Albuminuria Intensifies the Link Between Urinary Sodium Excretion and Central Pulse Pressure in the General Population: The Wakuya Study

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BACKGROUND

Central pulse pressure (cPP) is responsible for the hemodynamics of vital organs, and monitoring this parameter is important for cardiovascular disease (CVD) prevention. Excess sodium intake and (micro)albuminuria (a manifestation of renal microvascular damage) are known to be strong predictors of CVD. We sought to investigate the cross-sectional relationships among dietary sodium intake, albuminuria, and cPP in a general population cohort.

METHODS

The subjects were 933 apparently healthy adults (mean age, 56 ± 10 years). Radial pressure waveforms were recorded with applanation tonometry to estimate mean arterial pressure (MAP), cPP, forward and backward pressure amplitudes, and augmentation index. The urinary sodium/creatinine and albumin/creatinine ratios were measured in spot urine samples.

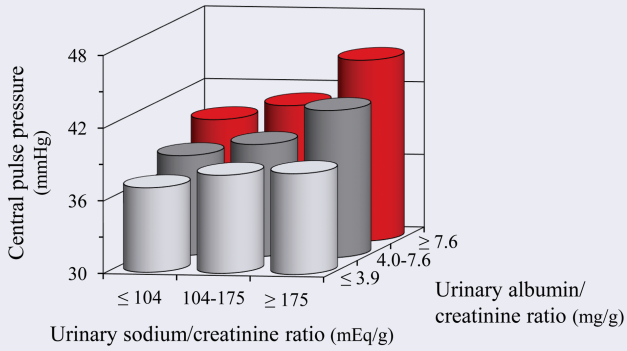
RESULTS

Both the urinary sodium/creatinine and albumin/creatinine ratios were positively correlated with cPP, even after adjusting for MAP ($P < 0.001$). Moreover, both ratios had a synergistic influence on increasing the cPP independent of age, sex, estimated glomerular filtration rate, hyperlipidemia, and diabetes (interaction $P = 0.04$). A similar synergistic influence was found on the forward pressure amplitude, but not on the backward pressure amplitude or augmentation index. The overall results were not altered when the urinary albumin/creatinine ratio was replaced with the existence of chronic kidney disease (CKD).

CONCLUSIONS

(Micro)albuminuria strengthens the positive association between urinary sodium excretion and cPP and systolic forward pressure. Excess sodium intake may magnify the cardiovascular risk by widening the aortic pulsatile pressure, particularly in the presence of concomitant CKD.

GRAPHICAL ABSTRACT



Keywords: aorta; blood pressure; chronic kidney disease; general population; hypertension; renal microvascular damage; salt intake

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The pulsatile nature of the central (aortic) hemodynamics has a hazardous impact on the vital organs.[1,2] Central pulse pressure (cPP) is a more powerful predictor of all-cause mortality than the traditional brachial pulse pressure (PP).[3,4] Moreover, a meta-analysis has demonstrated that cPP is a major risk factor for cardiovascular disease (CVD) morbidity (e.g., myocardial infarction and stroke),[5] whereas mean arterial pressure (MAP) is not.[6] cPP is a better predictor of cardiovascular outcomes than steady-state pressure and peripheral PP.[3]

Patients with chronic kidney disease (CKD) have a >2.5-fold higher CVD mortality risk than those without CKD.[7] Microalbuminuria (a manifestation of renal microvascular damage) and estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2, which are the structural components of CKD, are associated with CVD mortality in

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the general population.[8] Notably, even in normoalbuminuria, an albumin/creatinine ratio of ≥10 mg/g is an independent predictor of the CVD mortality risk.[8] In addition, a sodium intake of > 5 g/day is a strong predictor of CVD mortality.[9] However, the pathophysiological mechanisms explaining the relationships of CKD and sodium intake to CVD mortality are still unclear.

