examination. Furthermore, mortality outcome was analyzed according to urinary protein and sodium excretion. The study observations were closed on March 31, 2020. Patients with CKD G3 or higher were under close observation and were followed up at 1 month to 3 month intervals. If study outcome events occurred during the follow-up period, they were reported upon the occurrence of events by each participating center. The events were defined if at least 2 consecutive measurements of ≥50% eGFR decline were ascertained and the first day of occurrence was designated as the study end point. Then, Korean Cohort Study for Outcome in Patients with CKD investigators cross-checked among centers if the outcome events were true.

Statistical Analyses

Continuous variables are presented as means and standard deviations, whereas categorical variables are presented as counts and proportions. Variables with skewed distribution are presented in medians with interquartile ranges and compared using the Kruskal–Wallis test. The Kolmogorov–Smirnov test was used to confirm the normality of the distribution. First, we investigated the relationship among urinary sodium excretion, proteinuria, and other parameters using Pearson's correlation coefficient. The linear correlation between urinary sodium excretion and proteinuria was examined using multivariable linear regression analysis. Variables with a significance level of 0.1 in the univariate analysis were used for the multivariate analysis. Cox proportional hazard regression models were used after incremental adjustments to investigate the association between urinary sodium and protein excretion and the risk of primary outcomes. For primary outcome analysis of CKD progression, we employed cause-specific models, where death that

occurred before reaching the kidney outcome was considered a competing risk and thus censored. Model 1 presents the HR adjusted for participant's demographic, social, and medical characteristics, including age, sex, body mass index, smoking status (never, current, or former), primary renal disease, Charlson comorbidity index, DPI, and participating centers. Model 2 was further adjusted for systolic BP and laboratory parameters, including hemoglobin, phosphate, eGFR, albumin, total cholesterol, natural log-transformed 24-hour urinary potassium excretion, and natural log-transformed 24-hour urinary creatinine excretion. Model 3 was further adjusted for medications (diuretics, RAAS blockers, and calcium channel blockers) to fully adjust for confounding factors associated with adverse kidney outcomes. Adjusted cumulative incidence curves and cubic spline curves for the primary outcome events were employed. Cubic spline curves were employed using 4 knots, with the first knot as a reference. Statistical significance of nonlinearity was tested by comparing the spline curve with the linear curve and that of linearity was tested by comparing the linear curve with the model including only the covariates. Likelihood ratios tests were used for goodness-of-fit of both linear and nonlinear models. Further spline curves according to protein excretion subgroups were conducted to visualize the association between urinary sodium excretion and primary outcome. A sensitivity analysis was performed to test the robustness of our findings using multiple measures of urinary sodium and protein excretion. For this analysis, we used average values of 24-hour urinary sodium and protein excretion measured at baseline and the third year. Finally, we further analyzed the association of the primary outcomes with different cut-off values of urinary sodium excretion (4.0 g/d) and proteinuria (1.0 g/d). All statistical analyses were performed using STATA version 15. (Stata Corporation, College Station, TX, USA).

Ethics Statement

All study procedures were performed in accordance with the Declaration of Helsinki guidelines, and the study protocol was approved by the institutional review boards of the participating clinical centers. The centers participating in this study were as follows: Seoul National University Hospital (1104-089-359), Seoul National University Bundang Hospital (B-1106/129-008), Yonsei University Severance Hospital (4-2011-0163), Kangbuk Samsung Medical Center (2011-01-076), Seoul St Mary's Hospital (KC11OIMI0441), Gil Hospital (GIRBA2553), Eulji General Hospital (201105-01), Chonnam National University Hospital (CNUH-2011-092), and Pusan Paik Hospital (11-091).

RESULTS

Baseline Characteristics

The baseline characteristics of the 967 participants according to the 4 groups based on the 24-hour urinary sodium and protein excretions are presented in Table 1. The mean age was 55.4 ± 11.8 years, and 604 (62.5%) participants were men. The mean eGFR was 52.7 ± 29.7 ml/min per 1.73 m^2, and the median proteinuria was 0.56 (interquartile range, 0.19–1.57) g/d. The distribution of the 24-hour urinary sodium and protein excretion is shown in Supplementary Figure S2. Because 24-hour urinary protein excretion data showed a skewed distribution, natural logarithm transformation was performed in our analysis. Among patients with 24-hour urinary protein excretion of <0.5 g/d, BP and eGFR were higher in patients with sodium excretion of ≥3.4 g/d than in those with sodium excretion of <3.4 g/d. These findings were similar among patients with a 24-hour protein excretion of ≥0.5 g/d. Accordingly, the number of BP medications increased in patients with higher urinary excretion of protein and sodium. On the contrary, there were more patients without BP medications in lower protein and sodium excretion groups. Protein intake, assessed by DPI was higher in patients with higher urinary sodium excretion.

