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Original Scientific Paper

UROMODULIN – A LINK BETWEEN SODIUM EXCRETION AND ALTERATION IN CIRCADIAN BLOOD PRESSURE PATTERN IN PREHYPERTENSIVES

Josipa Josipović[1,6] , Livija Šimičević[2], Živka Dika[3,4], Nikola Bulj[4,5], Mislav Vrsalović[4,5] and Bojan Jelaković[3,4]

[1]Department of Internal Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;
[2]Department of Laboratory Diagnostics, Zagreb University Hospital Center, School of Medicine, University of Zagreb, Zagreb, Croatia;
[3]Department of Nephrology, Hypertension, Dialysis and Transplantation, Zagreb University Hospital Center, Zagreb, Croatia;
[4]School of Medicine, University of Zagreb, Zagreb, Croatia;
[5]Department of Cardiology and Angiology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;
[6]Catholic University of Croatia, School of Medicine, Zagreb, Croatia

SUMMARY – Although changes in dietary sodium intake alter blood pressure (BP) in salt-sensitive individuals, pathophysiological mechanisms are still unknown. It has been reported that uromodulin is involved in sodium tubular transport, and genome-wide association studies pointed to *UMOD* gene as one of the most important gene candidates for arterial hypertension. Our aim was to analyze urinary uromodulin, salt intake and BP in 326 young middle-aged subjects (mean age 36±8 years, 49.4% male). In a subgroup of 175 individuals, ambulatory blood pressure monitoring and echocardiogram were performed. Uromodulin was determined by ELISA. According to the JNC-7 criteria, subjects were classified as optimal BP (n=103, men 72%), prehypertension (PHT) (n=143, men 43%) and hypertension (HT) (n= 80, men 38%). There were no differences in age, salt intake, estimated glomerular filtration rate, sodium excretion and uromodulin among BP groups. However, in PHT subjects, uromodulin was positively associated with fractional sodium excretion and negatively with 24-h sodium excretion and diastolic BP dip. These findings point to the effect of uromodulin on sodium reabsorption along the nephron and consequently circadian BP alteration in prehypertensives.

Key words: *Uromodulin; Sodium excretion; Ambulatory blood pressure monitoring; Prehypertension*

Introduction

Uromodulin (UMOD) is the most abundant urinary glycoprotein exclusively synthesized in epithelial cells of the thick ascending limb of the loop of Henle. Besides its well-known protective roles in urinary tract infection and kidney stone forming, recent studies revealed its important role in water and electrolyte homeostasis in the thick ascending limb of the loop of Henle[1]. Mutations of the *UMOD* gene cause autosomal dominant tubulointerstitial kidney diseases[1]. Moreover, genome-wide association studies found association of common variants in the promoter region of the *UMOD* gene with uromodulin excretion and susceptibility to chronic kidney disease and arterial hypertension (AH)[2-5]. It has been proposed that uromodulin regulates sodium uptake

Correspondence to: *Asst. Prof. Josipa Josipović, MD, PhD*, Department of Internal Medicine, Sestre milosrdnice University Hospital Center, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: josipa.josipovic01@gmail.com

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in the thick ascending limb of the loop of Henle by modulating the effect of tumor necrosis factor-α on NKCC2A expression[6]. Changes in dietary sodium intake in healthy salt-sensitive individuals modify both uromodulin excretion and nighttime blood pressure (BP) dipping[7,8]. Although a diminished potential for sodium excretion during excessive salt intake has been recognized in these individuals, the exact underlying mechanism is still unknown[9]. In addition to the effect on diurnal BP pattern, excessive salt intake increases the risk of prehypertension (PHT), another precursor of sustained hypertension that affects 25%-50% of adults worldwide[10-14].

Our aim was to analyze association of urinary uromodulin with diurnal BP pattern and sodium excretion in a group of middle-aged normotensives, prehypertensives and untreated mild hypertensives.

