ORIGINAL ARTICLE

Aldosterone-to-renin ratio and home blood pressure in subjects with higher and lower sodium intake: the Ohasama Study

Michihiro Satoh¹, Masahiro Kikuya¹, Azusa Hara², Takayoshi Ohkubo^{1,3}, Takefumi Mori⁴, Hirohito Metoki^{1,5}, Megumi T Utsugi⁶, Takuo Hirose¹, Taku Obara^{1,7}, Ryusuke Inoue⁸, Kei Asayama¹, Kazuhito Totsune^{1,9}, Haruhisa Hoshi¹⁰, Hiroshi Satoh¹¹ and Yutaka Imai¹

Aldosterone-to-renin ratio (ARR) is used to screen primary hyperaldosteronism. We investigated the association between ARR and the prevalence of hypertension using home blood pressure (HBP) measurements in community residents stratified for long-term habitual dietary sodium intake. We obtained HBP and conventional blood pressure (CBP) data for 514 participants aged ≥ 35 years not receiving antihypertensive treatment in the general population of Ohasama (mean age: 59.7 ± 10.8 years; 71.2% women). A standardized method was used to calculate habitual sodium intake from a food-frequency questionnaire. The prevalence of HBP hypertension ($\geq 135/85$ mm Hg) and CBP hypertension ($\geq 140/90$ mm Hg) were 12.6 and 20.2%, respectively. The median plasma renin activity (PRA), plasma aldosterone concentration (PAC) and ARR were $1.1 \text{ ng ml}^{-1} \text{ h}^{-1}$, $6.4 \text{ ng per } 100 \text{ ml}$ and $5.5 \text{ ng per } 100 \text{ ml per ng ml}^{-1} \text{ h}^{-1}$, respectively. After adjustment for possible confounding factors, each 1 s.d. increase in logARR was associated with the prevalence of HBP hypertension (odds ratio 1.37; $P=0.04$), but not with the prevalence of CBP hypertension ($P=0.2$). The association of ARR with HBP hypertension was strengthened for subjects with high sodium intake (greater than or equal to the median of 4822 mg day^{-1}), whereas it became nonsignificant for those with low sodium intake (interaction $P=0.03$). Among subjects with high sodium intake, HBP hypertensives had significantly lower PRA than normotensives, despite no differences in PAC. In conclusion, relative aldosterone excess or low-renin hypertension may have an important role in HBP hypertension in the general population with high sodium intake.

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INTRODUCTION

Aldosterone has been implicated in the pathogenesis of hypertension in several experimental and clinical studies. Many studies^{1–5} have indicated a positive association between aldosterone and hypertension; others^{6–8} have shown that hypertensive patients had normal^{6,8} or low⁷ aldosterone levels compared with values in normotensive subjects. One of the reasons for these inconsistent results could be the confounding effect of antihypertensive medications, differences in time of blood sampling, body position and dietary sodium intake, which significantly affect aldosterone levels.^{9,10} In most studies, long-term dietary sodium intake has not been considered. Most studies^{1,3–8} use spot urine samples,^{1,7,8} 24-h urine collection^{4,6} and short-term

dietary sodium restriction;^{5,6} only one study³ measured long-term habitual sodium intake using a dietary record. To evaluate the long-term effect of dietary sodium intake, we surveyed habitual dietary sodium intake.

The aldosterone-to-renin ratio (ARR) is believed to be a more robust screening test than aldosterone levels for primary aldosteronism, and could be an index for inappropriate aldosterone activity and salt sensitivity.^{9,11} However, limited information^{2,3} is available on the association of ARR with hypertension.

All the above-mentioned studies^{1–8} were based solely on conventional blood pressure (CBP) measurements. No studies have investigated the association between ARR and hypertension using home

¹Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan; ²Division of Epidemiology and Prevention, Research Center for Cancer Prevention and Screening National Cancer Center, Tokyo, Japan; ³Department of Health Science, Shiga University of Medical Science, Ohtsu, Japan; ⁴Division of Nephrology, Endocrinology, and Vascular Medicine, Department of Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan; ⁵Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan; ⁶National Institute of Health and Nutrition, Tokyo, Japan; ⁷Department of Pharmacy, Tohoku University Hospital, Sendai, Japan; ⁸Medical Informatics, Tohoku University Hospital, Sendai, Japan; ⁹Department of Social Welfare, Faculty of Synthetic Welfare, Tohoku Fukushi University, Sendai, Japan; ¹⁰Ohasama Hospital, Iwate, Japan and ¹¹Department of Environmental Health Sciences, Tohoku University Graduate School of Medicine, Sendai, Japan

Correspondence: Dr M Kikuya, Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences, 6-3 Aramaki-aza-Aoba, Aoba-ku, Sendai 980-8578, Japan.