Relationship Between Urinary Sodium Excretion and Proteinuria

Next, we examined the correlation among 24-hour urinary sodium excretion, proteinuria, and other key parameters. We found that urinary sodium excretion positively correlated with proteinuria ($\gamma = 0.133$; $P < 0.001$), systolic BP ($\gamma = 0.075$; $P = 0.019$), and eGFR ($\gamma = 0.149$; $P < 0.001$). Multiple linear regression analysis after adjustment for these factors showed that 24-hour sodium excretion was independently associated with proteinuria (coefficient = 0.119; $P = 0.001$). In other words, 24-hour urinary sodium excretion increased by 0.82 g per a 1 g increase in proteinuria (Supplementary Table S1 and Supplementary Figure S3).

Association of Urinary Sodium and Protein Excretion With Adverse Kidney Outcomes

During 3948.2 person-years of follow-up (median, 4.1 years), the primary outcome occurred in 287 (29.7%) participants (72.7 per 1000 person-years). The number of event occurrences in groups ranging from 1 to 4 were 33 (13.8 %), 18 (8.5 %), 109 (45.0 %), and 127 (446.5 %), with the corresponding incidence rates of 30.5, 17.6, 129.6, and 126.8 per 1000 person-years (Table 2), respectively. Moreover, death events occurred in 9 (3.1%), 11 (5.2 %), 19 (7.9%), and 10 (3.7%) in groups ranging from 1 to 4, with the

Table 1. Baseline characteristics of patients according to the 24-hour urinary sodium and protein excretion