Subjects and Methods

This cross-sectional study included 326 apparently healthy untreated subjects aged 18-45 years, randomly selected from general medicine practice registries. Exclusion criteria were kidney, heart, thyroid and liver diseases, psychiatric disorders, secondary hypertension, atherosclerotic peripheral disease, stroke, myocardial infarction, or any chronic or acute infection. Data were collected during a period from April 2016 until April 2018. All subjects were studied in the morning between 8:00 a.m. and 9:30 a.m. after an overnight fast. Basic anthropometric measurements were performed in all study subjects in a standardized manner. BP was measured in the sitting position using Omron M6 device with a cuff appropriate to the length and circumference of the arm after a 5-min rest and expressed in mm Hg and repeated 3 times in order to avoid bias. The 24-hour ambulatory blood pressure monitoring (ABPM) was recorded by Mobil-O-Graph® (I.E.M. GmbH, Stolberg, Germany) in 175 subjects, and 164 measurements were appropriate for further analyses according to the predefined criteria. It was programmed to measure BP every 20 minutes during daytime period (6 a.m.-11 p.m.) and every 30 minutes during nighttime period (11 p.m.- 6 a.m.), thus providing extended, continuous BP recordings during a patient's normal daily activities and while sleeping. Mobil-O-Graph® fulfilled the European Society of Hypertension (ESH) criteria[15]. Fasting venous blood samples (10.5 mL) and spot urine samples were collected in all subjects and 24-h urine collection was obtained in a subgroup of 175 participants. Complete blood count was determined by laser scattering technology (XN-1000, Sysmex analyzer, Sysmex Europe, Norderstedt, Germany); biochemistry panel was obtained after 10-min blood centrifugation. Serum creatinine and urinary creatinine were assessed by photometry with alkaline picrate (Architect analyzer, Abbott, IDMS, Abbott Park, IL, USA); serum urate levels were assessed by spectrophotometric uricase enzyme-based method; serum and urine electrolytes were determined by indirect potentiometric method; glomerular filtration rate (eGFR) was estimated using CKD-EPI creatinine equation {eGFR, mL/min/1.73 m^2=141 x min(SCr/κ, 1)$^{\alpha}$xmax(SCr /κ, 1)$^{-1.209}$x0.993^{Age}x1.018 [if female] x1.159 [if Black]}[16]. Creatinine clearance (CCr) was calculated from creatinine concentration in the collected urine sample, urine flow rate and plasma concentration (PCr). Fractional sodium excretion (FENa) was calculated using the equation [(urine sodium×serum creatinine)/(serum sodium×urine creatinine)]×100%[17]. Estimated 24-h sodium and potassium excretions were calculated using Tanaka equation[18]. Uromodulin was measured from urinary samples stored at -60 °C by enzyme-linked immunosorbent assay (ELISA, Bio-Vendor, Brno, Czech Republic) [nonidexed uromodulin (nUM)] and standardized to urinary creatinine [indexed uromodulin (iUM)]. The study protocol was consistent with the Declaration of Helsinki, as well as with local institutional guidelines, and was approved by the local ethics committees. Written informed consent was obtained from all participants.

Statistical analysis

Data were described using descriptive statistical methods. The variance of category variables was tested by the χ^2-test and Fisher exact test. Differences between variables in two independent groups were tested by Mann-Whitney U test. Differences among three and more groups were tested by ANOVA (post-hoc Bonferroni, Scheffe) or Kruskal-Wallis test (post-hoc Conover). The correlation between numerical variables was evaluated by Spearman's correlation coefficient ρ (rho). All p values were two-sided. The level of significance was set to α=0.05. The analysis was conducted using the MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) and IBM SPSS Statistics 23 (IBM Corp., Release 2015, IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY, USA).

Results

Basic demographic, anthropometric and clinical measures of enrolled subjects are shown in Table 1. Although not significantly different, optimal BP (OBP) and PHT groups were younger than HT group. PHT had intermediate values of body mass index (BMI) and waist circumference (WC) compared to OBP and HT groups, but significance was only present between OBP and HT, and PHT and HT (but not between OBP and PHT).

Significantly higher values of serum creatinine and uric acid were found in patients with PHT and HT

Table 1. Baseline data of participants according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) blood pressure categories