E-mail: kikuyam@m.tains.tohoku.ac.jp

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blood pressure (HBP) measurements, which are reportedly more reliable than CBP and avoid both observer and regression dilution biases.¹² HBP measurements eliminate the white-coat effect,¹² offer more prognostic significance than CBP measurements¹³ and are more indicative of target organ damage.¹⁴

The objective of this cross-sectional study was to investigate the association between ARR and the prevalence of hypertension using HBP measurements in community residents stratified for long-term dietary sodium intake, as assessed by a food-frequency questionnaire.

METHODS

Design

This investigation was a part of the Ohasama study. The socioeconomic and demographic characteristics of this region and details of the study project have been described previously.^{13,15} The institutional review boards of Tohoku University School of Medicine and the Department of Health of the Ohasama Municipal Government approved the study.

Study population

In 1997, the population of Ohasama included 7318 subjects. Of those, 4992 were ≥ 35 years old, and 2719 had a health check-up that year. Subjects ($n=888$) who did not undergo a health check-up were ineligible. Of the 1831 eligible individuals, 1350 subjects (74%, mean age: 61.5 ± 11.2 years; 65% women) gave informed consent and participated in the present study. For the current analysis, we excluded 597 individuals who did not measure their morning HBP ≥ 3 times.¹⁶ Furthermore, we excluded 228 subjects treated with antihypertensive drugs because of the effects of antihypertensive medications on the renin-angiotensin system.¹⁷ We also excluded 11 subjects because of insufficient data on nutrient intake. Therefore, 514 subjects were included in the analyses of HBP hypertension. We did not perform adrenal computed tomography scan, because primary aldosteronism was not suspected in any subjects. The 514 subjects were significantly younger and comprised a higher proportion of women than the excluded individuals.

BP measurements

Physicians and/or public health nurses instructed participants on how to perform HBP measurements. Participants were asked to measure their BP once every morning over 4 weeks using an oscillometric device¹⁸ (HEM701C, Omron Healthcare, Kyoto, Japan) within 1 h of waking, with measurements performed in a sitting position after >2 min of rest.¹⁹ The HBP of an individual was defined as the mean of all measurements obtained for that person.

CBP was measured twice consecutively during the health check-up held from 0900 to 1100 h or from 1300 to 1500 h. Measurements were taken by nurses or technicians at local medical centers using an automatic USM-700F sphygmomanometer¹⁸ (UEDA Electronic Works, Tokyo, Japan) based on the Korotkoff sound technique. All measurements were taken with subjects in the sitting position, after a minimum of 2-min rest. The mean of the two readings was defined as the CBP.

We defined HBP hypertension as BP ≥ 135 mm Hg systolic or ≥ 85 mm Hg diastolic; CBP hypertension was defined as BP ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic.

Physical and biochemical examinations

Blood for measurement of plasma renin activity (PRA, $\text{ng ml}^{-1} \text{h}^{-1}$) and plasma aldosterone concentrations (PAC, ng per 100 ml) was drawn with subjects in a sitting position after ~ 30 min of rest, between 0900 and 1100 h or between 1300 and 1500 h; most subjects had not fasted. Blood was collected in chilled EDTA tubes and measured by radioimmunoassay (SRL, Tokyo, Japan). The interassay coefficients of variation were 10.5% at $1.5 \text{ ng ml}^{-1} \text{h}^{-1}$ for PRA and 4.55% at $8.98 \text{ ng per 100 ml}$ for PAC. The intraassay coefficients of variation were 7.78% at $1.25 \text{ ng ml}^{-1} \text{h}^{-1}$ for PRA and 4.81% at $8.95 \text{ ng per 100 ml}$ for PAC. The lower limits of detections were $0.1 \text{ ng ml}^{-1} \text{h}^{-1}$ for PRA and 1 ng per 100 ml for PAC. Hypercholesterolemia was defined as total cholesterol $\geq 5.68 \text{ mmol l}^{-1}$ ($\geq 220 \text{ mg per 100 ml}$), use of medication for hypercholesterolemia and/or

a history of hypercholesterolemia. Diabetes mellitus was defined as a random blood glucose level $\geq 11.11 \text{ mmol l}^{-1}$ ($\geq 200 \text{ mg per 100 ml}$), HbA1c level $\geq 6.5\%$, use of medication for diabetes and/or a history of diabetes mellitus.²⁰

