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The relationship between estimated salt intake and central systolic blood pressure in Japanese outpatients with hypertension

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Abstract:

Background: Recent reports suggest that central blood pressure (BP) may be instrumental in the diagnosis and management of hypertension. Several reports have shown an association between salt intake and central hemodynamics, especially central systolic BP; however, this relationship remains unclear in Japanese outpatients with hypertension. Therefore, this study investigated the relationship between central systolic BP and salt intake in Japanese outpatients with hypertension. **Methods:** We recruited 141 Japanese outpatients with hypertension. Their daily salt intake was estimated using spot urine samples. Their central systolic BP was measured using an Omron HEM-9000AI device. **Results:** The median estimated salt intake was 9.81 (range, 8.34-11.47) g/day. The mean brachial systolic/diastolic BP and central systolic BP were 131.2 ± 16.5 /78.1 ± 10.9 mmHg and 135.6 ± 17.3 mmHg, respectively. The estimated salt intake was divided into four quartiles, with central systolic BP significantly higher in Q3 and Q4 than that in Q1 ($P < 0.01$). A significant positive correlation was observed between central systolic BP and estimated salt intake ($r=0.275$, $P=0.001$). Multiple regression analysis of central systolic BP showed that the estimated salt intake and BMI were significant factors ($P = 0.014$ and $P = 0.027$, respectively). **Conclusions:** We found that our Japanese outpatients with hypertension consumed higher amounts of salt than the target value recommended by Japanese guidelines. In addition, there was a moderate relationship between central systolic BP and the estimated salt intake. Therefore, a decrease in salt intake is important, even in outpatients with hypertension receiving antihypertensive medication.

Key words:

Salt intake, Hypertension, Central blood pressure

Introduction

The number of patients with hypertension has increased to ˜43 million in Japan, representing one-third of the Japanese adult population in 2010[1)]. Hypertension is a crucial risk factor in the progression of cardiovascular and cerebrovascular diseases and mortality[2-4)] and appropriate blood pressure (BP) control improves the prognosis of hypertensive patients[5,6)].

BP measured using the brachial artery has typically been used for patient evaluation and management. However, in recent years, attention has shifted to the central BP, defined as the sum of the forward pressure wave created by ventricular contraction and the pressure wave reflected from the peripheral arterial system. The central BP reflects the true load on the heart, kidneys, and brain and the central blood flow influences the local flow into these vital organs. Recent technological advances have enabled the noninvasive evaluation of pulsatile hemodynamics in the central aorta[7,8)] and it has become clear that the central BP is more closely related to cardiovascular events and target organ damage compared to brachial BP. The results of several studies have suggested

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that central systolic BP is an important parameter and a prognostic risk factor[9-14]. Additionally, in patients with similar brachial BP but different central systolic BP, lower central systolic BP levels resulted in more favorable clinical outcomes. These results suggest that central systolic BP has better predictive power for future cardiovascular events than that of brachial BP.

Salt, a ubiquitous food ingredient, is important for both food preservation and taste enhancement, leading to its consumption in large amounts. Epidemiological studies have found that excessive salt intake is associated with high brachial BP and an increased prevalence of hypertension[15,16]. In a recent Cochrane meta-analysis of data from 35 trials, a 100-mmol reduction in the 24-h urinary sodium level led to a reduction not only in the systolic/diastolic BP of 5.4/2.8 mmHg in hypertensive individuals but also of 2.4/1.0 mmHg in normotensive individuals[17]. In a study by Cook et al., high sodium intake was associated with an increased risk of mortality and was directly related to total mortality[18]. Therefore, implementing a salt-restrictive diet should become a target to reduce health problems associated with salt overuse.

The World Health Organization currently recommends limiting salt intake to less than 5 g/day[19] and the Japanese guidelines for the management of hypertension 2014 (JSH 2014) recommend limiting salt intake to 6 g/day in patients with hypertension[20]. However, the actual salt intake among Japanese outpatients with hypertension has not been clearly established. Additionally, several reports have shown an association between salt intake and central hemodynamics[21,22]; however, the relationship remains unclear in Japanese outpatients with hypertension.