	OBP	PHT	HT	p
	(n=103)	(n=140)	(n=80)	
*SBP (mm Hg)	108.3 (7.1)	126.9 (80.8)	143.9 (94.2)	**<0.001**‡
*DBP (mm Hg)	70.9 (6.2)	80.8 (6.5)	94.2 (8.2)	**<0.001**‡
Sex, M [n (%)]	74 (71.8)	61 (42.7)	30 (37.5)	**<0.001**†
Age, (g) [median (25%-75%)]	36 (30-42)	37 (29-44)	39 (33-45)	0.07
**BMI (kg/m^2)	25.6 (22.5-28.7)	26.6 (23.8-30)	28.56 (24.71-32.64)	**0.009**
**WC (cm)	90 (78.5 – 99.8)	92 (84-102)	99.5 (89.3-109.8)	**0.001**
Uric acid (μmol/L)	252 (211-307)	297 (244.5-370)	328 (274-412.8)	**<0.001**
Serum potassium (mmol/L)	4.3 (4.2-4.63)	4.4 (4.1-4.7)	4.3 (4.1-4.5)	0.09
Serum sodium (mmol/L)	140 (139-141)	140 (139-142)	140 (139-141)	0.48
§Serum creatinine μmol/L)	68 (63-76)	75 (65-86)	74 (65-86.3)	**0.001**
CKD-EPI eGFR (mL/min/1.73 m^2)	107 (96.3-115)	105 (91-113)	104.5 (94-110)	0.32
Potassium, spot urine (mmol/L)	32 (23-44)	35 (22.7- 48.3)	36.8 (26- 46)	0.12
Sodium, spot urine (mmol/L)	103 (74-149)	118 (89.5-162.5)	127 (91-160)	<0.09
**Albumin, urine portion (mg/L)	7.5 (4-13)	7 (5-13)	11 (5.4-18)	**0.02**
ACR urine (mg/g creatinine)	4.14 (2.64-6.05)	4.1 (2.3-6.6)	4.7 (2.8-8.3)	0.54
A1mCR urine (mg/g creatinine)	5.6 (3.3-7.7)	4.3 (3.2-6.7)	5.1 (3.6-8.4)	0.07
RVM urine (kg/L)	1018 (1013-1024)	1020 (1015-1025)	1018.5 (1015-1020)	0.05
§§Estimated 24h-kaliuria (mmol/24 h), Tanaka equation	42.4 (25-59.5)	44.9 (29-61.8)	52.4 (36-67.6)	**0.03**
Estimated 24-h natriuresis (mmol/24 h), Tanaka equation	134 (82-189)	138.5 (100.3-193.3)	158 (124-198)	0.09
Na/K ratio, urine	3.3 (2.5-4.5)	3.3 (2.4-5.2)	3.1 (2.4-4.1)	0.71
Salt intake (g/day)	8.9 (6.5-11)	8.7 (6.1-11.2)	9.8 (7.3-11.6)	0.42
FENa, urine (%)	0.6 (0.33-0.80)	0.60 (0.40-0.80)	0.60 (0.50-0.80)	0.47
Uromodulin (μg/mL)	49.8 (32-74.6)	56.1 (29.8-78)	52 (27-70)	0.56
Uromodulin (mg/g creatinine)	43 (27-66)	42.9 (25.5-65.3)	40.6 (24.1-60.4)	0.73

†χ^2-test; Kruskal Wallis test [median (25%-75%)]; ‡ANOVA; post hoc Conover; *significant differences OBP *vs.* PHT, OBP *vs.* HT, PHT *vs.* HT; **significant differences OBP *vs.* HT, PHT *vs.* HT; §significant differences OBP *vs.* PHT, OBP *vs.* HT; §§significant difference OBP *vs.* HT; OBP = optimal blood pressure; PHT = prehypertension; HT = hypertension; BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; ACR = albumin creatinine ratio in spot urine; A1mCR = alpha-1-microglobulin creatinine ratio in spot urine; RVM = urine relative volume mass; spot urine Na/K ratio = sodium to potassium ratio in spot urine; FENa = fractional sodium excretion

Table 2. Differences in laboratory and ambulatory blood pressure monitoring values in terciles of uromodulin between OBP and PHT groups

