Urinary Sodium Is a Potent Correlate of Proteinuria: Lessons from the Chronic Renal Insufficiency Cohort Study

Matthew R. Weir[a] Raymond R. Townsend[b] Jeffrey C. Fink[a] Valerie Teal[b]
Stephen M. Sozio[c] Cheryl A. Anderson[c] Lawrence J. Appel[c] Sharon Turban[c]
Jing Chen[d] Jiang He[d] Natasha Litbarg[e] Akinlolu Ojo[f] Mahboob Rahman[g]
Leigh Rosen[b] Susan Steigerwalt[h] Louise Strauss[g] Marshall M. Joffe[b]
on behalf of the CRIC Study Investigators

[a]University of Maryland School of Medicine, Baltimore, Md., [b]University of Pennsylvania, Philadelphia, Pa.,
[c]Johns Hopkins Medical Institutions, Baltimore, Md., [d]Tulane University School of Medicine, New Orleans, La.,
[e]University of Illinois School of Medicine, Chicago, Ill., [f]University of Michigan School of Medicine, Ann Arbor,
Mich., [g]Case Western Reserve School of Medicine, Cleveland, Ohio, and [h]St. Claire Specialty Center, Lakewood,
Wash., USA

Abstract

Background: While higher blood pressure is known to increase proteinuria, whether increased dietary sodium as estimated from 24-hour urinary excretion correlates with increased proteinuria in patients with chronic kidney disease (CKD) is not well studied. **Methods:** We measured 24-hour urinary sodium, potassium and protein excretion in 3,680 participants in the Chronic Renal Insufficiency Cohort study, to determine the relationship between urinary sodium and potassium and urinary protein excretion in patients with CKD. We stratified our data based on the presence or absence of diabetes given the absence of any data on this relationship and evidence that diabetics had greater urinary protein excretion at nearly every level of urinary sodium excretion. Multiple linear regressions were used with a stepwise inclusion of covariates such as systolic blood pressure, demographics, hemoglobin A1c and type of antihypertensive medications to evaluate the relationship between urinary electrolyte excretion and proteinuria. **Results:** Our data demonstrated that urinary sodium (+1 SD above the mean), as a univariate variable, explained 12% of the variation in proteinuria ($\beta = 0.29$, $p < 0.0001$), with rising urinary sodium excretion associated with increasing proteinuria. The significance of that relationship was only partially attenuated with adjustment for demographic and clinical factors and the addition of 24-hour urinary potassium to the model ($\beta = 0.13$, $R^2 = 0.35$, $p < 0.0001$). **Conclusions:** An understanding of the relationship between these clinical factors and dietary sodium may allow a more tailored approach for dietary salt restriction in patients with CKD.

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Introduction

Data from observational epidemiological studies and randomized controlled clinical trials demonstrate an association between dietary sodium intake and increased

Matthew R. Weir, MD
Division of Nephrology, University of Maryland School of Medicine Medical Center
22 S. Greene Street, Room N3W143
Baltimore, MD 21201 (USA)
E-Mail mweir@medicine.umaryland.edu

blood pressure, with few exceptions [1–5]. Moreover, in small clinical studies in patients with diabetic and nondiabetic kidney disease and proteinuria, there is evidence that increasing dietary salt intake offsets both the antihypertensive and antiproteinuric effect of drugs that block the renin-angiotensin system [6, 7], whether used alone or in conjunction with thiazide diuretics [7]. The influence of other clinical and demographic factors which may affect the relationship between dietary salt and proteinuria has also not been well studied.

Higher dietary salt intake may affect the kidneys through both blood pressure- dependent and blood pressure-independent effects [8, 9]. Although the mechanisms underlying the direct effect of dietary salt on the kidney are not well understood, experimental studies indicate that there may be a relationship between salt and endothelial dysfunction, primarily through an increase in oxidative stress [10], with less production of endogenous nitric oxide [11]. Structural changes of vascular beds in the brains of spontaneously hypertensive rats are also affected by dietary salt, independent of any change in systemic blood pressure [12].