Therefore, this study aimed to investigate the actual salt intake and its relationship to central systolic BP in Japanese outpatients with hypertension.

Methods

Patients with essential hypertension who visited the cardiovascular division of Shimane University Hospital between December 2012 and May 2016 were included in this study. The patients' conditions were stable and they had been taking a stable dosage of antihypertensive medication for at least one month. Patients who had recently changed any medications at the discretion of their attending physicians, those with apparent decompensated heart failure, those with acute or severe chronic renal failure (estimated glomerular filtration rate <15 mL/min/1.73 m^2), those on hemodialysis, those with infectious disease, and those with atrial fibrillation were excluded. Eventually, 141 outpatients with hypertension (65 men and 76 women; mean age, 67.6 ± 9.4 years) were enrolled in the study.

Body height and weight were measured and body mass index (BMI) (weight [kg]/height $[m]^2$) was calculated for all patients.

Patients with systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and those taking antihypertensive medications were considered to have hypertension. Patients were considered to have diabetes mellitus if their fasting plasma glucose level was ≥126 mg/dL, $HbA1_C$ was ≥6.5% in a recent blood sampling test, or if they used anti-diabetic medication. Patients with a low-density lipoprotein cholesterol level ≥140 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, and triglycerides level ≥150 mg/dL in a recent blood sampling test or those taking anti-dyslipidemic drugs were considered to have dyslipidemia. Those with a uric acid level ≥7.0 mg/dL in a recent blood sampling test or on anti-hyperuricemic medication were considered to have hyperuricemia.

The ethics committee of Shimane University approved this study protocol and written informed consent was obtained from all patients.

Estimation of salt intake

The daily dietary salt intake was estimated based on sodium (Na) and creatinine (Cr) concentrations measured in spot urine samples. This approach was selected for convenience because the estimation based on Na and Cr content in 24-h pooled urine, which is the most reliable method of evaluation of salt intake, is difficult to perform in outpatients in routine medical practice. The daily salt intake was measured using Tanaka's equation[23]. The estimated 24-h urinary salt excretion (g/day) was calculated as follows: 21.98 × [Na (mEq l^{-1})/ Cr (mg l^{-1}) in spot urine × expected 24-h Cr excretion]$^{0.392}$, where the expected 24-h Cr excretion (mg/day) = −2.04 × age (years) + 14.89 × weight (kg) + 16.14 × height (cm) − 2244.45. The Japanese Society of Hypertension (JSH 2014) recommends the use of Tanaka's equation for the estimation of salt intake[20]. Spot urine samples were collected at the time of patient visits, between 08:30 and 11:00 am.

Measurement of brachial and central systolic BP

All patients were examined in a quiet temperature-controlled room while in a seated position with their backs supported. After 5 minutes of seated rest, brachial systolic, diastolic, and central systolic BP were measured by a laboratory technician.

An automated device (HEM-9000AI; Omron Healthcare, Kyoto, Japan) was used to simultaneously record radial artery pressure waveforms and brachial BP, while brachial BP was measured using Omron's built-in oscillometric sphygmomanometer[7,8]. This device automatically estimates central systolic BP, augmentation index (AI), and augmentation index normalized to a heart rate of 75 bpm (AIP75) using applanation tonometry of the radial artery. In clinical situations, the procedure is simple and does not require an operator, which facilitates the assessment of central BP. The details of the measurements and reproducibility of this automatic method have been described previously[7,8,24].