Laboratory and ABPM value	UM	OBP			P*	PHT			p*
	nUM (μg/mL)	<32	33-47	>48		<32	33-47	>48	
	iUM (mg/g creatinine)	<32.1	32.2-54.9	>55		<32.1	32.2-54.9	>55	
Na/K, urine (mmol/L)	nUM	2.7 (1.9-3.7)	4.1 (2.6-6)	3.4 (2.7-4.3)	****0.03**	2.9 (2.2-4)	3.55 (2.6-4.8)	3.4 (2.5-5.6)	0.15
	iUM	2.6 (1.4-3.4)	3.85 (3-5.5)	3.5 (2.7-4.5)	**0.01**	3.1 (2.3-3.9)	3.2 (2.2-4.9)	3.8 (2.6-5.8)	0.07
Salt intake (g/day)	nUM	7.8 (6.2-9.9)	11.7 (7.9-13.9)	8.9 (6.7-10.9)	**†0.01**	10.3 (5.6-13.2)	9.7 (6.3-12.4)	8.7 (7.4-10.1)	0.32
	iUM	7.2 (5.9-9.4)	9.3 (6.7-12.3)	9.9 (8.3-11.1)	****0.01**	8.95 (5.9-11.6)	8.55 (6.1-11.1)	9.25 (7.9-11.3)	0.58
24h-natriuresis (mmol/dU)	nUM	120.5 (74-166.5)	199 (82-237)	141 (82-186.5)	0.08	175.5 (108.5- 241.3)	158 (103-215.5)	123 (98-165)	**§0.02**
	iUM	147 (115.3-224.3)	158 (106-177)	160 (125-194)	0.89	157 (112.5-205.5)	135 (113-202.5)	116 (91.8-175)	0.11
A1mCR (mg/g creatinine)	nUM	5.55 (4.4-7.5)	7.25 (4.3-8.5)	4.35 (2.7-7.7)	0.18	4.35 (3-7.2)	3 (2.4-6.5)	4.3 (3.6-6.7)	0.33
	iUM	5.05 (2.9-7.4)	4.35 (3.3-7.3)	6.8 (5.6-10.3)	**†0.02**	4.1 (2.6-5.6)	3.7 (3-5.9)	5.15 (4.2-8)	**†<0.001**
FENa (%)	nUM	0.6 (0.3-0.8)	0.75 (0.5-1)	0.55 (0.3-0.8)	0.13	0.65 (0.4-0.9)	0.65 (0.3-0.9)	0.6 (0.4-0.8)	0.83
	iUM	0.45 (0.2-0.6)	0.6 (0.3-0.9)	0.6 (0.5-0.8)	0.06	0.5 (0.3-0.8)	0.6 (0.4-0.7)	0.7 (0.5-1)	0.13
Sleep-through surge SBP	nUM	12.67 (1.1-21.1)	21.06 (5.2-33.3)	21.82 (15.5-26.8)	0.18	17.27 (4.1-23.7)	14.85 (5.4-16.8)	14.35 (6.1-22.8)	>0.99
	iUM	2.33 (-6-14.1)	17.98 (11.3-26.9)	24.96 (18.2-28.2)	****<0.001**	15.84 (8.2-22.8)	13.89 (4.8-22.4)	14.67 (0-28.1)	0.75
Dip DAT (mm Hg)	nUM	12.6 (9.5-18)	13.8 (8.5-19.1)	16.35 (12.3-22.9)	0.34	19.6 (12.9-22.6)	12.05 (9.3-20.2)	11.2 (8.1-14.9)	**†0.02**
	iUM	12.3 (5.9-13.6)	16.05 (9.5-22)	15.5 (10.9-21.6)	0.17	14.6 (8.8-21.5)	14.3 (9.4-20.4)	10 (6.3-14.8)	0.25

Kruskal Wallis test [median (25%-75%)], post hoc Conover: **significance 1st *vs.* 2nd, 1st *vs.* 3rd tercile; †significance 1st *vs.* 3rd, 2nd *vs.* 3rd tercile; §significance 1st *vs.* 3rd tercile; nUM = nonindexed uromodulin; iUM = indexed uromodulin; OBP = optimal blood pressure; PHT = prehypertension; A1mCR = alpha-1-microglobulin creatinine ratio; FENa = fractional sodium excretion; SBP = systolic blood pressure; Dip DAT = diastolic blood pressure dip

compared to OBP. There were no differences in eGFR, as well as in serum and urine electrolyte concentrations among BP groups (Table 1). There were no differences in creatinine clearance, urinary creatinine excretion, 24-h sodium and potassium excretion, as well as in 24-h albuminuria (data not shown). The estimated 24-h urine potassium excretion from spot urine using Tanaka equation was higher in HT compared to PHT and OBP, and the same trend was observed for estimated 24-h urine sodium excretion. There was a trend to higher fractional sodium excretion (FENa) in higher BP groups. Sodium/potassium ratio in urine (Na/K) and estimated salt intake were higher than recommended without differences among the groups. Trend to higher uromodulin values in higher BP groups was observed. However, we failed to find differences in uromodulin tercile distribution among BP categories. Significant differences were found

Table 3. Ambulatory blood pressure monitoring parameters of participants according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) blood pressure categories