		24-hour urinary protein excretion			
		< 0.5 g/d		≥ 0.5 g/d	
		24-h urinary sodium excretion			
		Low <3.4 g/d	High ≥3.4 g/d	Low <3.4 g/d	High ≥3.4 g/d
Characteristics	**Total (N = 967)**	**(n = 239)**	**(n = 213)**	**(n = 242)**	**(n = 273)**
Demographic data					
Age, y	55.4 ± 11.8	54.4 ± 13.6	56.1 ± 11.0	54.8 ± 11.5	56.2 ± 10.9
Female, *n* (%)	363 (37.5)	117 (49.0)	64 (30.0)	102 (42.1)	80 (29.3)
Systolic BP, mm Hg	127.1 ± 15.3	124.8 ± 13.4	125.7 ± 14.2	127.6 ± 16.2	129.5 ± 16.5
Diastolic BP, mm Hg	76.8 ± 11.0	76.6 ± 10.3	76.8 ± 10.9	75.9 ± 10.5	77.9 ± 12.0
Body mass index, kg/m^2	24.8 ± 3.4	23.9 ± 3.2	25.4 ± 3.4	24.2 ± 3.2	25.7 ± 3.3
Economic status, *n* (%)					
Low	233 (24.6)	56 (23.5)	40 (19.2)	57 (23.8)	80 (30.4)
Middle	487 (51.3)	122 (51.3)	104 (50.0)	132 (55.0)	129 (49.0)
High	229 (24.1)	60 (25.2)	64 (30.8)	51 (21.3)	54 (20.5)
Primary renal disease, *n* (%)					
Diabetic nephropathy	268 (27.7)	35 (14.6)	34 (16.0)	104 (43.0)	95 (34.8)
Hypertensive nephropathy	187 (19.3)	54 (22.6)	58 (27.2)	23 (9.5)	52 (19.0)
Glomerulonephritis	291 (30.1)	57 (23.8)	43 (20.2)	97 (40.1)	94 (34.4)
Polycystic kidney disease	126 (13.0)	70 (29.3)	45 (21.1)	5 (2.1)	6 (2.2)
Others	95 (9.8)	23 (9.6)	33 (15.5)	13 (5.4)	26 (9.5)
Comorbidities					
Hypertension, *n* (%)	925 (95.7)	218 (91.2)	199 (93.4)	238 (98.3)	270 (98.9)
Diabetes, *n* (%)	374 (38.7)	60 (25.1)	69 (32.4)	115 (47.5)	130 (47.6)
Myocardial infarction, *n* (%)	26 (2.7)	8 (3.3)	3 (1.4)	6 (2.5)	9 (3.3)
Congestion heart failure, *n* (%)	19 (2.0)	3 (1.3)	4 (1.9)	3 (1.2)	9 (3.3)
Cerebrovascular disease, *n* (%)	56 (5.8)	11 (4.6)	17 (8.0)	14 (5.8)	14 (5.1)
DPI ≥ 0.8g/d/kg, *n* (%)	718 (74.3)	146 (61.1)	183 (85.9)	146 (60.3)	243 (89.0)
Laboratory parameters					
Hemoglobin, g/dl	12.9 ± 2.1	13.0 ± 1.9	13.7 ± 1.9	12.3 ± 2.0	12.9 ± 2.2
Sodium, mmol/l	140.8 ± 2.5	140.8 ± 2.4	140.8 ± 2.3	140.5 ± 2.6	141.0 ± 2.7
Potassium, mmol/l	4.7 ± 0.6	4.6 ± 0.5	4.6 ± 0.5	4.8 ± 0.6	4.7 ± 0.6
Chloride, mmol/l	105.2 ± 3.5	104.8 ± 3.1	104.5 ± 3.2	105.3 ± 3.7	105.8 ± 3.8
Phosphate, mg/dl	3.7 ± 0.7	3.6 ± 0.6	3.4 ± 0.6	3.9 ± 0.8	3.7 ± 0.6
eGFR, ml/min per 1.73 m^2	52.7 ± 29.7	58.3 ± 30.2	62.0 ± 27.2	42.6 ± 27.6	49.5 ± 29.7
Albumin, g/dl	4.2 ± 0.4	4.4 ± 0.3	4.4 ± 0.3	4.0 ± 0.5	4.0 ± 0.5
Total cholesterol, mg/dl	172.7 ± 40.4	168.0 ± 37.5	173.1 ± 34.0	175.7 ± 44.1	173.9 ± 43.8
Triglyceride, mg/dl	161.5 ± 100.4	145.2 ± 94.2	151.7 ± 83.9	165.7 ± 104.6	179.6 ± 110.6
HDL-C, mg/dl	48.3 ± 14.5	49.3 ± 15.8	48.6 ± 13.4	48.2 ± 15.0	47.3 ± 13.9
LDL-C, mg/dl	96.1 ± 32.2	91.3 ± 29.1	99.3 ± 29.7	97.9 ± 34.1	96.1 ± 34.7
Urinary parameters					
Urine volume, ml	1840.0 (1450.0–2250.0)	1535.0 (1100.0–2000.0)	2000.0 (1630.0–2495.0)	1595.0 (1285.0–1900.0)	2080.0 (1800.0–2600.0)
Urine protein, g/d	0.56 (0.19–1.58)	0.17 (0.10–0.28)	0.18 (0.11–0.36)	1.34 (0.73–2.47)	1.67 (0.90–3.82)
Urine creatinine, g/d	1.17 (0.89–1.47)	0.99 (0.78–1.28)	1.33 (1.08–1.61)	1.00 (0.78–1.25)	1.30 (1.05–1.60)
Urine sodium, g/d	3.40 (2.46–4.51)	2.44 (1.79–2.88)	4.46 (3.86–5.34)	2.50 (1.86–2.97)	4.53 (3.90–5.47)
Urine potassium, g/d	1.95 (1.44–2.57)	1.59 (1.25–2.11)	2.34 (1.77–2.87)	1.56 (1.17–2.11)	2.30 (1.87–2.96)
Urine chloride, g/d	2.25 (3.78–6.93)	3.78 (2.87–4.72)	6.93 (6.19–8.32)	3.87 (2.77–4.55)	6.93 (6.01–8.65)
Use of medications					
RAAS blocker, *n* (%)	832 (86.0)	195 (81.6)	175 (82.2)	219 (90.5)	243 (89.0)
Diuretics, *n* (%)	309 (32.0)	55 (23.0)	62 (29.1)	93 (38.4)	99 (36.3)
Calcium channel blockers, *n* (%)	392 (40.5)	83 (34.7)	80 (37.6)	99 (40.9)	130 (47.6)
Number of BP medications, *n* (%)					
0	102 (10.5)	42 (17.6)	31 (14.6)	14 (5.8)	15 (5.5)
1	312 (32.3)	81 (33.9)	66 (31.0)	83 (34.3)	82 (30.0)
2	272 (28.1)	60 (25.1)	63 (29.6)	67 (27.7)	82 (30.0)
3	185 (19.1)	39 (16.3)	37 (17.4)	50 (20.7)	59 (21.6)
≥4	96 (9.9)	17 (7.1)	16 (7.5)	28 (11.6)	35 (12.8)