Excess sodium intake is known to be a pivotal factor increasing not only the brachial PP but also cPP in the general population and in patients with hypertension.[10,11] (Micro)albuminuria and decreased eGFR have also been shown to be associated with cPP in patients with CKD or hypertension.[1,2,12] The degree of blood pressure elevation in response to sodium loading (i.e., blood pressure sodium sensitivity) considerably varies among individuals; however, it is assumed to depend on kidney function.[1,13] Salt loading elicits a greater increase in the steady component of pressure (i.e., MAP) in patients with severe kidney disease than in those with moderate kidney disease.[14] However, little is known about the potential impact of kidney function on the relationship between sodium intake and the pulsatile component of pressure (i.e., cPP) in the general population. In this study, we sought to investigate the cross-sectional relationships among urinary sodium excretion, albuminuria, and cPP in a Japanese general population cohort. We hypothesized that a combination of excess salt intake and renal impairment (albuminuria and decreased eGFR) would increase cPP more than either of these factors.

METHODS

Subjects

A total of 977 adults were enrolled in this study. The subjects were residents of Wakuya Town or surrounding areas in Miyagi Prefecture, Japan. Forty-four subjects were excluded from this study because of unavailable eGFR data. Therefore, the final analysis included 933 adults (age, 29–82 years). Hypertension was defined as a brachial systolic/diastolic blood pressure of ≥140/90 mm Hg and/or use of antihypertensive drugs. The diagnosis of diabetes mellitus was based on antihyperglycemic drug therapy and/or a medical history of diabetes mellitus assessed using questionnaires, and the diagnosis of hypercholesterolemia was based on low-density lipoprotein cholesterol ≥140 mg/dl, triglyceride ≥150 mg/dl, and/or antihypercholesterolemic drug therapy. All subjects provided written informed consent, and the present study was approved by the Ethics Committee of Wakuya National Health Insurance Hospital.

Measurements

Central hemodynamics Hemodynamics were measured in a temperature-controlled room with the subjects in a seated position. After 10 minutes of rest, brachial blood pressure was measured twice using a cuff oscillometric device (HEM-9000AI; Omron Healthcare, Kyoto, Japan), and the average was used for data analysis. Radial pressure waveforms were recorded using automated applanation tonometry (HEM-9000AI). The pressure signals were obtained at a sample acquisition frequency of 500 Hz, and converted off-line to 128-Hz data through linear interpolation.[15] An arterial waveform analysis software with a validated generalized transfer function (SphygmoCor; AtCor Medical, New South Wales, Sydney, Australia) processed the data to estimate the central aortic pressure waveforms. The estimated aortic waveforms were calibrated to brachial diastolic pressure and MAP in order to determine the central systolic blood pressure, PP, augmented pressure, and augmentation index. Augmented pressure was defined as the difference between the early and late systolic peaks of aortic pulse waveforms, and the augmentation index was defined as the ratio of augmented pressure to cPP. Forward and backward pressure amplitudes and reflection magnitude (i.e., ratio of backward to forward pressure amplitude) were quantified using wave separation analysis.[16]

Anthropometric and biochemical parameters Body height and weight were recorded to determine the body mass index. Venous blood samples were collected to measure the levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, glutamate-oxaloacetate transaminase, and glutamate-pyruvate transaminase. Spot urine samples were obtained for the measurement of urinary creatinine, albumin, sodium, and potassium levels. Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as a urinary albumin/creatinine ratio (UACR) of <30, 30–299, and at least 300 mg/g, respectively. eGFR was determined on the basis of age, sex, and blood creatinine level using a modified equation specifically for use in the Japanese population.[17] The presence of kidney dysfunction was defined as eGFR <60 ml/min per 1.73 m^2. The existence of CKD was defined as UACR ≥30 mg/g and/or eGFR <60 ml/min per 1.73 m^2.[18] Urinary sodium/creatinine ratio (UNa/UCr) and sodium/potassium ratio (UNa/UK) were measured to evaluate urinary sodium excretion.

Statistical analysis

All data are expressed as mean ± standard deviation (if the distribution was normal), median with interquartile range (if the distribution was skewed), or frequency counts (for categorical data), unless otherwise indicated. Univariate linear relationships between renal parameters (eGFR and UACR) or sodium excretion indices (UNa/UCr and UNa/UK) and other continuous variables were analyzed using Pearson's correlation coefficients (r). Analysis of variance was used to evaluate the combined effects of renal parameters and sodium excretion indices (UNa/UCr and UNa/UK) on cPP, and to compare the subjects' characteristics divided according to cPP. Multivariate linear analysis was performed to determine the independent correlates of cPP and its related factors. According to a previous study,[19] a cPP of ≥50 mm Hg is considered abnormally high. Therefore, factors related to a high cPP were also examined using multivariate analysis. Statistical analyses were performed using SPSS 26.0 (IBM SPSS Japan, Tokyo, Japan). A P value of <0.05 was considered statistically significant.