Table 1. Characteristics of the study participants

	All
Number of patients	141
Age (years)	67.6±9.4
Gender (female, %)	76 (54%)
Body height (cm)	158.4±7.9
Body weight (kg)	59.1±10.2
Body mass index	23.4±3.4
Brachial systolic BP (mmHg)	131.2±16.5
Brachial diastolic BP (mmHg)	78.1±10.9
Central systolic BP (mmHg)	135.6±17.3
Heart rate (beats/min)	73.4±11.7
Estimated salt intake (g/day)	9.81 (8.31-11.47)
Comorbidities	
Dyslipidemia	82 (58%)
Diabetes mellitus	35 (25%)
Hyperuricemia	19 (14%)
Chronic kidney disease	16 (11%)
Coronary heart disease	24 (17%)
Antihypertensives	
ACEIs and/or ARBs	82 (58%)
Ca antagonist	74 (52%)
β-blocker	17 (12%)
α-blocker	3 (2%)
Diuretics	6 (4%)

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker

Statistical analysis

Continuous data are expressed as means ± SD or as medians (interquartile range), depending on data distribution. Categorical data are expressed as numbers (%). To analyze salt intake as a categorical variable, four quartiles representing estimated salt intake were established. To compare the baseline characteristics of patients assigned to the quartiles, analysis of covariance was used for continuous variables and χ^2 tests for dichotomous and categorical variables.

SPSS 22.0 for Windows (SPSS Japan, Tokyo, Japan) was used for statistical analysis. All *P*-values were two-tailed. *P*-values < 0.05 were considered to indicate statistical significance.

Results

The clinical characteristics of the 141 outpatients are shown in **Table 1**. The mean age, body height, body weight, and BMI were 67.6 ± 9.4 years, 158.4 ± 7.9 cm, 59.1 ± 10.2 kg, and 23.5 ± 3.4 kg/m^2, respectively. Eighty-two patients had dyslipidemia (58%), 35 had diabetes mellitus (25%), 19 had hyperuricemia (14%), 16 had chronic kidney disease (11%), and 24 had coronary heart disease (17%). Renin-angiotensin system blockade were the most commonly prescribed antihypertensive drugs (82 patients, 58%), followed by Ca-channel blockers (74 patients, 52%), β-blockers (17 patients, 12%), diuretics (6 patients, 4%), and α-blockers (3 patients, 2%).

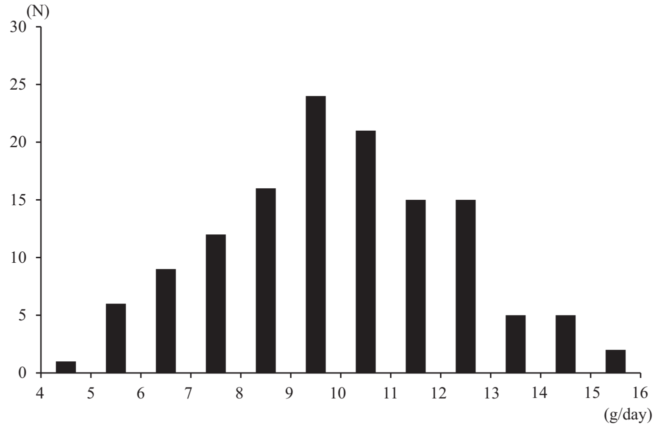

Figure 1. Distribution of the estimated salt intake in the study participants

The median salt intake measured by Tanaka's formula was 9.81 (range, 8.34-11.47) g/day. As shown in **Figure 1**, the values of the estimated salt intake ranged from 4.65 to 15.55 g/day. Only seven patients (5%) had a daily salt intake within the range recommended by JSH 2014 (<6.0 g/day).

The mean brachial systolic/diastolic BP was 131.2 ± 16.5/78.1 ± 10.9 mmHg and the mean heart rate was 73.4 ± 11.7 beats/min. The mean central systolic BP was 135.6 ± 17.3 mmHg.

The estimated salt intakes were separated into four quartiles (Q1: <8.34, Q2: 8.34-9.81, Q3: 9.81-11.47, and Q4: > 11.47 g/day). The clinical characteristics of the patients according to the quartile of salt intake are shown in **Table 2**. Brachial systolic BP, diastolic BP, and central systolic BP were significantly higher in Q4 than those in Q1 (**Figure 2**). Moreover, the linear regression analysis showed that not only brachial systolic and diastolic BP, but also central systolic BP had significant and positive correlations with estimated salt intake (**Figure 3**). Each coefficient of correlation did not show significant differences. The estimated salt intake was marginally correlated with AI and was significantly correlated with AIP 75 (r=0.166, p=0.050, **Figure 4**). Multiple regression analysis of central systolic BP showed that the estimated salt intake and BMI were significant factors (β =0.210, p=0.014 and β=0.182, p= 0.027, respectively, **Table 3**).