	OBP	PHT	HT	p*
	(n=47)	(n=68)	(n=60)	
§24 h SBP (mm Hg)	118.22 (7.72)	131.05 (10.76)	138.05 (15.21)	**<0.001**
§24 h DBP (mm Hg)	72.29 (5.83)	79.15 (6.73)	89.32 (11.13)	**<0.001**
§Daytime SBP (mm Hg)	120.98 (7.93)	134.08 (10.47)	139.93 (16.13)	**<0.001**
§Daytime DBP (mm Hg)	74.96 (6.22)	81.94 (6.89)	91.54 (10.97)	**<0.001**
§Nighttime SBP (mm Hg)	108.76 (9.45)	121.14 (13.13)	126.98 (18.53)	**<0.001**
§Nighttime DBP (mm Hg)	63.53 (6.89)	70.02 (8.27)	81.56 (12.66)	**<0.001**
§24 h PP (mm Hg)	44.93 (5.5)	51.35 (10.38)	47.9 (8.61)	**0.002**
§Daytime PP (mm Hg)	45.03 (5.7)	51.82 (10.48)	49.57 (11.27)	**0.004**
§Nighttime PP (mm Hg)	44.33 (5.56)	50.75 (11.35)	46.85 (10.13)	**0.005**
§24 h MAD (mm Hg)	92.77 (6.02)	101.19 (6.37)	110.42 (12.05)	**<0.001**
§Daytime MAD (mm Hg)	95.55 (6.38)	104.05 (6.15)	113.19 (12.19)	**<0.001**
§Nighttime MAD (mm Hg)	83.7 (7.29)	91.84 (8.96)	101.85 (13.09)	**<0.001**
24 h HR (/min)	76.36 (9.97)	75.77 (10.77)	77.48 (9.62)	0.65
Daytime HR (/min)	79.75 (10.83)	79.71 (10.95)	80.75 (9.9)	0.84
Nighttime HR (/min)	65.11 (9.55)	64.48 (10.39)	67.93 (10.2)	0.16
SBP dip (mm Hg) [median (25%-75%]	10.1 (5.6-14.4)	9.9 (6.25-13.38)	10 (6-12.4)	0.97†
‖DBP dip (mm Hg) [median (25%-75%)]	15.2 (9.8-19.7)	14.4 (9.35-20.58)	10.7 (5.6-16.1)	**0.02**†
CoV 24 h SBP	13.67 (2.59)	14.33 (4.26)	13.52 (4.52)	0.5
CoV 24 h DBP	11.41 (2.29)	11.37 (3.53)	10.48 (3.46)	0.25
Sleep-through surge SBP[median (25%-75%)]	19.6 (10.2-25.8)	15.1 (6.2-24.9)	16 (10.3-22.9)	0.80†
Sleep-through surge DBP [median (25%-75%)]	15.4 (6.8-23.8)	13.7 (7.6-21.2)	12.3 (7.8-21)	0.86†

*ANOVA [arithmetic mean (SD)], significant difference p<0.05 (§post hoc Scheffe) OBP *vs*. PHT, OBP *vs*. HT, PHT *vs*. HT; †Kruskal Wallis test, significant difference ‖p<0.05 (post hoc Conover) OBP *vs*. PHT and PHT *vs*. HT; OBP = optimal blood pressure; PHT = prehypertension; HT = hypertension; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MAD = mean arterial diastolic; CoV 24 h SBP = coefficient of variation of 24-h systolic blood pressure; CoV 24 h DBT = coefficient of variation of 24-h diastolic blood pressure; HR = heart rate