BP, blood pressure; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RAAS, renin-angiotensin-aldosterone system.
Data are presented as mean ± SD, number (percentage), or median (interquartile range).

Table 2. Outcome event rates according to the 24-hour urinary sodium and protein excretion

Outcomes	Total (N = 967)	Proteinuria <0.5 g/d Urine sodium <3.4 g/d (n = 239)	Proteinuria <0.5 g/d Urine sodium ≥3.4 g/d (n = 213)	Proteinuria ≥0.5 g/d Urine sodium <3.4 g/d (n = 242)	Proteinuria ≥0.5 g/d Urine sodium ≥3.4 g/d (n = 273)
Primary outcome					
Number of person-y	3948.2	1083.6	1021.7	841.2	1001.8
Number of events (%)	287 (29.7)	33 (13.8)	18 (8.5)	109 (45.0)	127 (46.5)
Incidence rate	72.7	30.5	17.6	129.6	126.8
All-cause mortality					
Number of person-y	4648.7	1160.6	1055.9	1117.8	1314.4
Number of events (%)	49 (5.1)	9 (3.1)	11 (5.2)	19 (7.9)	10 (3.7)
Incidence rate	10.5	7.8	10.4	17.0	7.6

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
The primary outcome was defined as CKD progression, which was defined as the first occurrence of a 50% decline in eGFR from the baseline value, or the onset of kidney failure with replacement therapy, and the analysis was performed using a cause-specific model by censoring the death event that occurred before reaching the kidney outcome.

corresponding incidence rates of 7.8, 10.4, 17.0, and 7.6 per 1000 person-years, respectively.

In the Cox proportional hazard model, high sodium excretion was associated with a higher risk of the primary outcomes (Table 3). There was a significant interaction between proteinuria and sodium excretion for adverse kidney outcomes (P = 0.006). We explored this association separately depending on the proteinuria level. In patients with proteinuria of <0.5 g/d, sodium excretion was not associated with the primary outcome (adjusted HR per 1.0 g/d of sodium excretion, 1.03; 95% CI, 0.76–1.40). In addition, the risk of kidney outcomes did not differ between patients with sodium excretion of <3.4 and ≥3.4 g/d (HR, 1.11; 95% CI, 0.60–2.07) (Table 4). In contrast, when proteinuria was ≥0.5 g/d, the HR associated with 1.0 g/d of sodium excretion was 1.29 (95% CI, 1.15–1.46). Moreover, in patients with proteinuria of ≥0.5 g/d, the HRs (95% CIs) for sodium excretion of <3.4 and ≥3.4 g/d were 2.32 (1.50–3.58), and 5.71 (3.58–9.11), respectively, compared with HRs for patients with proteinuria of <0.5 g/d and sodium excretion of <3.4 g/d (Table 4). In the cumulative incidence curve analysis, the cumulative primary outcome was significantly higher in group 3 and 4 compared with the other groups (Figure 2). Further cubic spline curves showed a linear association of urinary sodium excretion with adverse kidney outcome (Supplementary Figure S4). However, this relationship was observed only for patients with proteinuria ≥0.5 g/d (Supplementary Figure S5). We analyzed risk of mortality according to proteinuria and sodium excretion but the HRs did not differ among the 4 groups (Supplementary Table S2).