Long-term sodium and potassium intakes

A standardized method was used to calculate food consumption and related nutrients from data obtained in a Japanese version of the food-frequency questionnaire, which asked about the average frequency of consumption of each food during the previous year.²¹ We previously confirmed that the food-frequency questionnaire is reasonably reproducible and comparable with diet records, taking into account seasonal variations in food consumption.²¹ A standard portion size of one serving was specified for each food, and respondents were asked if their usual portion was larger (>1.5 times), the same or smaller (<0.5 times) than the standard. We then estimated sodium and potassium intakes.^{21,22} Estimated GFR (eGFR) was estimated from the serum creatinine using a Japanese equation.²³

Statistical analysis

PRA activity, PAC and ARR were natural log-transformed because of their positively skewed distributions. To analyze the relationship between tertiles of ARR and subject characteristics, we compared means and proportions using analysis of variance and the χ^2 -test for univariate analysis. For computing sex- and age-adjusted *P*-values, we used analysis of covariance and logistic regression analysis as appropriate. We examined the association of PRA, PAC and ARR with the prevalence of hypertension after adjustment for sex and age (adjusted model) using logistic regression analysis. In addition to the adjusted model, we further accounted for body mass index (BMI), smoking and drinking status, hypercholesterolemia, diabetes mellitus, history of cardiovascular disease, serum sodium and tertiles of dietary sodium intake (fully adjusted model). To test for the effect of dietary sodium, we stratified subjects according to sodium intake (low, less than median of 4822 mg day^{-1} ; high, greater than or equal to median). We also determined the significance of the interaction between sodium intake and ARR. Data are expressed as mean $\pm$ s.d. unless otherwise noted. SAS version 9.1 software (SAS Institute, Cary, NC, USA) was used for statistical analysis.

RESULTS

Participant characteristics

The 514 participants included 366 women (71.2%) and 65 patients with HBP hypertension (12.6%). Participants were 59.7 ± 10.8 years old, had a BMI of $23.3 \pm 2.9 \text{ kg m}^{-2}$ and a total cholesterol level of $5.06 \pm 0.86 \text{ mmol l}^{-1}$. At enrollment, 62 participants (12.1%) were current smokers, 182 (35.4%) reported intake of alcohol, 139 (27.0%) had hypercholesterolemia, 33 (6.4%) had diabetes mellitus and 19 (3.7%) had a history of cardiovascular disease. Two subjects (0.4%) had ARR $\geq 20 \text{ ng per 100 ml per ng ml}^{-1} \text{h}^{-1}$ in the presence of PAC $\geq 15 \text{ ng per 100 ml}$, which was the cutoff value to screen for primary aldosteronism;^{24,25} however, neither subject had hypertension or hypokalemia. The mean number of measurements for HBP was 23.2 ± 6.0 , and the mean systolic/diastolic HBP and CBP values of subjects were $117.2 \pm 13.6/73.2 \pm 8.8$ and $128.9 \pm 13.1/72.1 \pm 8.9 \text{ mm Hg}$, respectively. The HBP was significantly correlated with CBP in all subjects ($r=0.54$ for systolic BP, $r=0.50$ for diastolic BP), and in subjects with HBP hypertension ($r=0.40$ for systolic BP, $r=0.35$ for diastolic BP).