Table 1. Characteristics of subjects

Variables	Total
Clinical measures	
Age, years	56 ± 10
Women, *n* (%)	556 (60)
Height, cm	161 ± 9
Body mass, kg	62 ± 10
Body mass index, kg/m^2	23.8 ± 3.4
High-density lipoprotein cholesterol, mg/dl	67 ± 18
Low-density lipoprotein cholesterol, mg/dl	127 ± 31
Triglyceride, mg/dl	115 ± 74
Glutamate-oxaloacetate transaminase, U/l	24 ± 11
Glutamate-pyruvate transaminase, U/l	26 ± 18
Urinary creatinine, g/l	1.1 ± 0.7
Estimated glomerular filtration rate, ml/min per 1.73 m^2[a]	71 (64–80)
Urinary albumin/creatinine ratio, mg/g[a]	5 (4–11)
Urinary sodium/creatinine ratio, mEq/g[a]	139 (89–205)
Urinary sodium/potassium ratio, mEq/mEq[a]	4 (3–6)
Hypertension, *n* (%)	359 (38)
Hypercholesterolemia, *n* (%)	509 (55)
Diabetes mellitus, *n* (%)	49 (5)
Currently smoking, *n* (%)[b]	173 (19)
Pressure measures	
Brachial systolic blood pressure, mm Hg	125 ± 16
Brachial diastolic blood pressure, mm Hg	76 ± 11
Mean arterial pressure, mm Hg	94 ± 13
Heart rate, bpm	66 ± 10
Central systolic blood pressure, mm Hg	117 ± 16
Central pulse pressure, mm Hg	40 ± 10
Central augmented pressure, mm Hg	13 ± 6
Central augmentation index adjusted for heart rate 75 bpm, %	28 ± 9
Central forward pressure amplitude, mm Hg[c]	26 ± 6
Central backward pressure amplitude, mm Hg[c]	19 ± 5
Central reflection magnitude, %[c]	75 ± 16

[a]Data were shown as median (interquartile range).
[b,c]Data were available in 915 and 830 subjects, respectively.

RESULTS

Subjects' characteristics

The characteristics of the 933 subjects are presented in Table 1. The mean age was 56 ± 10 years. The mean brachial systolic/diastolic pressures were 125 ± 16/76 ± 11 mm Hg. The median value and interquartile range of UACR were 5 and 4–11 mg/g, respectively. Of the 933 total subjects, 860 (92%) had normoalbuminuria, 65 (7%) had microalbuminuria, and 8 (1%) had macroalbuminuria. The median eGFR was 71 ml/min per 1.73 m^2 (interquartile range: 64–80 ml/min per 1.73 m^2), and 149 (16%) of the total subjects had kidney dysfunction. CKD was observed in 202 (22%) subjects. The median values (interquartile ranges) of UNa/UCr and UNa/UK were 139 (89–205) mEq/g and 4 (3–6) mEq/mEq, respectively. Of the subjects, 359 (38%) had hypertension, 509 (55%) had hypercholesterolemia, and 49 (5%) had diabetes mellitus.

Relationships between sodium excretion indices and cPP

In the univariate analyses (Table 2), log-transformed UNa/UCr and UNa/UK had a positive correlation with cPP. UNa/UCr and UNa/UK were also positively correlated with the forward and backward pressure amplitudes. UNa/UCr, but not UNa/UK, was significantly related to the augmentation index and reflection magnitude (UNa/UCr: $r = 0.16$, $P < 0.001$; UNa/UK: $r = 0.03$, $P = 0.46$). UNa/UCr had no correlation with MAP or diastolic pressure. In contrast, UNa/UK was associated with MAP but not with diastolic pressure.

Relationships between renal parameters and cPP

The log-transformed UACR was positively correlated, whereas the log-transformed eGFR was inversely correlated with cPP (Table 2). These renal parameters were also significantly associated with MAP, diastolic pressure, and backward pressure amplitude, whereas they were not correlated with the augmentation index. UACR, but not eGFR, had a positive correlation with the forward pressure amplitude.