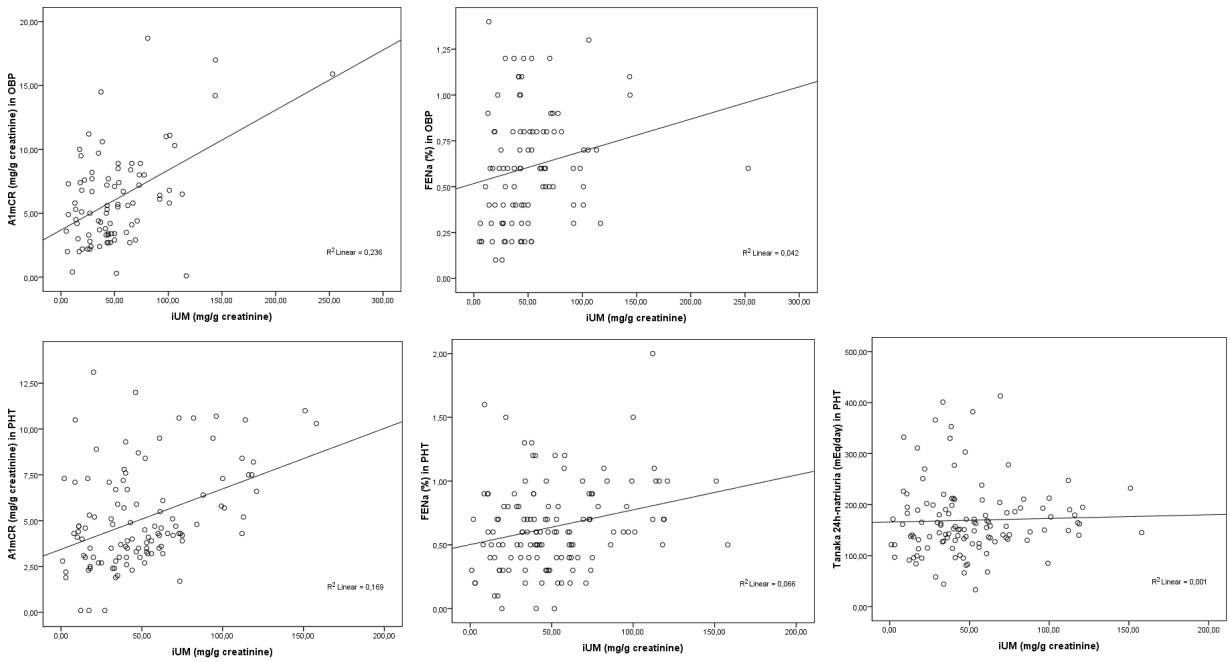

Fig. 1. Associations of A1mCR, FENa and natriuresis with iUM in OBP and PHT groups.

OBP = optimal blood pressure; PHT = prehypertension; iUM = indexed uromodulin; A1mCR = alpha-1-microglobulin creatinine ratio; FENa = fractional sodium excretion

in tubular function markers and ABPM parameters among uromodulin terciles according to BP categories (Table 2). However, the lowest values of estimated salt intake and spot urine Na/K ratio were recorded in first tercile nUM and iUM in OBP group (p=0.03). In PHT group, there were significant differences in 24-h potassium and 24-h sodium excretion (p<0.001 both) between the first and third tercile uromodulin, with the highest values in the first tercile. The highest values of A1mCR were found in third terciles compared to the first and second terciles of uromodulin in OBP and PHT groups (p=0.02 and p<0.001, respectively). The lowest value of FENa was observed in the first tercile uromodulin in OBP group, being statistically significant between the first and third terciles (p=0.03). Higher sodium excretion was observed in the first and second terciles compared to the third tercile uromodulin in HT group (p=0.01) (data not shown). As expected, PHT group had intermediate values of most ABPM variables compared to OBP and HT groups. Importantly, pulse pressure (PP) was highest in PHT (Table 3). Furthermore, there were no differences in nocturnal BP dipping distribution among the groups, but the lowest DBP dip was observed in HT (p=0.02). Interestingly, extreme dippers for DBP in the PHT group had the lowest values of nUM (27 *vs.* 56/52 μg/mL; p=0.006) and iUM (37 *vs.* 53/56 mg/g creatinine; p=0.02) compared to OBP/HT. The lowest value of SBP sleep-through surge was found in the first tercile of iUM compared to the second and third terciles in OBP group (p<0.001), and highest DBP dip was observed in the first tercile of nUM in PHT group (p=0.02) (Table 2). iUM correlated positively with spot urine sodium (Rho 0.207; p=0.04) and spot urine Na/K ratio (Rho 0.214; p=0.04), A1mCR (Rho 0.317; p<0.001) and FENa (Rho 0.272; p=0.01) in OBP (Fig. 1). iUM correlated positively with A1mCR (Rho 0.347; p<0.001) and FENa (Rho 0.208; p=0.02) in PHT group, but negatively with estimated 24-h sodium excretion (Tanaka equation) (Rho -0.188; p=0.03) in PHT. nUM correlated negatively with spot urine potassium (Rho -0.21; p=0.01) and sodium (Rho-0.187; p=0.03) in PHT (Fig. 1). iUM correlated negatively with measured 24-h sodium excretion (Rho -0.301; p=0.03) in HT group. We failed to find correlation of uromodulin and serum uric acid. nUM correlated positively with daytime systolic BP (SBP) (Rho 0.324; p=0.04) and SBP sleep-through surge (Rho 0.372; p=0.03) in OBP group, but negatively with diastolic BP (DBP) dip (Rho -0.287; p=0.03) in