The median (25–75th percentiles) PRA level was 1.1 (0.7 – 1.7) $\text{ng ml}^{-1} \text{h}^{-1}$, the median PAC level was 6.4 (4.8 – 8.2) ng per 100 ml and the median ARR level was 5.5 (3.5 – 9.0) $\text{ng per 100 ml per ng ml}^{-1} \text{h}^{-1}$. The proportion of women and the levels of BMI, HBP and serum sodium significantly increased with increases in ARR (Table 1). Among the 514 study subjects, we obtained home heart rate in 501 subjects, of whom 63 were HBP hypertensives. The levels of home heart rate significantly decreased with increases in ARR (67.3 ± 7.3 ,

Table 1 Clinical characteristics among groups classified by tertiles of ARR

Characteristic	Tertiles of ARR			P-value	Sex- and age- adjusted P-value
	< 4.22 (n=171)	4.22–7.40 (n=170)	≥ 7.40 (n=173)		
Women, %	60.2	73.5	79.8	0.0002	
Age, years	60.3 ± 10.9	59.3 ± 10.6	59.3 ± 10.9	0.6	
BMI, kg m ⁻²	22.6 ± 2.8	23.4 ± 3.0	23.8 ± 3.1	0.001	0.0009
BMI ≥ 25 kg m ⁻² , %	15.8	30.6	33.0	0.0005	0.0002
Past history of CVD, %	4.7	2.9	3.5	0.7	0.8
Diabetes, %	5.8	7.1	6.4	0.9	0.9
Hypercholesterolemia, %	25.7	25.9	29.5	0.7	0.7
Smoking, %	14.6	14.7	6.9	0.04	0.9
Drinking, %	42.1	34.1	30.1	0.06	0.3
HBP					
Systolic, mm Hg	116.2 ± 15.1	116.5 ± 11.9	119.0 ± 13.6	0.1	0.001
Diastolic, mm Hg	72.1 ± 9.5	73.2 ± 7.5	74.4 ± 9.0	0.047	<0.0001
Hypertension, %	12.3	9.4	16.2	0.2	0.02
CBP					
Systolic, mm Hg	128.0 ± 14.3	128.8 ± 12.1	129.9 ± 12.7	0.4	0.06
Diastolic, mm Hg	71.4 ± 9.9	72.1 ± 7.3	72.7 ± 9.3	0.4	0.1
Hypertension, %	20.5	15.9	24.3	0.2	0.1
Biochemical measurements					
HbA1c, %	5.15 ± 0.66	5.12 ± 0.63	5.13 ± 0.58	0.6	0.9
Total cholesterol, mg per 100 ml	193.7 ± 33.1	198.4 ± 33.6	196.3 ± 33.1	0.4	0.6
eGFR, ml min ⁻¹ per 1.73 m ²	87.5 ± 19.9	84.3 ± 18.3	87.6 ± 17.9	0.2	0.09
Uric acid, mg per 100 ml	4.21 ± 1.16	4.00 ± 1.16	3.94 ± 1.12	0.07	0.9
Serum sodium, mEq l ⁻¹	141.9 ± 1.8	142.1 ± 1.6	142.4 ± 1.6	0.02	0.04
Serum potassium, mEq l ⁻¹	4.29 ± 0.36	4.32 ± 0.35	4.36 ± 0.34	0.2	0.1
Dietary intake					
Energy, kcal day ⁻¹	2031 ± 895	1878 ± 672	1940 ± 747	0.3	0.5
Sodium, mg day ⁻¹	6358 ± 6140	5219 ± 3979	5754 ± 3742	0.1	0.048
Salt, g day ⁻¹	16.0 ± 15.5	13.1 ± 10.1	14.5 ± 9.5	0.09	0.04
Potassium, mg day ⁻¹	2978 ± 2492	2665 ± 1728	2808 ± 1593	0.4	0.3
Sodium/potassium	2.13 ± 0.93	1.93 ± 0.75	2.07 ± 0.90	0.06	0.04

Abbreviations: BMI, body mass index; CBP, conventional blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HBP, home blood pressure.

eGFR was estimated from the serum creatinine value using a Japanese equation: $\text{eGFR (ml min}^{-1} \text{ per 1.73 m}^2\text{)} = 194 \times \text{Age}^{-0.287} \times \text{S-Cr}^{-1.094}$ (if female $\times 0.739$).²³

Home hypertension and CBP hypertension were at least 135/85 and 140/90 mm Hg, respectively.