Combined effects of sodium excretion indices and renal parameters on increasing cPP

The subjects' characteristics were compared among the tertile groups classified by cPP (Supplementary Table S1 online). Subjects in the highest tertile of cPP were older, and included more female, diabetic, and hypertensive patients. No group differences were observed in body mass index, high- and low-density lipoprotein cholesterol, triglyceride, and the presence of hypercholesterolemia. When the subjects were divided into 9 groups according to the tertiles of UACR and UNa/UCr, cPP increased with increasing UACR and with increasing UNa/UCr (Figure 1, top panel). These associations remained significant after adjusting for MAP ($P < 0.001$). Combined effects of UACR and UNa/UCr on increasing cPP were not altered by age (<50 years or ≥50 years) and sex (<50 years: $P = 0.04$; ≥50 years: $P < 0.001$; male: $P = 0.03$; female: $P < 0.001$). Similarly, when the subjects were divided according to eGFR and UNa/UCr, a wider cPP was associated with a lower eGFR and a higher UNa/UCr (Figure 1, bottom panel). Even when UNa/UCr was replaced with UNa/UK, significant combined effects of sodium excretion and UACR, eGFR, or CKD on increasing cPP were observed (all $P < 0.001$) (Supplementary Figures S1 [bottom panel] and S2 online).

Table 2. Correlations between central blood pressure measures with sodium excretion and renal parameters

	UNa/UCr		UNa/UK		UACR		eGFR	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Pulse pressure	0.22	<0.001	0.15	<0.001	0.17	<0.001	−0.11	0.001
Mean arterial pressure	0.03	0.35	0.11	0.001	0.15	<0.001	−0.09	0.01
Augmentation index	0.19	<0.001	0.05	0.10	0.04	0.21	−0.04	0.27
Forward pressure amplitude	0.12	<0.001	0.13	<0.001	0.19	<0.001	−0.03	0.35
Backward pressure amplitude	0.21	<0.001	0.13	<0.001	0.13	<0.001	−0.09	0.01
Systolic blood pressure	0.11	0.001	0.14	<0.001	0.19	<0.001	−0.12	<0.001
Diastolic blood pressure	−0.05	0.17	0.07	0.047	0.12	<0.001	−0.07	0.04

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio; UNa/UCr, urinary sodium/creatinine ratio; UNa/UK, urinary sodium/potassium ratio.

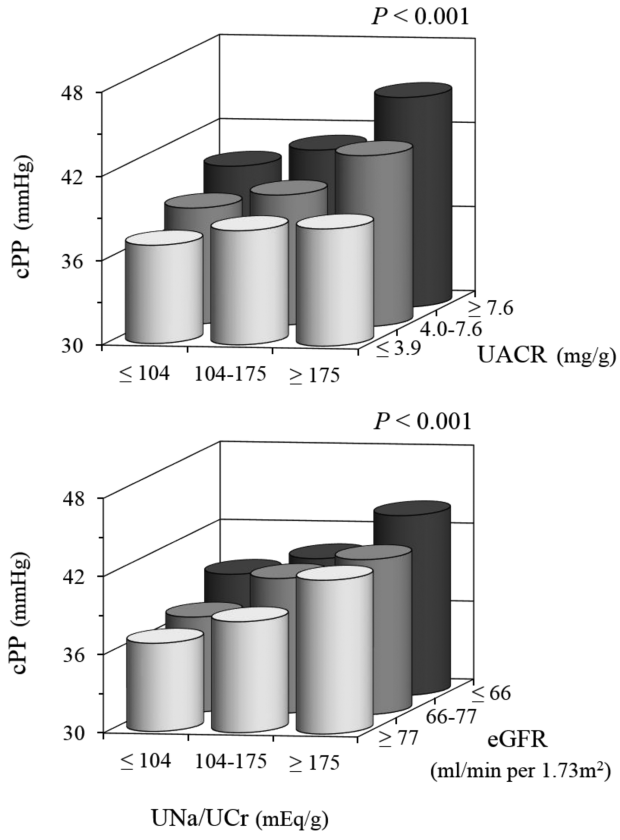

Figure 1. Central pulse pressure (cPP) in subgroups classified according to urinary sodium/creatinine ratio (UNa/UCr) and albumin/creatinine ratio (UACR) (top) and estimated glomerular filtration rate (eGFR, bottom). *P* values were evaluated using analysis of variance.