Table 3. Hazard ratios for primary outcomes based on the baseline 24-hour urinary sodium and hazard ratio per 1.0g/d of urinary sodium excretion

Primary outcome	HR (95% CI)	P value
Multivariable adjusted[a] without proteinuria	1.22 (1.10–1.36)	<0.001
Multivariable adjusted with proteinuria	1.18 (1.06–1.32)	0.003

HR per 1.0 g/d of urinary sodium excretion	Proteinuria <0.5 g/d		Proteinuria ≥0.5 g/d	
	HR (95% CI)	P value	HR (95% CI)	P value
	1.03 (0.76–1.40)	0.852	1.29 (1.15–1.46)	<0.001

BMI, body mass index; CCB, calcium channel blocker; CCI, charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAAS, renin-angiotensin-aldosterone system.
[a]The multivariable model was adjusted for age, sex, BMI, smoking history, systolic blood pressure, primary renal disease, CCI, DPI, hospital center, hemoglobin, phosphate, eGFR, albumin, total cholesterol, natural log-transformed 24-hour urine potassium, natural log-transformed 24-hour urine creatinine, and medications, including RAAS blockers, CCB, and diuretics.
The primary outcome was defined as CKD progression, which was defined as the first occurrence of a 50% decline in eGFR from the baseline value, or the onset of kidney failure with replacement therapy, and the analysis was performed using a cause-specific model by censoring the death event that occurred before reaching the kidney outcome.

Sensitivity Analyses

We performed a sensitivity analysis in 465 patients with 2 average measurements of 24-hour urinary sodium and protein excretion at baseline and the third year. In line with the primary analysis, groups 3 and 4 had a 4.8-fold (HR, 4.77; 95% CI, 2.00–11.38) and a 12.6-fold (HR, 12.6; 95% CI, 4.91–33.34) higher risk of the primary outcome, respectively, than group 1. The risk did not differ between groups 1 and 2 (Table 5). Further sensitivity analysis was performed using different cut-off values of baseline 24-hour urine sodium. This cut-off was determined by a cubic spline curve showing that the risk began to increase from the point of 24-hour urinary sodium excretion of ≥4.0 g/d (Supplementary Figure S4). In this analysis, a higher proteinuria cut-off of 1.0 g/d was used. The results showed a significantly higher risk of primary outcomes in groups 3 and 4 than in group 1 (Supplementary Table S3 and Supplementary Table S4).

DISCUSSION

In this study, we investigated the association of 24-hour urinary sodium and protein excretion with the risk of adverse kidney outcomes. There was a significant positive interaction between 24-hour urinary

Table 4. Hazard ratios for primary outcome based on baseline 24-hour urinary sodium and protein excretion

	24-hour urine protein and sodium excretion category							
	Proteinuria <0.5 g/d Urine sodium <3.4 g/d		Proteinuria <0.5 g/d Urine sodium ≥3.4 g/d		Proteinuria ≥0.5 g/d Urine sodium <3.4 g/d		Proteinuria ≥0.5 g/d Urine sodium ≥3.4 g/d	
Models	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 1	Reference		0.69 (0.38–1.24)	0.213	4.22 (2.77–6.42)	<0.001	5.82 (3.82–8.88)	<0.001
Model 2	Reference		1.19 (0.64–2.20)	0.577	2.33 (1.51–3.59)	<0.001	5.94 (3.73–9.48)	<0.001
Model 3	Reference		1.11 (0.60–2.07)	0.730	2.32 (1.50–3.58)	<0.001	5.71 (3.58–9.11)	<0.001

BMI, body mass index; CCB, calcium channel blocker; CCI, charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAAS, renin-angiotensin-aldosterone system.
Model 1: age, sex, BMI, smoking history, primary renal disease, CCI, DPI, and hospital center.
Model 2: model 1 plus systolic blood pressure and laboratory parameters, including hemoglobin, phosphate, eGFR, albumin, total cholesterol, natural log 24-hour urine potassium, and natural log 24-hour urine creatinine.
Model 3: model 2 plus medications, including RAAS blockers, CCB, and diuretics.
The primary outcome was defined as CKD progression, which was defined as the first occurrence of a 50% decline in eGFR from the baseline value, or the onset of kidney failure with replacement therapy, and analysis was performed using a cause-specific model by censoring the death event that occurred before reaching the kidney outcome.

sodium and protein excretion. We found that sodium excretion was not associated with adverse kidney outcomes in patients with proteinuria of <0.5 g/d. However, this association was significant in patients with proteinuria of ≥0.5 g/d. In patients with higher proteinuria, the magnitude of the HR was greater in those with urinary sodium excretion of ≥3.4 g/d than in those with sodium excretion of <3.4 g/d. Additional analysis of the average sodium and protein excretion also confirmed these findings. Our findings suggest that high sodium excretion may be more meaningful, particularly in the presence of severe proteinuria with respect to adverse kidney outcomes.