Discussion

In this study, our Japanese outpatients with hypertension consumed more salt than the target value recommended by the Japanese guidelines. To our knowledge, this is the first study to show the relationship between central systolic BP and estimated salt intake in Japanese outpatients with hypertension.

Although the average salt intake in Japan has decreased in recent years, it remains high, at up to 9.9 g/day in 2016 according to a recent national survey[25]. The JSH 2014 guidelines recommend that salt intake be reduced to 6 g/day in

Table 2. Clinical characteristics of the patients according to the quartiles of salt intake

	All (n=141)	Q1 (n=35) SI, <8.34	Q2 (n=36) SI, 8.34-9.81	Q3 (n=35) SI, 9.81-11.47	Q4 (n=35) SI, 11.47<	P-values
Age (years)	67.6±9.4	68.7±11.3	68.4±9.0	66.9±8.1	66.6±9.2	0.740
Sex (men)	65 (46%)	17 (49%)	17 (47%)	14 (40%)	17 (49%)	0.870
Dyslipidemia	82 (58%)	19 (54%)	21 (58%)	20 (57%)	22 (63%)	0.908
Diabetes mellitus	35 (25%)	8 (23%)	6 (17%)	11 (31%)	10 (29%)	0.487
Hyperuricemia	19 (14%)	6 (17%)	2 (6%)	5 (14%)	6 (17%)	0.429
Chronic Kidney Diseases	16 (11%)	1 (3%)	5 (14%)	2 (6%)	8 (23%)	0.038
Coronary Heart Diseases	24 (17%)	8 (23%)	8 (22%)	2 (6%)	6 (17%)	0.195
ACEIs and/or ARBs	82 (58%)	21 (60%)	20 (56%)	17 (49%)	24 (69%)	0.387
Ca antagonist	74 (52%)	22 (63%)	18 (50%)	15 (43%)	19 (54%)	0.400
β-blocker	17 (12%)	4 (11%)	4 (11%)	5 (14%)	4 (11%)	0.974
α-blocker	3 (2%)	0 (0%)	1 (3%)	1 (3%)	1 (3%)	0.798
Diuretics	6 (4%)	1 (3%)	1 (3%)	1 (3%)	3 (9%)	0.546
Body height (cm)	158.4±7.9	155.7±8.2	158.7±8.2	159.6±5.8	159.7±8.6	0.114
Body weight (kg)	59.1±10.2	55.7±10.4	57.4±8.5	60.9±10.3	62.5±10.5*	0.019
Body mass index	23.5±3.4	22.9±3.9	22.7±2.9	23.8±3.1	24.5±3.5	0.090
Brachial systolic BP (mmHg)	131.2±16.5	125.7±16.2	129.9±15.0	133.1±16.3	136.3±17.4*	0.048
Brachial diastolic BP (mmHg)	78.1±10.9	72.8±11.1	77.4±8.8	81.2±9.3**	81.2±12.2**	0.002
Central systolic BP (mmHg)	135.6±17.3	127.9±17.3	134.4±16.3	139.6±16.1*	140.5±17.4*	0.008
Heart Rates (beats/min)	73.4±11.7	74.1±11.7	72.1±13.8	73.5±11.7	74.0±9.4	0.879

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, *vs. Q1, p<0.05, **vs. Q1, p<0.01