Synergistic effects of sodium excretion indices and albuminuria or CKD on increasing cPP

Table 3 summarizes the results of the multivariate analysis examining the determinants of cPP. In the initial model (model 1), which considered multiple covariates except renal parameters, UNa/UCr was found to be independently associated with cPP ($P = 0.02$). The other independent factors associated with cPP included age, sex, heart rate, and diabetes. When renal parameters (UACR and eGFR) were included in this model as additional covariates (model 2), both UNa/UCr ($P = 0.04$) and UACR ($P = 0.02$) were found to be significantly related factors to cPP independent of multiple confounders, whereas eGFR was not. Notably, when an interaction term between UNa/UCr and UACR was added into a multivariate model (model 3), it emerged as an independent correlate of cPP ($P = 0.04$). When UACR and eGFR were replaced with the existence of CKD, the UNa/UCr-related increase in cPP was strikingly greater in the presence of CKD ($P = 0.02$) (Supplementary Table S2 online, model 1). When UNa/UCr was replaced with UNa/UK in multivariate models (Supplementary Table S2 online, model 2), UNa/UK was also an independently related factor, and the effect of UNa/UK on cPP was dependent on the interaction with CKD ($P = 0.01$). However, UNa/UK-dependent increase in cPP was slightly affected by UACR (Supplementary Table S3 online).

Data on the independent factors related to central pressure measures except cPP are available in Supplementary Tables S4 and S5 online).

Independent related factors of high cPP (≥50 mm Hg)

Supplementary Figures S3–S5 online show the distribution of cPP at different values of UNa/UCr and/or increasing UACR (Supplementary Figure S3 online), in the existence of CKD (Supplementary Figure S4 online), and at decreasing eGFR values (Supplementary Figure S5 online), as detailed in the Supplemental Digital Content online. Table 4 summarizes the independent factors related to a high cPP (≥50 mm Hg) in multivariate logistic regression models. The combined effect of UNa/UCr and UACR ≥10 mg/g (adjusted odds ratio: 7.63, $P = 0.001$) and the combined effect of UNa/UCr and the existence of CKD (adjusted odds ratio: 8.44, $P = 0.01$) had a significant impact on the widening of cPP (models 1 and 3).

DISCUSSION

We investigated the relationships among sodium excretion, albuminuria, and cPP in the general population. We found that UNa/UCr and UACR both had a positive

Table 3. Independent determinants of central pulse pressure

	Model 1 (covariates)			Model 2 (covariates + eGFR + UACR)			Model 3 (covariates + eGFR + UACR + UNa/UCr*UACR)		
Variables	β	R^2 increment, %	*P*	β	R^2 increment, %	*P*	β	R^2 increment, %	*P*
Age, years	0.28	20.1	<0.001	0.27	19.1	<0.001	0.27	18.3	<0.001
Sex, men/women	−0.14	10.3	<0.001	−0.13	9.5	<0.001	−0.14	9.4	<0.001
Heart rate, bpm	−0.32	23.4	<0.001	−0.33	23.1	<0.001	−0.33	22.2	<0.001
Diabetes mellitus, yes/no	0.11	8.3	<0.001	0.10	7.3	<0.001	0.11	7.2	<0.001
UNa/UCr, mEq/g	0.07	5.3	0.02	0.07	4.6	0.04	0.06	3.9	0.07
eGFR, ml/min per 1.73 m^2				0.02	1.2	0.57	0.02	1.3	0.52
UACR, mg/g				0.07	5.1	0.02	0.07	4.5	0.03
UNa/UCr*UACR							0.06	4.0	0.04

Note: β indicates standardized regression coefficient. Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin/creatinine ratio; UNa/UCr, urinary sodium/creatinine ratio. Covariates were age, sex, body mass index, heart rate, triglyceride, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase, diabetes mellitus, hypercholesterolemia, currently smoking, and UNa/UCr. R^2 for each model (1, 2, and 3) were 0.28, 0.28, and 0.28, respectively. All models were $P < 0.001$.

