Effects of salt intake on blood pressure in patients under antihypertensive treatment; Shimane CoHRE Study

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Running title: Salt intake and BP under antihypertensive treatment

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Abstract

Purpose: Salt intake has been recognized as a strong risk factor for hypertension in a general population. On the other hand, because of the availability of various types of antihypertensive drugs, salt consumption in hypertensive patients seems less focused. In this study, we evaluated whether blood pressure (BP) was correlated with 24-hours salt intake in patients treated with antihypertensive drugs.

Methods: In health examinations, 1501 consecutive participants were recruited. According to the antihypertensive medication checked on the prescriptions, participants were divided into two groups, the control without (N=1009) and the hypertensive patients with antihypertensive treatment (N=492). Twenty-four-hours urinary sodium excretion (24h-uNa), which was a good surrogate parameter for a daily salt intake, was estimated with the formula suggested by Kawano et al (ref. 12).

Results: A univariate analysis indicated that the 24h-uNa correlated positively with systolic BP both in the hypertensive subjects with antihypertensive medication and in the control subjects, which was confirmed in a multiple linear regression analysis under the adjustment with other confounding factors (the control subjects: $B=1.45\pm0.26$, $p<0.001$, the hypertensive subjects: $B=0.75\pm0.28$, $p=0.01$). Further, the salt intake correlated with pulse pressure in the hypertensive subjects with the medication ($B=0.55\pm0.24$, $p=0.02$) as well as in the control ($B=0.92\pm0.19$, $p<0.001$).

Conclusions: These results suggested the importance of reduction of the salt intake in the hypertensive patients with medication as well as in a general population. Careful

check of salt intake in hypertensive patients with medication may be needed for better therapeutic outcomes.

Keywords: Salt intake, hypertension, antihypertensive treatment

Introduction

Hypertension is the most prevalent lifestyle-related disease in the world; the number of hypertensive patients reaches one billion worldwide, and 40 million in Japan.[1,2] Hypertension is well known as a risk for cerebral stroke, cardiac and kidney diseases, which may have an adverse effect on healthy life expectancy.[3,4] In fact, among the young seniors (age less than 64), higher blood pressure (BP) was a clear risk for cardiovascular diseases and mortality.[5] In addition, it was recently found that hypertension caused deterioration of cognitive function.[6] These observations emphasize the importance of antihypertensive treatment in the elderly to keep a healthy longevity.

In spite of that, it was reported that 50 % of patients using antihypertensive drugs did not accomplish their goal of BP reduction in Japan.[7] According to the guideline by the Japanese Society of Hypertension, patients with the stage I hypertension are recommended to change their lifestyle before prescription of antihypertensive drugs.[8] Although the modification of lifestyle is important for patients using antihypertensive drugs as well, such patients may rely on the medication too much to care about their lifestyle, which may result in the low rate of the patients achieving an adequate BP after the drug treatment.

The most important lifestyle influencing BP is salt intake.[9,10] We therefore hypothesized that, even among patients using antihypertensive drugs, salt intake had a significant influence on BP. In this study, we showed that salt intake indeed had a significant effect on BP even in patients using antihypertensive drugs.

Methods

Subjects

This study was a part of a cohort study (Shimane CoHRE Study) conducted by the Center for the Community-based Health Research and Education (CoHRE), Shimane University. A total of 1501 consecutive participants (571 males and 930 females) were recruited from health check examinations performed in rural areas of Shimane Prefecture in 2012. Ages of the participants were limited to the range between 40 and 74. Information about physical activity, smoking, drinking, and the use of antihypertensive drugs was obtained through an interview. Participants were divided into two groups according to whether they received antihypertensive medication or not. As a result, we had the hypertensive subjects with the medication (N=492) and the control subjects without the medication (N=1009). International Standardized Physical Activity Questionnaire was employed to obtain 24-hours physical activity of participants and the exercise count (ex) was calculated according to the previous studies.[11,12] Participants were categorized into two groups (with low and high physical activity) at the median of the exercise count (=56 ex/day). Habitual smokers and drinkers were defined as who took a cigarette/day or more, and 20g alcohol/day or more, respectively.