65.2 ± 8.9 and 65.2 ± 8.7 beats min⁻¹ for ascending tertiles, P for trend=0.03), whereas this association was not observed in HBP hypertensives (65.8 ± 8.8, 66.1 ± 8.1 and 63.0 ± 14.9 beats min⁻¹ for ascending tertiles, P for trend=0.5). No other variables showed a consistent association with ARR. There was no correlation between logPAC and serum potassium ($r=0.06$, $P=0.2$) or between logPAC and BMI ($r=0.01$, $P=0.9$) in any subject. Similarly, in HBP hypertensives, logPAC was not correlated with either serum potassium or BMI ($|r| \leq 0.10$, $P \leq 0.5$).

LogARR and prevalence of hypertension

Of the 514 study subjects, 65 (12.6%) had HBP hypertension, and 104 (20.2%) had CBP hypertension. A 1 s.d. increase in logARR was significantly associated with the prevalence of HBP hypertension (odds ratio (OR) 1.37; 95% confidence interval (CI) 1.01–1.86; $P=0.04$) in fully adjusted models (Table 2). LogPRA showed a marginally significant relation with hypertension (odds ratio 0.76; 95% confidence interval 0.56–1.02; $P=0.07$). On the other hand,

logPAC was not associated with hypertension. When HBP of an individual was defined as the mean of two measurements for the initial 2 days, similar results were obtained (data not shown). We did not find any significant associations between logPRA, logPAC or logARR and CBP hypertension ($P \geq 0.2$).

To compare HBP and CBP in terms of predictive power of ARR, we performed a multiple regression model including logARR as the dependent variable and HBP level, CBP level and other confounding factors as independent variables. LogARR was predicted by HBP levels ($P=0.01$ for systolic BP, $P=0.0004$ for diastolic BP), but not by CBP levels ($P=0.5$ for systolic BP, $P=0.8$ for diastolic BP).

Interaction between logARR and sodium intake on HBP hypertension

We stratified subjects by median sodium intake (4822 mg day⁻¹). The associations of lower logPRA and higher logARR with an increased prevalence of HBP hypertension were strengthened for subjects with high sodium intake, whereas they became nonsignificant for those

Table 2 ORs for prevalence of hypertension per s.d. increase in LogPRA, LogPAC and LogARR

Dependent variable	Independent variable	OR (95% CI) for prevalence of hypertension					
		Unadjusted	P-value	Sex- and age- adjusted	P-value	Fully adjusted	P-value
HBP hypertension	logPRA	0.83 (0.64–1.08)	0.2	0.74 (0.56–0.98)	0.04	0.76 (0.56–1.02)	0.07
	logPAC	0.87 (0.67–1.13)	0.3	1.00 (0.75–1.33)	1.0	1.04 (0.76–1.41)	0.8
	logARR	1.11 (0.86–1.44)	0.4	1.37 (1.03–1.82)	0.03	1.37 (1.01–1.86)	0.04
CBP hypertension	logPRA	0.83 (0.66–1.03)	0.09	0.82 (0.65–1.03)	0.09	0.85 (0.66–1.08)	0.2
	logPAC	0.84 (0.68–1.05)	0.1	0.96 (0.76–1.21)	0.7	0.96 (0.75–1.22)	0.7
	logARR	1.10 (0.89–1.37)	0.4	1.19 (0.95–1.50)	0.1	1.16 (0.91–1.47)	0.2

Abbreviations: ARR, aldosterone-to-renin ratio; BMI, body mass index; CBP, conventional blood pressure; CI, confidence interval; CVD, cardiovascular disease; HBP, home blood pressure; OR, odds ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

The fully adjusted model was accounted for sex, age, BMI, habitual smoking, habitual drinking, diabetes mellitus, hypercholesterolemia, past history of cardiovascular disease, serum sodium and salt intake.

Home hypertension and CBP hypertension were at least 135/85 and 140/90 mm Hg, respectively.

Of the 514 study subjects, 65 (12.6%) had HBP hypertension and 104 (20.2%) had CBP hypertension.