Given the known relationships between increasing dietary salt and increasing blood pressure, particularly in individuals with chronic kidney disease (CKD), and the evidence from small clinical studies indicating that increasing dietary sodium intake offsets both the antihypertensive and antiproteinuric effects of drugs that block the renin-angiotensin system, it is important to understand the contribution of demographics, other medical comorbidities and antihypertensive treatment to the relationship between this important dietary electrolyte and proteinuria in a large cohort of patients with CKD. Thus, we performed multiple linear regressions in a large, well-characterized cohort to examine the possible influence of plausible demographic and clinical variables and antihypertensive treatment on the relationship between urinary sodium and 24-hour urinary protein excretion. These observations may be particularly important in formulating health care recommendations regarding diet in specific populations of individuals with CKD.

Methods

Study Population

The Chronic Renal Insufficiency Cohort (CRIC) study included a racially and ethnically diverse group of adults 21–74 years of age with both diabetic and nondiabetic kidney disease. Details on the assembly of the cohort are described elsewhere [13]. Inclusion in the CRIC study was based on age-specific estimated glomerular filtration rate (eGFR) levels as follows: eGFR of 20–70 ml/min/1.73 m^2 for participants aged 21–44 years, 20–60 ml/min/1.73 m^2 for participants aged 45–64 and 20–50 ml/min/1.73m^2 for participants aged 65–74. A total of 3,939 participants were recruited into the CRIC study, 3,680 of whom had complete 24-hour urine collections. CRIC participants were recruited between June 2003 and March 2007 from 13 sites and 7 centers in the USA (Baltimore, Md.; Philadelphia, Pa.; Cleveland, Ohio; Ann Arbor/Detroit, Mich.; Chicago, Ill.; New Orleans, La., and Oakland/San Francisco, Calif.).

Procedures

At each CRIC study visit, several core measurements were ascertained and have been described elsewhere [13]. Most pertinent to this study, three brachial blood pressure measures were obtained in the sitting position after at least 5 min of quiet rest by trained and certified staff according to a standard protocol. A Tyco aneroid sphygmomanometer was used, with cuff size based on the participant's arm circumference. Participants were advised to refrain from coffee, tea or alcohol intake, cigarette smoking and vigorous exercise for at least 30 min before their examination. All blood pressure observers were certified for the blood pressure measurement protocol.

A 24-hour urine collection for protein and creatinine was obtained from each participant on the day of the blood pressure measures. Protocol-specified laboratory measurements were obtained from participants at each annual visit. Laboratory testing was performed at the central laboratory of the University of Pennsylvania. The eGFR was determined according to the abbreviated Modification of Diet in Renal Disease formula [14], using creatinine values calibrated to the Cleveland Clinic laboratory. Ethnicity was self-described by each participant.

Statistical Analyses

Continuous variables are presented as means ± SD or 95% confidence intervals. Categorical variables are expressed as numbers (percentage). Certain variables (urinary sodium and clinical data) were prespecified in the basic model. In the analyses, we initially fit a joint model including both diabetics and nondiabetics. The log-transformed 24-hour urinary protein was designated as the outcome variable in this cross-sectional analysis, and measures including systolic blood pressure (SBP) and diastolic blood pressure, demographics, glycohemoglobin, type of antihypertensive medication(s) and urinary potassium were considered as key predictors, because of their possible relationship to proteinuria. Multiple linear regressions were performed sequentially. First, urinary sodium and clinical site were included in the model. Next, we included blood pressure, followed by several demographic and clinical variables known to be associated with proteinuria and designated as key confounders, including age, ethnicity, gender, eGFR, smoking status and waist circumference. Subsequently, glucose levels, glycohemoglobin, antihypertensive medications (diuretics, renin-angiotensin system blockers and calcium channel blockers), 24-hour urinary potassium and the urinary sodium to potassium ratio were entered into the regression model. We included the urinary sodium to potassium ratio as a variable, as prior studies have indicated that higher urinary potassium, especially in patients with higher urinary sodium, may be associated with lower blood pressure and target organ injury [15]. All analyses were subsequently stratified based on diabetic status, given the