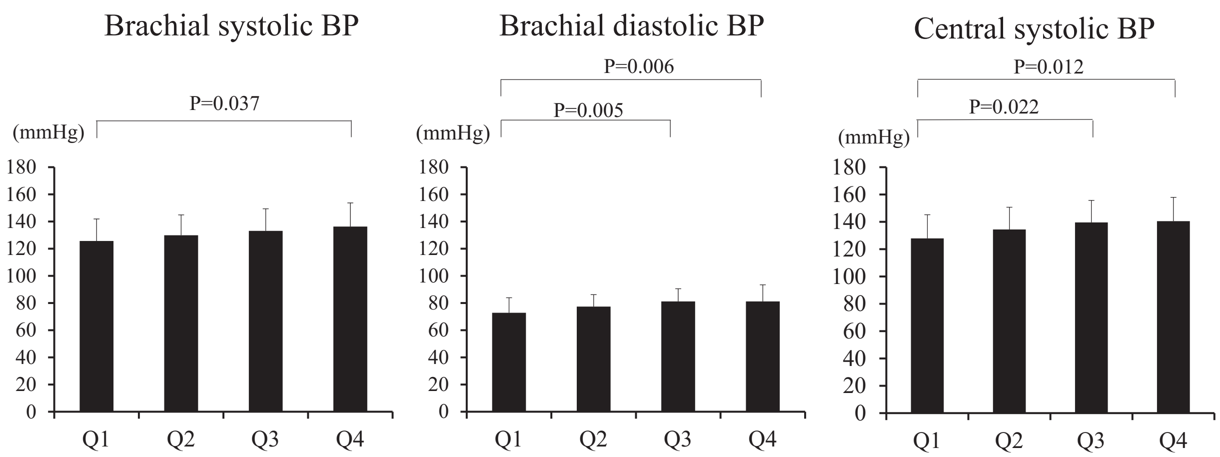

Figure 2. Relationships between the quartiles of estimated salt intake, brachial systolic/diastolic BP, and central systolic BP

patients with hypertension[20]; however, the actual salt intake in Japanese outpatients with hypertension remains to be precisely determined.

In the present study, the median salt intake in our Japanese outpatients with hypertension was 9.81 (range, 8.34-11.47) g/day, which greatly exceeds the 6.0 g/day limit recommended by the JSH 2014 guidelines. Only seven patients (5%) in our study had a daily salt intake of <6.0 g. Previous studies reported the salt intake in Japanese outpatients with hypertension to range from 9.6 to 9.7 g/day[26,27]. Recently, we also demonstrated a mean salt intake in 236 Japanese outpatients with hypertension of 9.72 ± 2.43 g/day and only 4% of the patients had a daily salt intake of <6.0 g[28]. Therefore, the results of this study appear to reflect the unpleasant truth regarding excessive salt intake in Japanese outpatients with hypertension, which has not yet decreased sufficiently.

For many years, BP has generally been measured at the brachial artery and the brachial BP has been widely used for the diagnosis and treatment of hypertension. However, central BP has recently attracted attention. Central BP is speculated to reflect the true burden to the heart, kidneys, and brain and also influences the local flow to these vital organs. Additionally, the elevation of central BP may have a direct adverse effect on the target organs and, consequently, on the cardiovascular prognosis of patients with hypertension.

However, until quite recently, central hemodynamics were rarely estimated because their assessment required invasive catheterization. The development of noninvasive methods has removed this requirement, making it easy to measure central hemodynamics. One of the recently introduced auto-