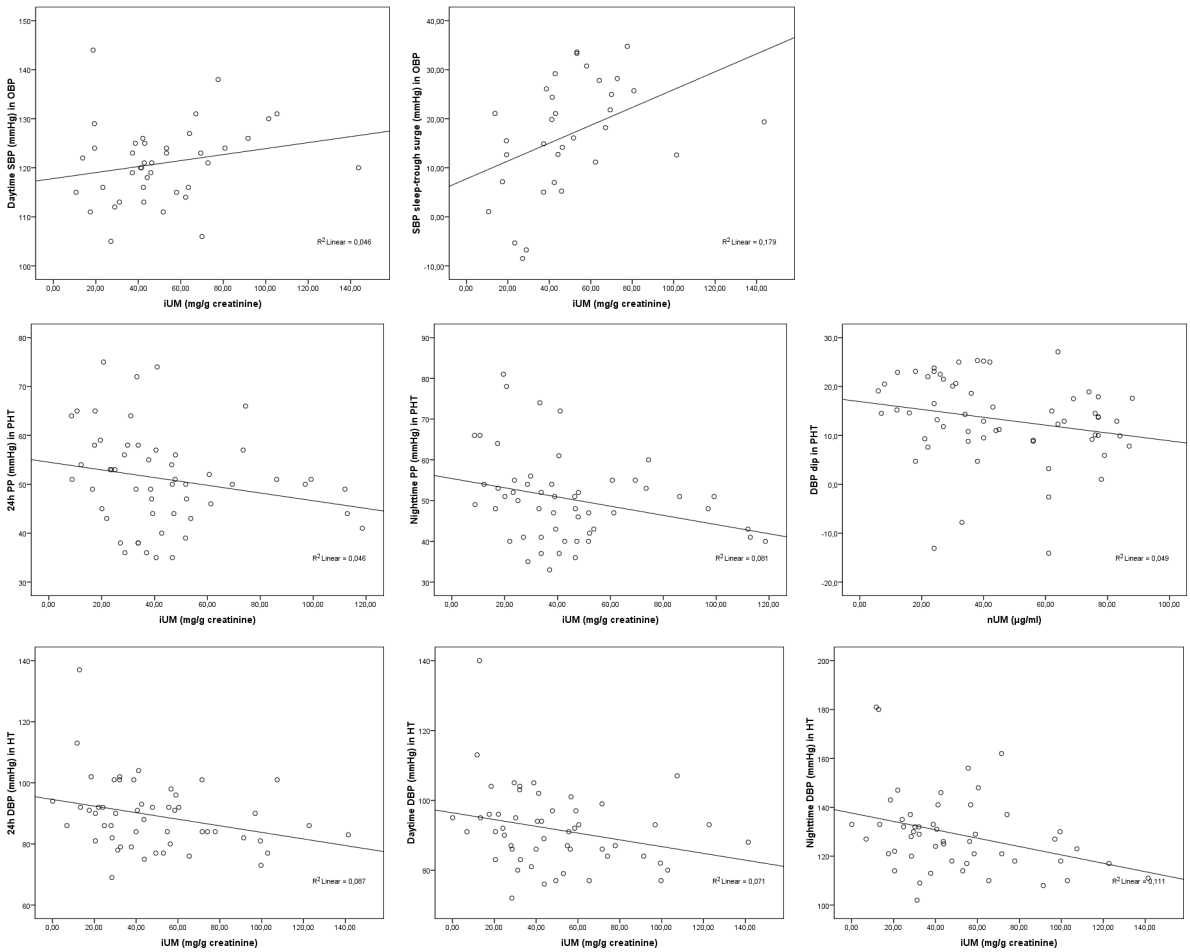

Fig. 2. Associations of ABPM parameters and iUM in OBP, PHT and HT.

ABPM = ambulatory blood pressure monitoring; OBP = optimal blood pressure; PHT = prehypertension; iUM = indexed uromodulin; SBP = systolic blood pressure; PP = pulse pressure; DBP = diastolic blood pressure

PHT and 24-h mean arterial pressure (MAP) (Rho-0.289; p=0.04) in HT group (Fig. 2). iUM correlated positively with daytime SBP (Rho 0.324; p=0.04), SBP sleep-through (Rho 0.519; p=0.002) and DBP sleep-through surge (Rho 0.384; p=0.03) in OBP group, negatively with 24-h PP (Rho -0.281; p=0.04) and nighttime PP (Rho -0.311; p=0.02) in PHT, and negatively with 24-h DBP (Rho -0.289; p=0.04), daytime DBP (Rho -0.273; p=0.04), nighttime SBP (Rho -0.293; p=0.04) and daytime MAP (Rho -0.294; p=0.03) in HT group (Fig. 2).

Discussion

This study revealed association of urinary uromodulin with sodium excretion and BP in the young middle-aged, apparently healthy subjects. Since distal nephron is the site of both uromodulin synthesis and electrolyte transport, this association is expected and in line with previous experimental, genetic and observational studies[4-7,19,20]. Negative associations of uromodulin and urinary electrolytes have been observed, especially in the condition of high salt intake, as found in this study, conversely to positive associations reported in two population-based studies that included older participants with chronic diseases and pharmacotherapy[4-7,19,20]. According to our knowledge, this is the first study that revealed bi-directional association of uromodulin with sodium excretion and diurnal ambulatory BP parameters among the BP categories, positive in OBP and negative in PHT group.