Table 1. Clinical and demographic characteristics

	All (n = 3,673)	Nondiabetics			Diabetics		
		UPr ≤0.15 g (n = 1,094)	UPr >0.15 g (n = 813)	p	UPr ≤0.15 g (n = 606)	UPr >0.15 g (n = 1,160)	p
Demographics							
Age, years	58.4 ± 10.9	59.6 ± 10.4	54.1 ± 12.8	<0.001	61.7 ± 9.1	58.5 ± 9.8	<0.001
Male, n	2,020 (55)	511 (46.6)	516 (63.3)	<0.001	267 (44)	726 (62.5)	<0.001
Female, n	1,660 (45)	585 (53.4)	299 (36.7)		340 (56)	436 (37.5)	
Race/ethnicity, n							
Non-Hispanic White	1,590 (43)	615 (56.1)	345 (42.3)	<0.001	269 (44.3)	361 (31.1)	<0.001
Non-Hispanic Black	1,530 (42)	387 (35.3)	358 (43.9)		256 (42.2)	529 (45.5)	
Hispanic	415 (11)	55 (5)	78 (9.6)		60 (9.9)	222 (19.1)	
Other	145 (4)	39 (3.6)	34 (4.2)		22 (3.6)	50 (4.3)	
Current smoking, n	479 (13)	125 (11.4)	146 (17.9)	<0.001	51 (8.4)	157 (13.5)	0.002
Body mass index	32.1 ± 7.9	30.0 ± 6.8	30.8 ± 7.5	0.011	34.8 ± 8.7	33.7 ± 7.8	0.007
Waist, cm	106.0 ± 17.5	100.7 ± 15.6	102.7 ± 17.4	0.010	111.1 ± 17.4	110.6 ± 17.6	0.531
Medications, n							
ACE inhibitors/ARBs	2,517 (69)	584 (53.5)	532 (66)	<0.001	502 (83.1)	899 (77.9)	0.010
Diuretics	2,179 (60)	556 (51)	369 (45.8)	0.026	435 (72)	819 (71)	0.644
Calcium channel blockers	1,488 (41)	321 (29.4)	344 (42.7)	<0.001	233 (38.6)	590 (51.1)	<0.001
Clinical and lab measures							
Total cholesterol, mg/dl	183.0 ± 45.0	188.2 ± 39.2	188.5 ± 44.7	0.858	170.7 ± 40.5	180.6 ± 50.7	<0.001
Non-HDL cholesterol, mg/dl	135.4 ± 43.1	136.3 ± 37.6	141.4 ± 42.8	0.007	124.3 ± 39.2	136.2 ± 48.7	<0.001
SBP, mm Hg	128.0 ± 21.9	120.3 ± 18.5	127.6 ± 21.8	<0.001	123.0 ± 18.5	138.3 ± 22.5	<0.001
DBP, mm Hg	71.3 ± 12.7	70.5 ± 11.4	76.3 ± 13.2	<0.001	65.0 ± 11.1	71.8 ± 12.8	<0.001
eGFR, ml/min/1.73 m^2	42.8 ± 13.4	48.2 ± 12.8	40.1 ± 13.6	<0.001	44.7 ± 12.7	38.8 ± 12.3	<0.001
eGFR (CRIC), ml/min/1.73 m^2	44.9 ± 16.7	53.4 ± 17.3	41.7 ± 16.0	<0.001	46.5 ± 15.9	38.4 ± 13.2	<0.001
Glucose, mg/dl	114.9 ± 51.2	91.5 ± 11.3	91.6 ± 11.9	0.966	129.7 ± 50.4	145.5 ± 69.3	<0.001

Figures in parentheses represent percentages. UPr = 24-Hour urinary protein; ARBs = angiotensin receptor blockers; HDL = high-density lipoprotein; DBP = diastolic blood pressure.

sufficient numbers of participants to examine whether there may be differences in the relationship between urine electrolytes and proteinuria in diabetic versus nondiabetic kidney disease. Figure 1 was obtained from a locally weighted polynomial regression fit. Confidence intervals were computed locally assuming linear relationships, independent errors and normality. The value R^2 is the proportion of variability that is accounted for by the model. All analyses were executed in SAS 9.2 (SAS Institute, Cary, N.C., USA).