Table 4. Independent determinants of central pulse pressure (≥50 mm Hg) in multivariate logistic regression models

	Model 1 (covariates + eGFR + UACR + UNa/UCr*UACR)		Model 2 (covariates + eGFR + UACR + UNa/UCr*eGFR)		Model 3 (covariates + CKD + UNa/UCr*CKD)	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, years	1.09 (1.07–1.12)	<0.001	1.09 (1.07–1.12)	<0.001	1.10 (1.07–1.12)	<0.001
Sex, men/women	0.49 (0.32–0.76)	0.001	0.47 (0.31–0.73)	0.001	0.53 (0.35–0.81)	0.003
Heart rate, bpm	0.94 (0.92–0.96)	<0.001	0.94 (0.92–0.96)	<0.001	0.94 (0.92–0.96)	<0.001
Triglyceride, mg/dl	1.00 (1.00–1.01)	0.049	1.00 (1.00–1.01)	0.06	—	0.12
Diabetes mellitus, yes/no	2.73 (1.35–5.52)	0.01	2.66 (1.32–5.34)	0.01	2.56 (1.28–5.14)	0.01
UNa/UCr, mEq/g	—	0.82	—	0.07	—	0.45
eGFR <60 ml/min per 1.73 m^2, yes/no	—	0.28	—	0.56	—	—
UACR >10 mg/g, yes/no	—	0.10	1.73 (1.15–2.62)	0.01	—	—
UNa/UCr*UACR ≥10 mg/g	7.63 (2.20–26.54)	0.001	—	—	—	—
UNa/UCr*eGFR <60 ml/min per 1.73 m^2	—	—	—	0.40	—	—
CKD, yes/no	—	—	—	—	—	0.07
UNa/UCr*CKD	—	—	—	—	8.44 (1.78–40.08)	0.01

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR: estimated glomerular filtration rate; OR, odds ratio; UACR, urinary albumin/creatinine ratio; UNa/UCr, urinary sodium/creatinine ratio. Covariates were selected by stepwise procedure from age, sex, body mass index, heart rate, triglyceride, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase, diabetes mellitus, hypercholesterolemia, currently smoking, and UNa/UCr.

correlation with cPP, as well as a synergistic effect on cPP widening. A similar synergistic effect was found on forward pressure amplitude, but not on MAP, backward pressure amplitude, or augmentation index. The entire results did not change when UACR was replaced with the existence of CKD. Moreover, a UACR of ≥10 mg/g and the existence of CKD strongly reinforced the relationship between the prevalence of high cPP (≥50 mm Hg) and urinary sodium excretion. To our knowledge, the current study is the first to demonstrate that microalbuminuria (and the existence of CKD) strengthens the positive association between urinary sodium excretion and cPP in the general population.

A previous study has reported that the increase in MAP with switching from low to high-sodium intake is greater in type 2 diabetic patients with microalbuminuria (median: 91 μg/min) than in those with normoalbuminuria (10 μg/min).[20] Similar switching causes a larger increase in MAP in hypertensive patients with microalbuminuria than in those with normoalbuminuria.[21] The results of the present study are in agreement with and further extend previous findings in terms of the following points. First, the present study used pulsatile pressure (cPP) rather than steady-state pressure, which is known to be better related to target organ damage and cardiovascular outcomes.[2,5,22,23] Second, 92%

of the general population cohort in the present study had normoalbuminuria, and only 22% had CKD. Even a slight increase in urinary albumin within the normoalbuminuric range was associated with an increase in cPP. Third, the present study demonstrated that increased sodium excretion and albuminuria had a synergistic effect on increasing forward (but not backward) pressure amplitude. These findings indicate that even mild damage to the renal microvasculature heightens the increase in central forward propagating waves caused by excess sodium intake.