Previous studies have shown that high salt intake is significantly related to elevated BP and an increased risk of cardiovascular events, including congestive heart failure, myocardial infarction, and stroke.[4,5,31] Given that cardiovascular events are the leading cause of death in patients with CKD, salt restriction is the first-line lifestyle modification in these patients. Notably, most studies on the association between salt intake and clinically hard outcomes are observational studies and there have been few RCTs on this issue. Most RCTs to date have examined the effects of salt restriction on BP control, and long-term RCTs on the effects of dietary intervention on cardiovascular disease and mortality are scarce. Although several meta-analyses favored lower sodium intake with respect to cardiovascular events,[22,32] these were based on combined cohort studies and *post hoc* analyses of RCTs on BP control that reported cardiovascular outcomes and death. Unfortunately, nephrologists are facing the same debate in the field of cardiology because the causal relationship between salt intake and adverse kidney outcomes remains controversial in patients with CKD.[17–21,33] Nevertheless, many guidelines for CKD care have adopted the

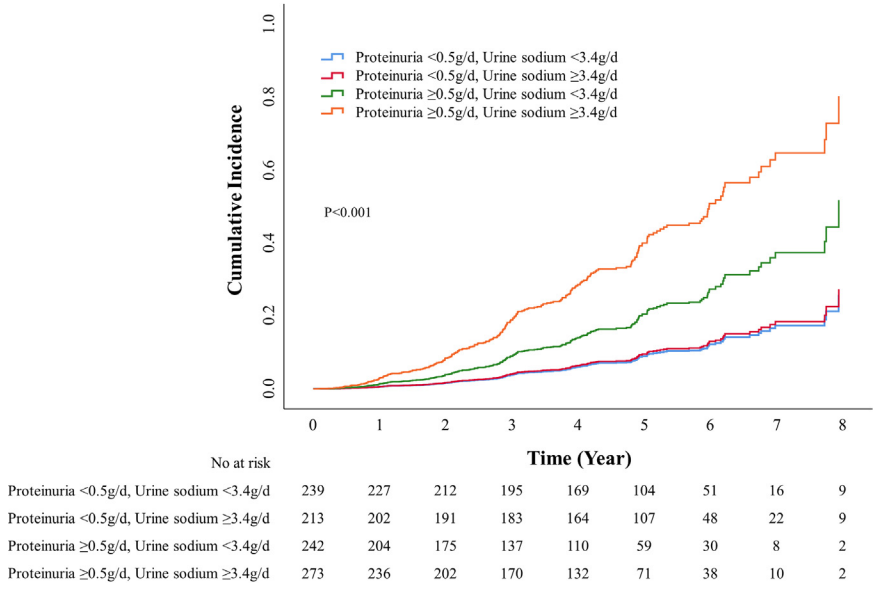

Figure 2. Cumulative incidence curve for primary outcomes according to the baseline 24-hour urinary sodium and protein excretion.

Table 5. Hazard ratios for the primary outcomes based on the 2 average measurements of the mean 24-hour urinary sodium and protein excretion

	24-hour urine protein and sodium excretion category							
	Proteinuria <0.5 g/d Urine sodium <3.4 g/d		Proteinuria <0.5 g/d Urine sodium ≥3.4 g/d		Proteinuria ≥0.5 g/d Urine sodium <3.4 g/d		Proteinuria ≥0.5 g/d Urine sodium ≥3.4 g/d	
Models	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sensitivity Analysis[a]								
Model 1	Reference		0.58 (0.17–1.99)	0.386	6.77 (2.84–16.13)	<0.001	10.47 (4.26–25.70)	<0.001
Model 2	Reference		0.84 (0.23–3.03)	0.784	4.95 (2.10–11.66)	<0.001	12.51 (4.89–32.00)	<0.001
Model 3	Reference		0.72 (0.20–2.55)	0.606	4.77 (2.00–11.38)	<0.001	12.60 (4.91–32.34)	<0.001