Results

Demographic Characteristics

The entire CRIC cohort of 3,939 participants included 3,673 who had complete 24-hour urine collections (non-diabetic, n = 1,907; diabetic, n = 1,766). Table 1 shows the important demographic and clinical characteristics of the CRIC participants. Note that in the analytic cohort, the ethnicity percentage was similar between minority populations and non-Hispanic whites, and there were slightly more men. A large proportion of patients were on renin-angiotensin system-blocking drugs (69%), and only 13% were current smokers.

The mean blood pressure of 128/71 mm Hg indicated good control, but the mean waist circumference and body mass index were high (106 cm and 32, respectively). Mean eGFR was 42.8 ml/min/1.73 m^2, and mean 24-hour urinary protein was 790 mg.

Patients with proteinuria of more than 150 mg/day were more likely to be current smokers and receiving renin-angiotensin blockers and calcium channel blockers. In addition, they had higher non-high-density lipoprotein cholesterol and higher SBP and diastolic blood pressure and, if diabetic, higher glycosylated hemoglobin. They also had a lower eGFR.

Table 2 depicts the mean and median urinary sodium, urinary potassium and urinary sodium to potassium ra-

Table 2. Urine laboratory data

	All (n = 3,673)	Nondiabetics			Diabetics		
		UPr ≤0.15 g (n = 1,094)	UPr >0.15 g (n = 813)	p	UPr ≤0.15 g (n = 606)	UPr >0.15 g (n = 1,160)	p
Urinary sodium excretion, mmol/24 h							
Mean ± SD	162.0 ± 77.6	146.2 ± 73.3	171.2 ± 80.1	<0.001	158.8 ± 71.6	172.0 ± 80.4	<0.001
Median	150.9	135.3	161.1	<0.001	148.6	162.0	0.002
IQR	108.5–201.6	94.5–182.5	117.3–214.2		109.7–198.8	115.7–213.4	
Urinary potassium excretion, mmol/24 h							
Mean ± SD	55.3 ± 26.3	55.1 ± 26.3	54.1 ± 24.9	0.375	54.1 ± 24.3	56.9 (28.2)	0.034
Median	51.3	52.5	50.1	0.312	49.6	51.9	0.061
IQR	37.5–68.6	35.6–69.2	36.7–67.1		38.3–67.9	39.0–69.1	
Urinary sodium/potassium ratio							
Mean ± SD	3.3 ± 1.6	3.0 ± 1.7	3.6 ± 1.7	<0.001	3.2 ± 1.4	3.3 ± 1.5	0.198
Median	3.0	2.7	3.2	<0.001	3.0	3.1	0.344
IQR	2.2–4.0	1.9–3.8	2.3–4.4		2.3–3.9	2.3–4.0	

UPr = 24-Hour urinary protein; IQR= interquartile range.

tio in the CRIC participants. This analysis was considered as there is some evidence that increased dietary potassium may offset some of the adverse effects of dietary sodium [15]. The table also divides the participants into nondiabetics and diabetics and splits them further into two groups based on whether their 24-hour urinary protein excretion is less than or equal to 150 mg per day or above this level. Both nondiabetics and diabetics had a similar prevalence of increased urinary sodium excretion in the groups with more than 150 mg of protein per day. Urinary potassium excretion did not differ in the non-diabetics across the levels of proteinuria. However, in diabetics, the more proteinuric participants excreted slightly more potassium in their urine compared to the group with less proteinuria (p = 0.06). Likewise, the sodium to potassium ratio in the urine was statistically greater in nondiabetics with more than 150 mg/day proteinuria (p < 0.001), whereas in diabetics, there was no difference in the sodium to potassium ratio based on the amount of proteinuria.

Figure 1 depicts the unadjusted data of urinary protein excretion in grams per 24 h compared to urinary sodium excretion (millimoles per 24 h) for both diabetics and nondiabetics. Note the similar upward trend between the unadjusted urinary sodium excretion and 24-hour urinary protein excretion in both diabetics and nondiabetics. Overall, diabetics had greater 24-hour urinary protein excretion at almost every level of urinary sodium excretion except at the highest levels (greater than 350 mmol/24 h).