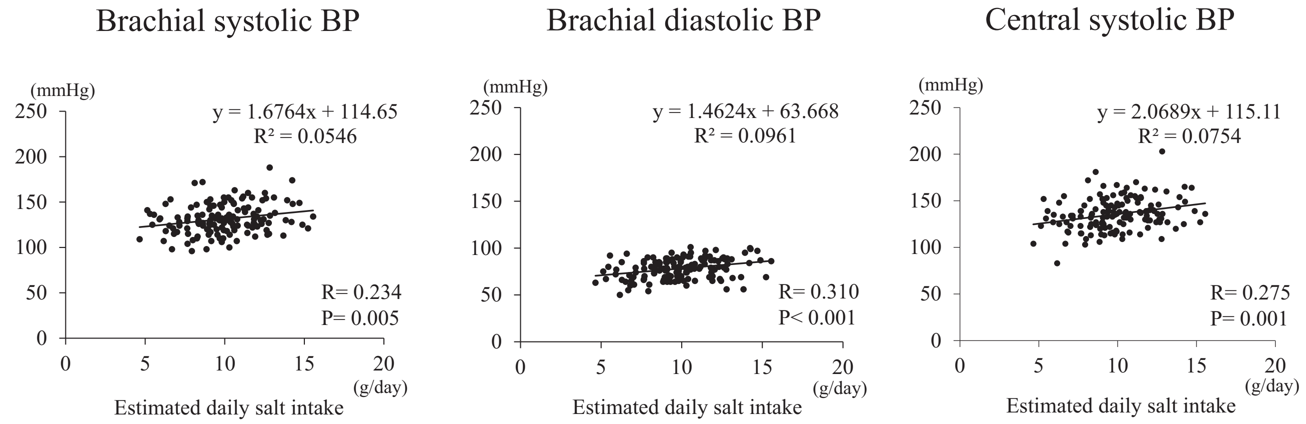

Figure 3. Linear regression analysis of the estimated salt intake, brachial systolic/diastolic BP, and central systolic BP

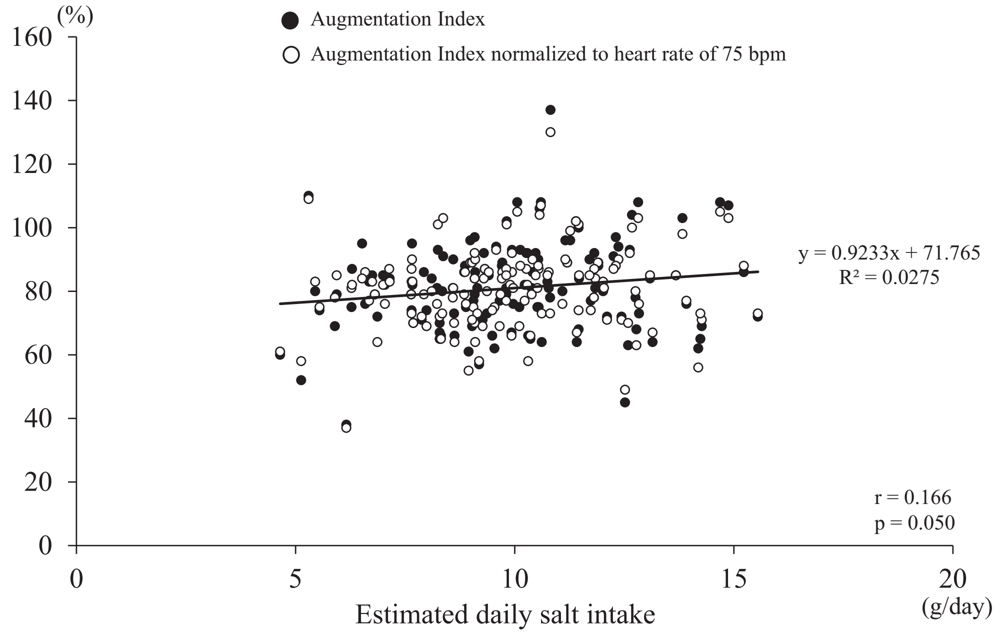

Figure 4. Linear regression analysis of the estimated salt intake, augmentation index, and augmentation index normalized to a heart rate of 75 bpm

mated devices for the estimation of central hemodynamics is the HEM-9000AI. This device automatically records the radial pulse waveform, while the BP equivalent to the second systolic peak is measured by adjustment against the brachial BP. A regression equation is then used to estimate the central systolic BP. Owing to the simplicity of these measurements, this device is now widely used in Japan. These non-invasive estimates are closely correlated with the results of invasive measurements of central BP in the ascending aorta[7,8]. Studies have demonstrated that central BP measured non-invasively predicts cardiovascular events and target organ damage independently and is considered a better indicator than conventional brachial BP for the treatment of hypertension. Studies have also suggested that central systolic BP is an important parameter and a prognostic risk factor[9-14]. Additionally, Williams et al. demonstrated that lower central systolic BP levels resulted in more favorable clinical outcomes in patients with similar brachial systolic BP but different central systolic BP[9]. These results suggest that central systolic BP has a better predictive power for future cardiovascular events than that of brachial BP.