Written informed consent was obtained from each participant. The study protocol was approved by the local ethics committee of Shimane University.

Data collection

BP was measured 2 times after a 15-min rest at the sitting position. The lower of the 2 measurements was taken as the representative BP at site. Venous blood was collected after overnight fasting. Triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured by standard enzymatic methods. Sodium and creatinine were measured in a spot urine collected at the health examination, and 24-hour urinary sodium excretion was estimated using the equation proposed by Kawano et al.[13] Because most of the salt (sodium) ingested is thought to be excreted in urine in individuals with normal renal function, we regarded the 24-hour urinary sodium excretion as a daily sodium intake as recommended by the Japanese Society of Hypertension.[14]

Statistics

Data were expressed as mean ± S.D. As several parameters were highly skewed, log-transformation was done on several parameters before all the analyses.

Correlation between BP and other continuous variables was analyzed by the Spearman's rank correlation coefficient. Effects of categorical parameters on BP was analyzed by the Student's t-test. Multiple regression analysis was performed on the effect of each variable on BP as well.

All statistical analyses were performed with the SPSS statistical software (ver. 21).

$P<0.05$ was assumed to be statistically significant.

Results

Table 1 shows demographic data of the studied subjects. It is of note that no significant

difference in the estimated salt intake between the control and the hypertensive subjects. As expected, the hypertensive subjects had significantly greater age, systolic and diastolic BP (SBP and DBP) and body mass index (BMI) than those of the control subjects. Higher LDL-C, TG and lower HDL-C were observed in the hypertensive subjects that were probably due to greater BMI. The proportion of subjects with low physical activity was slightly but significantly greater in the hypertensive subjects. No significant differences were found in the smoking and drinking habit between the two groups.

Among the hypertensive subjects, we had 23 individuals treated with diuretics. As diuretics might cause an overestimation of the salt intake, we compared the estimated salt intake between the hypertensive subjects with and without diuretics. The salt intake in the subjects using diuretics was estimated 10.5±3.1 g/day (N=23), which was not significantly different from that in those without diuretics (9.6±2.5 g/day; N=306, p=0.1). We therefore included all the hypertensive subjects in the following analyses.

Table 2 showed a correlation of various parameters with SBP and DBP in the two groups. The salt intake showed a significant positive correlation with SBP and DBP both in the control and the hypertensive subjects.

The multiple linear regression analysis was performed on SBP and DBP including the parameters showing correlations with the blood pressure in the univariate analysis. As shown in Table 3(A), the salt intake was independently associated with SBP and DBP in the control subjects. Further, even in the hypertensive subjects treated with antihypertensive drugs, it had an independent association with SBP along with age and

BMI [Table 3(B)]. The same analysis was performed on the hypertensive subjects after 23 subjects using diuretics were excluded, and the result indicated that the salt intake was still an independent factor associated with SBP (B=0.72±0.28, p=0.01, Table S1).

Discussion

In the present study, we showed that salt intake estimated from the sodium concentration of a spot urine was positively correlated with SBP even in hypertensive subjects treated with antihypertensive drugs. Averaged salt intake is still high in the general population worldwide as well as in Japan, which probably plays an important role in the high prevalence of hypertension as well as the high morbidity by cardiovascular diseases.[15,16] The present study showed that, even in treated hypertensive patients, it was important to reduce salt intake to make the treatment more effective. Although this result was feasible and expected, no clear evidence supporting it has been so far reported to the best of our knowledge. We therefore think that this study has a clinical importance.

Both in the control and hypertensive subjects, it was rather unexpected observation that sex was not a significant parameter affecting SBP (see Table 3). One of possible reasons was the advanced age of the studied population (averaged age was 66.4 years). In fact, a previous report showed that the increase in SBP due to aging was greater in women than in men in the elderly subjects.[1, 17] In contrast, it is of interest that the female sex showed a significant negative effect on DBP both in the subjects with and without antihypertensive medication (Table 3). These observations on SBP and DBP in

women indicated that pulse pressure was greater in women in this population, and, indeed, a linear regression analysis revealed that the female sex had a strong positive effect on pulse pressure both in the hypertensive and control subjects as shown in Table 4. Considering the advanced age of the population, this result suggested that women had a greater risk to develop arterial stiffness than in men in this population.[18,19]

Of note, salt intake was another independent factor influencing the pulse pressure no matter whether subjects were received antihypertensive treatment or not (Table 4). This observation suggested that salt intake in elderly subjects promoted arterial stiffness, which may cause greater incidence of cardiovascular events as well as the white matter lesion in the brain.[18-20] It is warranted to evaluate the effect of salt intake on incidence of cardiovascular diseases in the elderly in a prospective study.