Regression Model
Table 3 shows our basic model including urinary sodium and clinical site. These two covariates in the joint model for participants with a urinary sodium excretion value more than 1 SD above the norm yielded similar β coefficients and R^2 values for both diabetics and nondiabetics, indicating a consistent positive association between urinary sodium and proteinuria across the populations studied. Yet, as a univariate variable, urinary sodium explained only 12% of the variation in proteinuria. Progressive adjustment for demographic and clinical variables did not remove the cross-sectional relationship between urinary sodium and proteinuria. This relationship persisted for both diabetics and nondiabetics. We describe the influence of demographic and clinical variables in the next few paragraphs.

In the joint model, with the addition of SBP to the model, one can see a slight decrease in the β coefficient relating urinary sodium to proteinuria. Similar changes occurred in both diabetic and nondiabetic populations. There was a substantial increase in R^2 with the inclusion of SBP for both diabetic and nondiabetic populations, indicating that SBP explains some of the variability.

With the subsequent stepwise inclusion of demographic variables for the whole cohort, a decline in the β coefficient to 0.15 was observed. These changes were similar in both nondiabetics (0.28 to 0.18) and diabetics (0.24 to 0.11). Within the demographic category, female gender was associated with a negative slope, whereas non-Hispanic blacks and Hispanics had a significant positive slope. It is possible that these slope differences may asso-
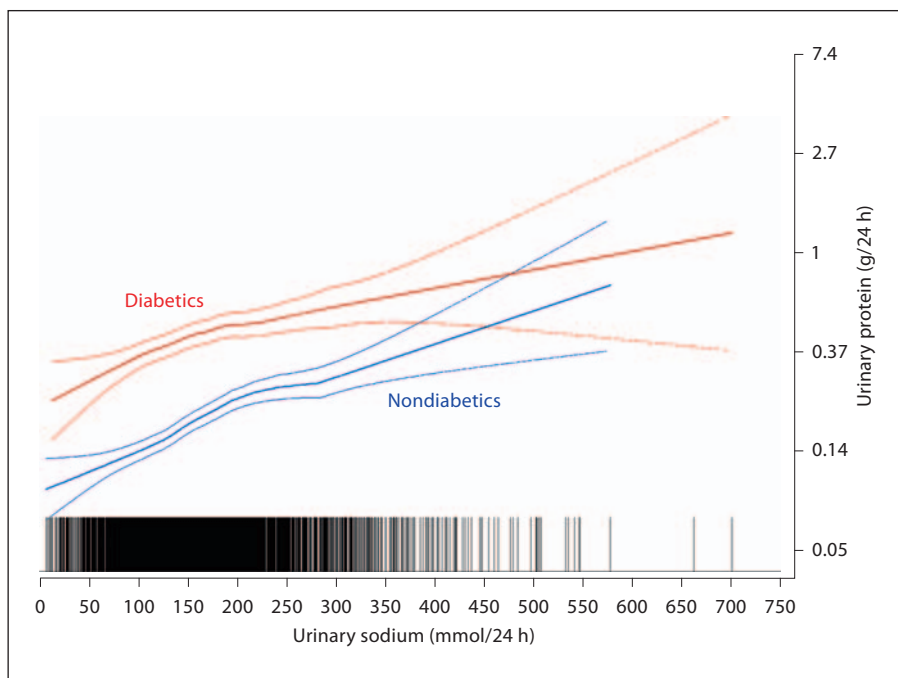
Fig. 1. Unadjusted data of 24-hour urinary protein excretion in relation to 24-hour urinary excretion of sodium for both diabetics and nondiabetics. Confidence intervals are represented by thin lines. Vertical lines at the bottom of the figure indicate the numbers of patients.

Table 3. Multivariable regression model to examine the relationship between 24-hour urinary sodium and log-transformed 24-hour urinary protein