As other authors found correlation between uromodulin and sodium reabsorption in proximal tubule, we also observed positive associations of uromodulin with FENa and A1mCR, two markers of proximal tubule function[19-23]. Although we did not find significant differences in uromodulin excretion between the BP groups, we observed differences in A1mCR and sodium excretion between the uromodulin terciles according to the BP categories. Specifically, the highest value of A1mCR was found in the third tercile of iUM in OBP and PHT groups, which is consistent with the proposed mechanism of uromodulin induced higher sodium reabsorption in Henle's loop and consequently, lower sodium reabsorption in the proximal tubule[24,25]. Opposite to A1mCR, the lowest sodium excretion was found in the third tercile of nUM only in PHT group. As there were no differences in salt intake among the BP groups, this might suggest higher sodium reabsorption exclusively in Henle's loop and therefore, higher global sodium retention in PHT compared to OBP group. As another study failed to find association of hyperuricemia with prehypertension in a Croatian adult population, we found no relation of uromodulin with uric acid either[26].

We found positive associations of uromodulin and ABPM values in OBP, but negative in PHT and HT groups. Other authors also report on positive or negative correlation of uromodulin and BP depending on population characteristics, study design and methodology, but this is the first study that found associations with diurnal BP parameters[4,20,27,28]. More precisely, uromodulin was associated positively with morning BP surge in OBP group, and negatively with DBP dip in PHT group, with the highest measured nUM. The lowest morning BP surge observed in the first tercile of iUM in OBP and the highest DBP dip in the first tercile of nUM in PHT group support the idea of favorable effect of lower uromodulin excretion on diurnal BP pattern. Furthermore, the lowest values of uUM and iUM were observed in the subgroup of extreme DBP dippers of PHT.

Since there were no differences in uromodulin excretion among BP categories, these findings might suggest that factors other than the amount of excreted protein itself could predispose prehypertensives to the effect of uromodulin on tubular function and consequently, circadian BP alteration as an early forerunner of sustained hypertension.

The advantage of this study was a relatively homogeneous cohort of middle-aged apparently healthy, untreated subjects with normal renal function. Measurements were performed in standardized conditions using validated methods. The main drawback might be a relatively small number of all participants and not well-matched groups in terms of number and gender. A cross-sectional character of our study also was a limiting factor for causality and mechanistic conclusions, and additional studies are necessary to explore the pathways linking BP, thick ascending limb of the loop of Henle function, and uromodulin excretion in specific cohorts and in a larger number of subjects.

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Sažetak

UROMODULIN – POVEZNICA IZMEĐU NATRIURIJE I DNEVNOG RITMA ARTERIJSKOG TLAKA KOD PREDHIPERTONIČARA

J. Josipović, L. Šimičević, Ž. Dika, N. Bulj, M. Vrsalović i *B. Jelaković*

Promjene u dnevnom unosu kuhinjske soli u osoba osjetljivih na sol utječu na arterijski tlak (AT), ali točan patofiziološki mehanizam još nije u potpunosti razjašnjen. Cilj ove studije je bio istražiti izlučivanje uromodulina (UM) i natrija mokraćom i povezanost s AT u mlađih odraslih osoba. U 326 ispitanika (medijan dobi 36, IQR 18-48, 64,6% muškarci) analizirani su uzorci krvi i mokraće uzeti natašte i izmjeren je AT u ordinaciji, a kod 175 ispitanika učinjeno je kontinuirano mjerenje arterijskoga tlaka. UM je određen metodom ELISA. Prema klasifikaciji JNC-7 optimalni AT, predhipertenzija (PHT) i hipertenzija (HT) su dijagnosticirani u 103 (72% m), 143 (43% m) i 80 (38% m) ispitanika. Nije bilo razlike u dobi, unosu kuhinjske soli, procijenjenoj stopi glomerularne filtracije niti u izlučivanju natrija i UM mokraćom između kategorija AT. Uočena je pozitivna povezanost UM s frakcijskom ekskrecijom natrija, a negativna s 24-satnom natriurijom i noćnim sniženjem dijastoličkoga AT u PHT. Ovi rezultati upućuju na povezanost UM s tubularnom reapsorpcijom natrija i promjenama dnevnoga ritma AT u predhipertoničara.

Ključne riječi: *Uromodulin; Natriurija; Kontinuirano mjerenje arterijskog tlaka; Predhipertenzija*