Figure 1 Association of plasma renin activity (PRA), plasma aldosterone concentration (PAC) and aldosterone-to-renin ratio (ARR) with the prevalence of home blood pressure (HBP) hypertension by median of sodium intake. Adjusted odds ratio (95% confidence intervals) for prevalence of HBP hypertension per 1 s.d. increase in logPRA, logPAC and logARR by median sodium intake (4822 mg day⁻¹). Home hypertension was at least 135/85 mm Hg. Odds ratios for prevalence of HBP hypertension were adjusted for sex, age, body mass index (BMI), habitual smoking, habitual drinking, diabetes mellitus, hypercholesterolemia, past history of cardiovascular disease and serum sodium. Respectively, 30 and 35 subjects had HBP hypertension among subgroups with high ($n=257$) and low ($n=257$) sodium intake. * $P<0.01$.

with low sodium intake (Figure 1). There were significant interactions between sodium intake and logPRA or logARR on the prevalence of HBP hypertension (Figure 1, $P=0.03$). LogPAC was not consistently associated with HBP hypertension. We then analyzed HBP as a continuous variable and observed consistent results. In subjects with high sodium intake, a 1 s.d. decrease in logPRA was associated with systolic HBP ($\beta=-2.47$, $P=0.0007$) and diastolic HBP ($\beta=-1.71$, $P=0.0002$) in fully adjusted models. A 1 s.d. increase in logARR was also associated with HBP levels ($\beta=2.43$, $P=0.0006$ for systolic BP; $\beta=1.81$, $P<0.0001$ for diastolic BP). However, in subjects with low sodium intake, logPRA and logARR were no longer associated with HBP ($P\geq 0.1$).

In the subgroup of subjects with high sodium intake, individuals with HBP hypertension ($n=30$) had significantly lower PRA and higher ARR than those with HBP normotension ($n=227$) after adjustment for sex and age (Figure 2). Adjustments for potassium intake or serum potassium levels did not change the results (data not shown).

Figure 2 Levels of plasma renin activity (PRA), plasma aldosterone concentration (PAC) and aldosterone-to-renin ratio (ARR) in home blood pressure (HBP) normotensives and hypertensives. Means (95% confidence intervals) of PRA, PAC and ARR in a subgroup of subjects with high sodium intake (above the median of 4822 mg day⁻¹) after adjusting for sex and age. Home hypertension was at least 135/85 mm Hg.

We also performed stratified analyses. Sex (men/women), age ($<65/\geq 65$ years), BMI ($<25/\geq 25$ kg m⁻²), total energy intake (below or above median of 1790 kcal day⁻¹) or potassium intake (below or above median of 2427 mg day⁻¹) did not significantly affect the associations of logPRA, logPAC and logARR with the prevalence of HBP hypertension ($P>0.05$ for all interactions).

DISCUSSION

The present cross-sectional study found that ARR was significantly and independently associated with the prevalence of HBP hypertension in a general population, after adjusting for sex, age, BMI, smoking and drinking status, hypercholesterolemia, diabetes mellitus, history of cardiovascular disease, serum sodium level and dietary sodium intake. Furthermore, the association of ARR with HBP hypertension was strengthened for subjects with high sodium intake.

To date, a few general population studies^{2,3} have reported on the association of ARR with BP, and these studies^{2,3} were based solely on CBP. To our knowledge, ours is the first study to report on the association of ARR with HBP hypertension in a general population. HBP, a technique that makes it possible to obtain multiple measurements under well-controlled conditions, has been reported to be more reliable than CBP measurement because it avoids both observer and regression dilution biases and eliminates the white-coat effect or diurnal variation.^{12,24,26} In fact, we observed that ARR was more

closely related to hypertension diagnosed by HBP than by CBP (Table 2). Consequently, HBP measurements should be included in clinical studies to identify aldosterone effects on BP independent of CBP.

In the analyses of all subjects, our findings are in agreement with a Framingham Offspring study² that found that the prevalence of CBP hypertension was associated with higher ARR levels in a stepwise regression analysis of 3326 subjects. However, regarding the interaction between sodium intake and ARR on hypertension, one nested case-control study³ of 1984 subjects from a general French population provided different result from ours. They reported that ARR was associated with progression of CBP hypertension only in the lowest tertile of dietary sodium intake (<2737 mg day⁻¹).³ The differences in study design (prospective vs. cross-sectional) and BP measurements (CBP vs. HBP) may have influenced the variation in results between the French study and our findings.

Salt-sensitive hypertension

After adjustment for possible confounding factors, ARR was significantly associated with the prevalence of HBP hypertension, especially for subjects with high sodium intake. These results indicate that salt sensitivity may have a role in the association between high ARR and HBP hypertension. It is thought that salt-sensitive hypertension includes two main types, that is, low-renin hypertension (also called relative aldosterone excess) and non-modulating hypertension. We discuss the possible implications of these two subtypes of hypertension below.