Model	All (n = 3,673)			Nondiabetics (n = 1,904)			Diabetics (n = 1,766)		
	estimate	p	R^2	estimate	p	R^2	estimate	p	R^2
Urinary sodium/SD, CRIC site only	0.287	<0.0001	11.6%	0.292	<0.0001	12.2%	0.234	<0.0001	8.7%
Addition of									
SBP	0.272	<0.0001	21.1%	0.282	<0.0001	15.0%	0.238	<0.0001	22.9%
Demographics, SBP	0.146	<0.0001	31.4%	0.181	<0.0001	25.1%	0.113	0.0014	35.5%
Demographics, SBP, glucose	0.151	<0.0001	34.6%	0.192	<0.0001	25.3%	0.119	0.0009	36.5%
Demographics, SBP, glucose, urinary potassium	0.132	<0.0001	34.6%	0.192	<0.0001	25.3%	0.075	0.0648	36.7%
Demographics, SBP, glucose, medications	0.145	<0.0001	35.1%	0.181	<0.0001	26.6%	0.115	0.0013	37.2%
No urinary sodium, demographics, SBP, glucose, medications	−0.434	<0.0001	34.3%	−0.369	<0.0001	25.1%	−0.513	<0.0001	36.8%

ciate with differential risk for progression of renal disease.

With the subsequent inclusion of glucose measures in the joint model overall, the β coefficient increases slightly. Similar modest increases in the β coefficient with glucose measures occur in both nondiabetics and diabetics. In this section of the joint model, glycosylated hemoglobin was a more important predictive value for the β coefficient than the single glucose measurement. Thus, glucose measures did not contribute substantially to explain the relationship between urinary sodium and proteinuria.

Next, we included antihypertensive medications in the model. In the joint model, one can see little change in the β coefficient relating urinary sodium to proteinuria. This was true for both nondiabetics and diabetics. There was also a difference in the β coefficient for the whole cohort, as well as the diabetics, when we compared calcium channel blockers to diuretics and angiotensin-converting enzyme (ACE) inhibitors, suggesting differential glomerular hemodynamic effects of these medications. There were similar changes in the joint model for both diabetics and nondiabetics.

In the next model, we evaluated the influence of 24-hour urinary potassium excretion. This addition had little impact on the association between urinary sodium and proteinuria. The β coefficient and R^2 values are negligibly changed, indicating little influence of urinary potassium on the relationship of urinary sodium to proteinuria. We saw minimal influence of the sodium to potassium ratio as well (data not shown).

At the bottom of table 3, we removed urinary sodium from the model to examine the independent relationship of each demographic and clinical variable with proteinuria. Of note, one can see the powerful relationship of SBP and demographic factors with proteinuria independent of urinary sodium.

Discussion

Secondary analyses of clinical trials and observational studies in patients with CKD have demonstrated the importance of proteinuria as a predictor of adverse renal outcomes [16–18]. Moreover, epidemiological studies have demonstrated the value of proteinuria as a biomarker of increased risk for cardiovascular events [19]. Clinical studies have demonstrated that increasing dietary sodium intake is associated with increasing blood pressure and increasing proteinuria in patients with CKD [6, 7, 20–22]. The goal of our study was to evaluate the cross-sectional relationship between 24-hour measurements of urinary sodium and potassium and proteinuria in almost 3,700 participants in the CRIC study. We stratified our analysis based on the presence or absence of diabetes as there were no prior studies examining this relationship, and there could be potential differences of clinical relevance. In addition, as illustrated in figure 1, diabetic patients exhibited greater 24-hour urinary protein excretion at almost every level of urinary sodium. In this analysis, we demonstrate that there is a correlation between urinary sodium excretion and 24-hour urinary protein. However, our results indicate that urinary sodium (+1 SD above the mean) as a single variable only explains 12% of the variation in proteinuria. Moreover, with the stepwise inclusion of other demographic variables, the β coefficient declines, indicating that the apparently independent contribution of 24-hour urinary sodium is reduced after considering a variety of demographic and clinical factors. Similarly, with the removal of urinary sodium from the model, one can see the powerful influence of SBP and demographic factors on 24-hour urinary protein measures.