BMI, body mass index; CCB, calcium channel blocker; CCI, charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAAS, renin-angiotensin-aldosterone system.
[a]Sensitivity analysis: Mean urine sodium excretion was calculated using the average urine sodium excretion at baseline and 3 years later.
Model 1: age, sex, BMI, smoking history, primary renal disease, CCI, DPI, and hospital center.
Model 2: model 1 plus systolic blood pressure and laboratory parameters, including hemoglobin, phosphate, eGFR, albumin, total cholesterol, natural log of average 24-hour urine potassium, and natural log of average 24-hour urine creatinine.
Model 3: model 2 plus medications, including RAAS blockers, CCB, and diuretics.
The primary outcome was defined as CKD progression, which was defined as the first occurrence of a 50% decline in eGFR from the baseline value, or the onset of kidney failure with replacement therapy, and the analysis was performed using a cause-specific model by censoring the death event that occurred before reaching the kidney outcome.

recommendation of salt restriction, as suggested by the World Health Organization and other European and American cardiology guidelines.[16,34,35]

It is unclear why many observational studies have yielded conflicting results. One possible explanation for these discrepant findings is errors in the measurement of sodium intake. In clinical practice, questionnaires, spot urine samples, and single 24-hour urine samples are used to assess sodium intake. However, these methods have several limitations that lead to measurement errors. Although questionnaires can assess a participant's long-term dietary intake, they can inaccurately estimate the sodium intake of all nutrients and foods.[36,37] In addition, formulas such as Kawasaki, Tanaka, and INTERSALT are commonly used to calculate sodium intake based on spot urine sodium; however, these methods are biased with overestimation at lower levels and underestimation at higher levels of sodium intake.[38,39] Because >90% of ingested salt is eliminated by the kidney,[29,30] 24-hour urinary sodium excretion has been the gold standard for estimating salt intake. However, owing to the high variability of salt consumption, this method also has a limitation in evaluating the dietary habits of individual patients by a single urine collection.[40] In fact, sodium intake or excretion may be confounded by other factors such as proteinuria severity, protein intake, or the use of diuretics. Nevertheless, our study has the strength of using 24-hour urinary sodium excretion to estimate sodium intake. In support of our findings, the Chonic Renal Insufficiency Cohort Study investigators also showed that higher urinary sodium excretion using 24-hour urine collection was associated with significantly increased risk of CKD progression.[41] Furthermore, we used the average of 2 measurements of the 24-hour urinary sodium and protein excretion to reduce individual variability and enhance the accuracy of sodium intake. We believe that our analytical approach can reveal the association between urinary sodium and protein excretion and adverse kidney outcomes.

Proteinuria may modify the association between sodium intake and kidney outcomes. In the Modification of Diet in Renal Disease study, stratified analysis by proteinuria and sodium excretion showed that higher urine sodium was associated with an increased risk of kidney failure in patients with baseline proteinuria of <1 g/d and lower risk of kidney failure in those with baseline proteinuria of ≥1 g/d when urinary sodium excretion was <3 g/d.[42] In addition, in the *post hoc* analysis of the Ramipril Efficacy in Nephropathy trials, an increase in dietary sodium intake per 100 mmol/g was associated with a 61% increased risk of kidney failure requiring kidney replacement therapy. However, this association was markedly attenuated and became nonsignificant after adjusting for proteinuria.[43] Interestingly, these findings are not in agreement with our study. We showed that in patients with proteinuria of ≥0.5 g/d, sodium excretion was synergistically associated with a significantly increased risk of adverse kidney outcomes, whereas this association was not seen when proteinuria was <0.5 g/d. The discrepant findings among studies can be explained by greater salt sensitivity in East Asians compared to that in Western Caucasians.[44] Generally, Asians consume more salt than Western populations,[45] and there is evidence that the increased frequency of salt sensitivity in Japanese is partly related to increased frequencies of variants in some genes such as *RAS*.[46] Our findings can be supported by the findings from the large-scale, epidemiological Prospective Urban Rural Epidemiology study, showing that the association between systolic BP and sodium intake was the strongest for sodium excretion of >5.0 g/d and this association was weaker when Chinese individuals were excluded.[3,47] Therefore, given that patients with CKD are more salt-sensitive,[48] patients

with higher sodium and protein excretion are more likely to have higher BP, resulting in more kidney injury.