Epidemiological studies have shown a correlation between excessive salt intake, BP measured at the brachial artery, and the prevalence of hypertension[15-17]. A recent Japanese study also demonstrated a significant positive correlation between estimated salt intake and brachial BP in both treated and untreated individuals with hypertension[29]. However, the relationship between central hemodynamics and salt intake in Japanese outpatients with hypertension was unclear. The results of the present study showed the moderate relationship between salt intake and not only brachial systolic/diastolic BP but also central systolic BP. This finding emphasizes the importance of a reduction in salt intake in Japanese outpatients with hypertension, even in those taking antihypertensive medication. Additionally, because elevated central systolic BP is associated with future cardiovascular events, the

Table 3 Univariate and multivariate analysis of the central systolic BP

	Univariate analysis		Multivariate analysis	
	β	P-value	β	P-value
Age	0.069	0.417		
Gender (female)	0.119	0.159		
Body height	-0.097	0.252		
Body weight	0.139	0.099		
Body mass index	0.233	0.005	0.182	0.027
Heart rates	0.028	0.738		
Estimated salt intake	0.275	0.001	0.210	0.014
Comorbidities				
Dyslipidemia	0.078	0.356		
Diabetes mellitus	0.069	0.413		
Hyperuricemia	0.068	0.422		
Chronic kidney disease	0.184	0.029	0.116	0.162
Coronary heart disease	-0.160	0.059		
Antihypertensives				
ACEIs and/or ARBs	-0.084	0.323		
Ca antagonist	-0.111	0.190		
β-blocker	-0.008	0.928		
α-blocker	0.060	0.477		
Diuretics	0.060	0.481		

ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, β: standard partial regression coefficient

reduction of salt intake may be an important strategy to suppress the elevation of central systolic BP.

Central aortic pressure comprises a forward traveling wave from the heart and a reflected wave from the periphery. AI is widely used as an index of pulse wave reflection; that is, arterial stiffness. Several reports demonstrated that AI predicts cardiovascular events and mortality independent of peripheral BP[30,31]. Additionally, recent reports demonstrated that high salt intake may have a BP-independent effect on vascular wall function[32-34]. The present study demonstrated the significant relationship between estimated salt intake and AIP75 (**Figure 4**). The results suggest that salt intake influences arterial stiffness, similar to the results of previous studies, and may be one of the mechanisms by which salt intake increases central systolic BP.

Limitations

This study has several limitations. First, its cross-sectional nature resulted in an inability to speculate on the causality between the estimated salt intake and central systolic BP. Second, the number of patients was very small and only patients from the cardiovascular division of Shimane University Hospital were recruited. These patients might slightly differ in terms of clinical characteristics from those of patients visiting a general medical practitioner. Third, the measurement of daily urinary salt excretion in a spot urine sample might be less accurate than that made using 24-h urine collection. Although 24-h urine collection is the most accurate method for evaluating salt intake, it is difficult to obtain a complete and accurate sample in outpatients. Fourth, both central systolic BP and estimated salt intake were measured only once. Finally, although the study evaluated the relationship between central systolic BP and estimated salt intake, it did not determine whether a decrease in salt intake reduces central systolic BP.

Therefore, further studies are required to validate this method of estimating daily salt intake and to evaluate the relationship between central systolic BP and estimated salt intake in detail.

Conclusion

We found that our Japanese outpatients with hypertension consumed higher amounts of salt than the target value recommended by Japanese guidelines. In addition, there was a moderate relationship between the central systolic BP and the estimated salt intake. These results suggest that a reduction in salt intake is important, even in outpatients with hypertension receiving antihypertensive medication.

Conflicts of Interest
The authors declare no conflicts of interest.

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