Previous small studies have demonstrated that increasing urinary sodium excretion, as a measure of dietary sodium ingestion, is associated with an attenuation of the antihypertensive and antiproteinuric effects of drugs that block the renin-angiotensin system, such as ACE inhibitors or angiotensin receptor blockers [6, 7]. This is evident whether these medicines are used alone or in conjunction with thiazide diuretics [7]. However, none of these studies adjusted for clinical and demographic factors as we have, nor did they have such a large number of patients with both diabetic and nondiabetic kidney disease. Our cross-sectional study does not provide specific information on whether or not a high level of urinary sodium excretion may attenuate the effects of renin-angiotensin system blockade on proteinuria. What it does provide are a number of interesting associations between urinary sodium and protein excretion in patients with CKD, taking into account several clinical and demographic variables. When adjusting for clinical and demographic factors, there was a reduced contribution of urinary sodium to 24-hour urinary protein excretion. We suspect that this may in part be related to the well-controlled blood pressure in our participants (mean 128/71 mm Hg). If greater dietary salt intake increases proteinuria through blood pressure-dependent effects, conceivably it would be quenched under circumstances of more effective control of blood pressure. However, one could also view that the persistence of the relationship between urinary sodium excretion and proteinuria despite adjustment for confounders suggests that there are blood pressure-independent effects of salt on glomerular permeability to proteins or renal tubular epithelial cell uptake mechanisms. Some investigators have suggested that increasing dietary salt may induce endothelial dysfunction through oxidative stress and diminish the production of endogenous nitrous oxide [23]. Likewise, other investigators have demonstrated the effect of increasing dietary salt on vascular beds in the brain in hypertensive rats independent of changes in blood pressure [9]. Thus, there may be vascular effects of dietary salt which occur despite well-treated blood pressure.

Amongst the demographic variables, it is notable that female gender was associated with a lesser risk of proteinuria, whereas non-Hispanic Blacks and Hispanics had significantly more proteinuria. These factors were important in diminishing the association of urinary sodium excretion and urinary protein excretion. Not surprisingly, SBP, which was associated with more proteinuria, diminished the contribution of urinary sodium excretion to 24-hour urinary protein when added to the model. He-

moglobin A1c was correlated with increased proteinuria but added little to the overall model with stepwise inclusion. There were also differences in the association of urinary sodium excretion with proteinuria based on the different antihypertensive medications. Both diabetics and nondiabetics had greater β coefficients with calcium channel blockers than they did with diuretics or ACE inhibitors. This may be related to the effects of calcium channel blockers in preferentially dilating the afferent glomerular arteriole. Overall, however, the use of antihypertensive medications did not alter the association of urinary sodium excretion and proteinuria. Similarly, measurement of 24-hour urinary potassium excretion did not appear to alter the contribution of urinary sodium to urinary protein excretion. It has been suggested that increasing dietary potassium ingestion can offset the antihypertensive effects of increased dietary sodium [15]. It is possible that with higher levels of blood pressure than those observed in our participants (128/71 mm Hg), one could see a potential vasodepressor response to increased potassium ingestion. It is also possible that with higher blood pressures, increasing dietary potassium could be associated with reduced urinary protein excretion. Our patients received no specific dietary counseling during this cohort study except that offered during the course of their routine clinical care.

Our results have some limitations. It is important to consider that the CRIC population that we studied is not necessarily representative of the US CKD population. We describe only a cross-sectional relationship between urinary sodium and urinary protein excretion after adjustment for a variety of clinical and demographic factors. Urinary electrolyte excretion may not be an accurate representation of dietary electrolyte consumption. In addition, only a single 24-hour urine collection was available. Others have described that 3 overnight urine collections may be a more accurate way to calculate dietary ingestion of sodium [24]. However, the advantage of our study is the large number of cross-sectional measures in both diabetics and nondiabetics with well-controlled blood pressure, many of whom were receiving renin-angiotensin system-blocking therapy. Thus, these observations may provide perspective for the relative association of dietary salt and proteinuria in patients with CKD whose blood pressure is well controlled on a renin-angiotensin-blocking regimen. As others have suggested [25, 26], dietary sodium modification may be an important consideration in many, if not most, patients with CKD.

Our results suggest that in the aggregate, there is a relationship between 24-hour urinary sodium excretion and proteinuria. We clearly demonstrate that a number of clinical and demographic factors reduce the contribution of dietary sodium to 24-hour protein excretion. A more complete understanding of the longitudinal relationship between dietary electrolytes as reflected in urinary electrolyte excretion is needed. This may allow a more rational approach to diet modification as a means of facilitating proteinuria reduction in patients with CKD.

Disclosure Statement

No conflicts of interest to declare.

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