In the interpretation of the present results, use of diuretics may cause some disturbance because diuretics may elicit an overestimation of salt intake due to increased sodium excretion. As the salt intake in the subjects using diuretics did not differ significantly from that in those without diuretics (see Results), we included those subjects in the analysis. The conclusion of the analysis seemed robust as the effect of salt intake on SBP was significant even after we excluded those subjects from the analysis (Table S1). Sakaki et al. indicated that patients with poor compliance to salt restriction treatment tended to have more diuretics.[21] This observation suggested another possibility that the use of diuretics was not a cause but a result of higher salt consumption in the present population.

Although the present result may have a clinical significance, it has a limitation if it is

applied in clinics; the estimated salt intake used in this study is not reliable enough to assess the salt intake in an individual subject though it is feasible to estimate the average of a large population.[13] Therefore, it is necessary to confirm the present result using 24-hours urine collection before the clinical application. In addition, one may need to perform sodium restriction with caution since it may cause hyponatremia in the elderly.[22]

In conclusion, we showed that salt intake estimated from a spot urine harbored an independent effect on SBP as well as pulse pressure even in subjects under antihypertensive treatment. Careful check on salt intake may be necessary in such patients for better therapeutic outcomes.

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Table1. Demographic data of the studied population

	Control	Hypertensives under medication	*P**
	mean±SD or number (%)	mean±SD or number (%)	
Number	1009	492	
Age, years	65.5±7.3	68.4±5.1	＜0.001
Systolic blood pressure, mmHg	125.6±17.1	133.8±15.0	＜0.001
Diastolic blood pressure, mmHg	76.8±10.6	80.2±9.2	＜0.001
Body mass index, kg/m^2	22.1±3.1	23.6±3.2	＜0.001
Salt intake, g/day	9.6±2.0	9.7±2.5	0.24
HDL-C, mg/dl	65.7±16.4	62.2±15.7	＜0.001
LDL-C, mg/dl	125.9±29.5	117.3±26.4	＜0.001
TG, g/dl	99.9±60.5	107.9±59.4	0.02
Sex, male	387 (38.4)	184 (37.4)	0.72
Low physical activity	484 (48.0)	265 (53.9)	0.04
Habitual smokers	102 (10.1)	49 (10)	0.93
Habitual drinkers	187 (18.5)	107 (21.7)	0.14

*: By Student's t-test or the contingency table analysis
Low physical activity: ＜56 ex/day, Habitual smokers: ≥ one cigarette/day, Habitual drinkers : ≧ ethanol 20g/day,
HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride

Table 2. Correlation with blood pressure

(A) Control

	SBP		DBP	
	ρ or t*	*P*	ρ or t*	*P*
Age	0.16	＜0.001	0.02	0.58
BMI	0.21	＜0.001	0.23	＜0.001
Salt intake	0.22	＜0.001	0.17	＜0.001
HDL-C	-0.10	0.003	-0.10	0.001
LDL-C	0.07	0.03	0.02	0.56
TG	0.20	＜0.001	0.20	＜0.001
Sex, male vs. female	3.30	0.001	8.46	＜0.001
Physical activity, low vs. high	-1.40	0.16	-2.13	0.03
Habitual smoker, yes vs. no	1.93	0.05	4.07	＜0.001
Habitual drinker, yes vs. no	4.53	＜0.001	6.68	＜0.001

(B) Hypertensives under medication

	SBP		DBP	
	ρ or t*	*P*	ρ or t*	*P*
Age	0.05	0.27	-0.16	0.001
BMI	0.14	0.002	0.060	0.19
Salt intake	0.17	＜0.001	0.12	0.006
HDL-C	-0.08	0.07	-0.03	0.530
LDL-C	0.04	0.44	0.006	0.89
TG	0.19	＜0.001	0.10	0.03
Sex, male vs. female	-0.61	0.55	4.38	＜0.001
Physical activity, low vs. high	0.26	0.80	0.87	0.38
Habitual smoker, yes vs. no	-0.11	0.92	1.04	0.30
Habitual drinker, yes vs. no	-0.33	0.74	4.32	＜0.001

*: Correlation with SBP/DBP was examined by Spearman's ρ and Student's t-test when variables were continuous and categorical, respectively.