Relative aldosterone excess

In the present study, low PRA was associated with an increased prevalence of HBP hypertension (Table 2 and Figure 1), and HBP hypertensive subjects had lower PRA than normotensive subjects in the high sodium intake subgroup (Figure 2). Thus, these HBP hypertensive subjects with high sodium intake were considered to have low-renin hypertension.²⁷ In most cases, low-renin hypertensive patients have a sodium-volume-dependent hypertension,^{27,28} implying that sodium-volume overload had occurred in HBP hypertensive subjects with high sodium intake in our study. In response to suppressed renin and volume expansion, a decrease in aldosterone would be expected in normal subjects. However, in the present study, PAC was not decreased in HBP hypertensive subjects with high sodium intake (Figure 2). Such a form of low renin and normal aldosterone is called *relative aldosterone excess*, which is responsible for hypertension because of inappropriate sodium and fluid retention or impaired nitric oxide.^{28,29} Therefore, our findings suggest that even in the general population, relative aldosterone excess may have an important role in salt-sensitive hypertension.

Some patients with primary aldosteronism have a low renin level but a normal aldosterone level. Thus, we cannot exclude the possibility that primary aldosteronism was present in some individuals with HBP hypertension in the high sodium intake subgroup. Weak mineralocorticoid excess might be related to the suppression of renin as it is reported that low renin was induced not only by aldosterone but also by mineralocorticoids, such as 11-deoxycorticosterone, 18-hydroxy-deoxycorticosterone, 18-hydroxycortisol and 18-hydroxycorticosterone.³⁰ Although it is thought that aldosterone secretion is also suppressed by mineralocorticoid excess,³⁰ these hormones might have affected ARR levels in the present study.

Non-modulating hypertension

In normal subjects, an increase in sodium intake produces an increase in renal blood flow, thereby enhancing the ability of the kidney to excrete sodium.³¹ However, individuals with non-modulating

hypertension do not show increased renal blood flow when sodium intake is increased.³¹ Therefore, they would retain sodium and water, which could underlie their salt sensitivity.³¹ Individuals with non-modulating hypertension most often have normal or high renin levels.³¹ Thus, it is less likely that non-modulating hypertension contributed to our results of HBP hypertension with high sodium intake.

It is suggested that aldosterone excess is associated with obesity or insulin resistance.³² Our study also showed that BMI is associated with tertiles of ARR (Table 1). Although BMI might not affect the association between ARR and the prevalence of HBP hypertension, there is a possibility that relative aldosterone excess may contribute to obesity or insulin resistance (and vice versa) in a general population. Further prospective study is needed to clarify this issue.

This study has several limitations. First, the study population predominantly included middle-aged, elderly and female individuals with relatively high salt intake; the mean salt intake was 14.6 g day⁻¹. These imbalances might, to some extent, limit the external validity of the findings. Second, this study was cross-sectional, and thus cause-and-effect relations of ARR on hypertension cannot be made. Third, subjects underwent blood sampling between 0900 and 1100 h or between 1300 and 1500 h and most often had not fasted. Therefore, both PRA and PAC might be affected by time of day and diet before the health check-up. Fourth, data on urinary sodium and potassium excretion were not collected. We obtained data on sodium intake from the 1-year food-frequency questionnaire, which has been validated by a standard procedure from the viewpoint of nutriology.^{21,22} However, the validation was not confirmed by direct comparison with urinary sodium excretion. This might weaken the interaction between logARR and sodium intake on HBP observed in this study. Fifth, we did not have information about adrenocorticotrophic hormone, mineralocorticoid hormones other than PAC, urinary excretion of aldosterone or these metabolites. Sixth, some of the findings may have been the result of chance because of multiple comparisons and, therefore, they need to be reproduced in future studies.

In conclusion, the study provides evidence for relative aldosterone excess contributing to salt-sensitive hypertension even in a general population. These results suggest that relative aldosterone excess or low-renin hypertension contributes to salt-sensitive hypertension in the general population. Prospective studies based on HBP are needed to determine whether ARR predicts the progression of BP, target organ damage and prognosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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