Excessive dietary sodium intake is known to increase MAP, even in the short-term (e.g., 1 week).[13] This response is strongly increased by an individual's blood pressure salt sensitivity. After sodium loading, MAP increases more in salt-sensitive subjects than in non-salt-sensitive subjects.[24,25] Importantly, renal injury and loss of functional nephrons elicit blood pressure salt sensitivity.[25,26] Surgical removal of about 70% of kidney mass increases the salt sensitivity of blood pressure.[26] Salt loading causes a greater increase in MAP in patients with severe kidney disease than in those with moderate kidney disease.[14] However, (micro)albuminuria may be more importantly related to a salt-dependent increase in MAP than the glomerular filtration rate.[21] Thus, Hall has reported that renal microvascular damage, even if slight, increases the blood pressure salt sensitivity.[27] In the present study, the positive relationship between urinary sodium excretion and cPP, which is a better predictor of CVD than MAP, was further strengthened in the presence of CKD, particularly with albuminuria. This finding is far more intriguing than the relationship between renal microvascular damage and salt-dependent increase in MAP. Notably, although most subjects in this study had normoalbuminuria, UACR ≥10 mg/g had a major impact on sodium excretion-related cPP widening (≥50 mm Hg). These results indicate that even slight albuminuria has a deleterious effect on the association between sodium excretion and cPP in the general population. Albuminuria (UACR ≥10 mg/g) is a powerful predictor of CVD mortality risk in the general population.[8] The present observation may provide important evidence that even slight albuminuria increases the CVD risk by widening cPP.

High salt intake increases stroke volume with an increase in plasma volume.[28] The increases in intravascular fluid volume and MAP after salt intake are more pronounced in patients with severe kidney disease than in those with moderate kidney disease,[14] suggesting that renal microvascular damage magnifies an increase in stroke volume caused by excess salt intake. In the present study, the synergistic influence of urinary sodium excretion and albuminuria was found on the forward pressure amplitude, but not on the backward pressure amplitude or augmentation index. Given a large dependence of the forward wave on stroke volume, the observed synergistic influence on cPP might be attributable to an increase in pressure volume rather than in peripheral wave reflection.

In contrast to UNa/UCr, UNa/UK was not capable of reflecting the synergistic influence of urinary sodium excretion and UACR on cPP. This might be explained by the relationship between sodium intake and potassium excretion. Urinary potassium excretion decreases with a high-sodium diet in salt-sensitive subjects,[29] and this response may be induced by activating the sodium/potassium 2-chloride (Na/K-2Cl) cotransporter in the distal tubules.[30] The possibility exists that increased salt sensitivity with renal microvascular damage induces a decrease in potassium excretion and a resultant exaggerated increase in UNa/UK in response to sodium intake due to increased Na/K-2Cl cotransporter activity.

The present study found that UACR intensifies the positive correlation between urinary sodium excretion and cPP. However, cPP also contributes to the development of renal microvascular damage.[2] Owing to the cross-sectional design, the present study cannot substantiate a direct causality between renal microvascular damage and cPP widening attributed to excess sodium intake. Prospective studies are required to confirm the mechanistic hypothesis obtained from our data.

This study had some limitations. First, the cross-sectional nature of the present study does not allow the establishment of causal relationships among sodium excretion, renal microvascular damage, and central pulsatile pressure. Second, we assessed urinary sodium excretion indices using spot urine sampling. This might not reflect daily variations in sodium intake. However, measurement of UNa/UCr in spot urine is a practical alternative for general medical facilities, and this method has been validated.[31] Third, our study cohort was a general population sample, and most subjects had no CKD (78%). Whether similar results could be obtained in patients with moderate to severe CKD needs to be confirmed. Fourth, the information on the use of diuretics and sodium-glucose cotransporter 2 inhibitor (SGLT2) inhibitor was not available in this study. However, diuretics (e.g., thiazide) does not change urinary sodium excretion after 1-week treatment.[32] Although SGLT2 inhibitor transiently increases urinary sodium excretion,[33] treatment with long-term SGLT2 inhibitor may not affect urinary sodium excretion.[34] Further studies are needed to clarify whether these drug treatments would affect the relationships among dietary sodium intake, albuminuria, and cPP.

In summary, the present study indicates that (micro)albuminuria strengthens the positive association between urinary sodium excretion and cPP. In addition, a UACR of ≥10 mg/g and the existence of CKD strongly reinforced the relationship between the prevalence of high cPP (≥50 mm Hg) and urinary sodium excretion. Excess sodium intake may magnify CVD risk through widening aortic pulsatile pressure particularly in the existence of albuminuria.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

The authors declared no conflict of interest.

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