Uromodulin, Salt, and 24-Hour Blood Pressure in the General Population

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Uromodulin is a key protein involved in the risk of CKD and hypertension, essentially produced by the cells lining the thick ascending limb of the loop of Henle (1). Uromodulin regulates sodium and potassium transport activity in the thick ascending limb, and its deletion in mice leads to salt wasting and lower BP (2). Conversely, transgenic mice overexpressing uromodulin develop salt-sensitive hypertension due to activated NKCC2, whereas hypertensive individuals harboring genetic variants driving higher uromodulin expression show an increased response to furosemide (3). Although these data suggest that uromodulin regulates sodium handling, its influence on the link between sodium intake and BP regulation in the general population remains unknown.

We tested the hypothesis that uromodulin levels modulate sodium effect on BP using a population-based approach. We obtained uromodulin and sodium levels in 24-hour urine collections from 1020 participants of the Swiss Kidney Project on Genes in Hypertension study (4), including 948 (93%) participants with 24-hour ambulatory BP monitoring. We applied multivariable mixed linear regression models to determine the independent association of 24-hour urinary sodium excretion with 24-hour systolic and diastolic BP, according to sex-specific median urinary levels of uromodulin. The fully adjusted model included age, sex, center, body mass index, diabetes, treated hypertension, smoking, eGFR, 24-hour urinary volume, 24-hour creatinine excretion, and 24-hour potassium excretion. For diastolic BP, age squared was added to the models to account for the quadratic relationship between diastolic BP and age. Covariates were inserted as fixed effects in the models, and family dependency was accounted for using a likelihood ratio test. P<0.05 confirmed that the association between urinary sodium and BP was dependent on uromodulin levels.

There were 533 (56%) women, and mean age (± SD) was 48± 17 years. Median uromodulin levels were 28 mg/24 h (p25–p75: 19–34 mg/24 h) and 56 mg/24 h (p25–p75: 47–67 mg/24 h) in the lower and higher uromodulin categories, respectively. Patients with higher uromodulin levels were younger and had less diabetes, but they had higher 24-hour diastolic BP, eGFR, and 24-hour urinary sodium, potassium, and creatinine excretions than those with lower levels. Office systolic and diastolic BP, 24-hour systolic BP, body mass index, sex, smoking, and treated hypertension prevalence were similar. In each strata, 25 participants were on diuretics, mostly thiazides.

Figure 1 illustrates the associations of the adjusted residuals for 24-hour systolic and diastolic BP with sodium by urinary uromodulin categories. The likelihood ratio test values confirmed that the effect of urinary sodium on BP was different in low- and high-uromodulin participants. Higher urinary sodium was associated with higher 24-hour ambulatory systolic BP (coefficient, 0.78; 95% confidence interval, 0.28 to 1.28) in the highest uromodulin strata only. On the contrary, higher urinary sodium tended to be associated with lower 24-hour diastolic BP only in the lowest strata (coefficient, −0.30; 95% confidence interval, −0.60 to −0.01). For both systolic and diastolic BP, the direction of the association was similar: there was a trend for higher BP at higher sodium intake in the highest uromodulin strata, but an inverse association in the lowest one. To note, 179 (19%) individuals had taken some nonsteroidal anti-inflammatory drugs during the past 2 weeks. However, there was no difference between the low- and high-uromodulin strata groups, and considering nonsteroidal anti-inflammatory drug intake in the multivariable model, it changed neither the association between sodium excretion and BP nor the interaction of sodium with uromodulin.

We had genetic information on the UMOD promoter variant rs12917707 in 809 (79%) of the participants. There were 19 (2%) homozygous TT individuals, 577 (71%) homozygous GG, and 213 (26%) heterozygous TG. The median 24-hour uromodulin excretion was higher in GG than in TG and TT groups (P value for trend <0.001), confirming results obtained in other cohorts (3). In contrast, the median 24-hour urinary sodium excretion was not significantly associated with the UMOD genotype.

Our findings substantiate the role of uromodulin in the salt-sensitive component of BP regulation. Uromodulin levels may help in stratifying patients as “salt
sensitive,” developing higher systolic BP, or “inverse salt sensitive,” developing lower diastolic BP—under high–salt intake conditions (5). They support that the level of uromodulin expression, reflected in the urine, influences NaCl retention by regulating the activity of NKCC2 (1). Noteworthy, the expression of uromodulin may be modulated by dietary sodium (1), as suggested by the fact that individuals with higher uromodulin levels show a 20% higher 24-hour urinary sodium excretion. Together, these data suggest that urinary uromodulin levels could help in identifying patients who are hypertensive whose BP is responsive to salt intake, and better understanding the role of salt intake in BP control. Interventional studies to reduce BP by acting on NKCC2 as a function of uromodulin levels (or UMOD genotype) will be needed to confirm the role of uromodulin in salt-sensitive hypertension.

Disclosures

M. Bochud reports employment with the Center for Primary Care and Public Health; receiving honoraria from various Swiss federal agencies (Swiss Federal Office of Food Security and Veterinary Affairs and Swiss Federal Office of Public Health); and serving as a member of the council of the National Institute for Cancer Epidemiology and Registration (NICER) Foundation, a scientific advisor or member of Nutrients and Hypertension, a member of the Swiss Society of Nephrology, and a member of the Swiss Society of Public Health Plus. M. Burnier reports consultancy agreements with Galapagos, Otsuka Pharmaceuticals, and Sanofi; receiving research funding from Otsuka Pharmaceuticals and Roche; and serving on the editorial board for CJASN, Kidney International, Nephrology Dialysis Transplantation, Orphanet Journal of Rare Diseases (OJRD), Peritonal Dialysis International, and Pflügers Archiv. M. Pruijm reports consultancy agreements with Novo Nordisk and Vifor and speakers bureau for Vifor. All remaining authors have nothing to disclose.

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