Although the causality is uncertain, the harmful association of salt with adverse kidney outcomes can be explained by several mechanisms, as previously proposed. High salt intake increases BP and proteinuria by activating the RAAS, which attenuates the proteinuria lowering effects of RAAS blockers.[7,49] Moreover, high salt intake increases glomerular capillary pressure, generates reactive oxygen species, and promotes inflammation of local tissues and endothelial dysfunction.[9] All of these mechanisms increase proteinuria and eventually deteriorate kidney function. There is also experimental evidence that dietary salt directly causes kidney damage by overexpressing transforming growth factor-beta, which ultimately leads to kidney fibrosis.[50,51]

Our study has several limitations. First, because this study is an observational study, the causality is uncertain and potential confounding factors might not be completely controlled. In addition, there were substantial missing data for 24-hour urinary potassium excretion, which might cause selection bias. However, this study included patients with CKD alone, employed rigorously adjusted models, and showed consistent findings using various analytical methods. Second, a single measurement of 24-hour urinary sodium excretion may not adequately reflect the general dietary pattern. Multiple 24-hour urine collections can minimize measurement errors; however, this method is burdensome and time-consuming. Nevertheless, we performed a sensitivity analysis using 2 measurements of sodium excretion at baseline and the third year and found a similar association with the primary analysis. Third, because 24-hour urine collection is time-consuming, patients might not follow the standard collection protocol. Our research nurses deliberately explained urine collection and informed the participants to collect every drop of urine over 24 hours. Fourth, we did not perform detailed dietary surveys such as 24-hour recall and food questionnaires; thus, we could not adjust for other dietary factors. However, these methods cannot account for day-to-day variation and require multiple surveys to accurately assess diet patterns.[37] Moreover, 24-hour urinary excretion is a more accurate measure of salt intake than dietary surveys. Lastly, there are vast differences in salt intake and dietary patterns worldwide. Therefore, the inclusion of Koreans alone may limit the generalizability of our findings to other racial and ethnic groups.

In conclusion, high sodium excretion is significantly associated with an increased risk of adverse kidney outcomes in patients with CKD. This association was not observed in patients with lower proteinuria but was more prominent in those with higher proteinuria. Our findings provide new insights into the relationship between salt intake and kidney outcomes in clinical practice.

DISCLOSURE

All the authors declared no competing interests.

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Data Availability Statement

The data are not publicly available because the ownership belongs to Seoul National University Hospital Medical Research Cooperation Center. However, the data will be shared on reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

The authors' responsibilities were as follows: research idea and study design were done by HJK and SHH; data acquisition was done by HJK, SKP, YHK, SAS, YYH, and K-HO; data analysis/interpretation were conducted by HJK, JTP, T-HY, S-WK, and SHH; statistical analysis was performed by HJK, C-YJ, and HWK; writing was done by HJK; supervision or mentorship was done by JTP, T-HY, S-WK, and SHH. All authors read the draft and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementry File (PDF)

Figure S1. Study design concept of the mean urine sodium excretion and patient flow diagram.

Figure S2. Distribution of the 24-hour urinary sodium and protein excretion. (a) The distribution of the 24-hour urinary sodium excretion. (b) The distribution of the 24-hour urinary protein excretion.

Figure S3. A scatter plot for the association between 24-hour urinary sodium and protein excretion.

Figure S4. Association of 24-hour urinary sodium excretion with the hazard ratio of the primary outcome.

Figure S5. Association of 24-hour urinary sodium excretion with the hazard ratio of the primary outcome according to subgroups. (a) urinary protein excretion $<$ 0.5 g/d (b) urinary protein excretion $\geq$0.5 g/d.

Table S1. Correlation analysis and multiple linear regression analysis of variables significantly associated with indices of 24-hour urinary sodium.

Table S2. Hazard ratios for death outcomes based on baseline 24-hour urinary sodium and protein excretion

Table S3. Hazard ratios for primary outcomes based on different cut-off values of the baseline 24-hour protein excretion.

Table S4. Hazard ratios for primary outcomes based on different cut-off values of the baseline 24-hour urinary sodium and protein excretion.

STORBE Statement.

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