SBP,Systolic blood pressure
DBP,Diastolic blood pressure
BMI,Body mass index, kg/m^2

Table 3. Multiple linear regression anslysis on blood pressure

(A) Control

Variables	SBP					DBP				
	B	(95% CI)	standardized β	t	*P*	B	(95% CI)	standardized β	t	*P*
Age	0.52	(0.38, 0.66)	0.22	7.40	＜0.001	0.12	(0.03, 0.21)	0.08	2.75	0.01
BMI	0.96	(0.59, 1.32)	0.17	5.11	＜0.001	0.66	(0.44, 0.89)	0.19	5.72	＜0.001
Salt intake	1.45	(0.94, 1.96)	0.17	5.60	＜0.001	0.53	(0.22, 0.85)	0.10	3.32	0.001
HDL-C	0.03	(-0.04,0.11)	0.03	0.94	0.35	0.04	(-0.01,0.08)	0.06	1.65	0.10
LDL-C	0.02	(-0.01,0.06)	0.04	1.19	0.24	0.01	(-0.01,0.03)	0.02	0.78	0.44
TG	0.02	(0.01,0.04)	0.08	2.45	0.01	0.02	(0.003,0.03)	0.09	2.50	0.01
Sex, male vs. female	-0.93	(-3.37,1.51)	0.03	0.75	0.45	3.27	(1.76, 4.78)	0.15	4.25	＜0.001
Habitual smoker, yes vs. no	2.61	(-0.96, 6.17)	0.05	1.44	0.15	1.50	(-0.71, 3.71)	0.04	1.33	0.18
Habitual drinker, yes vs.no	5.38	(2.43, 8.32)	0.12	3.58	＜0.001	2.90	(1.08, 4.73)	0.11	3.12	0.002

(B) Hypertensives under medication

Variable	SBP					DBP				
	B	(95% CI)	standardized β	t	*P*	B	(95% CI)	standardized β	t	*P*
Age	0.29	(0.03, 0.56)	0.10	2.18	0.03	-0.24	(-0.40, -0.08)	-0.13	-2.95	0.003
BMI	0.54	(0.11, 0.96)	0.120	2.46	0.01	0.08	(-0.18, 0.34)	0.03	0.58	0.56
Salt intake	0.75	(0.21, 1.29)	0.12	2.74	0.01	0.20	(-0.13, 0.53)	0.05	1.21	0.23
TG	0.02	(0.001,0.05)	0.09	2.01	0.05	0.01	(-0.01,0.02)	0.04	0.80	0.42
Sex, male vs. female	-1.88	(-5.03, 1.27)	-0.06	-1.17	0.24	2.46	(0.55, 4.37)	0.13	2.53	0.01
Habitual drinker, yes vs. no	0.43	(-3.27, 4.13)	0.01	0.23	0.82	2.25	(0.004, 4.49)	0.10	1.97	0.05

Table 4. Multiple linear regression anslysis on pulse pressure

(A) Control

Variables	pulse pressure				
	B	(95% CI)	standardized β	t	*P*
Age	0.40	(0.30, 0.50)	0.24	7.89	＜0.001
BMI	0.29	(0.03, 0.56)	0.07	2.18	0.030
Salt intake	0.92	(0.55, 1.29)	0.15	4.90	＜0.001
HDL-C	-0.003	(-0.06,0.05)	-0.004	-0.12	0.91
LDL-C	0.01	(-0.01,0.04)	0.03	0.97	0.33
TG	0.01	(-0.01,0.02)	0.04	1.26	0.21
Sex, male vs. female	-4.20	(-5.96,-2.44)	-0.17	-4.69	＜0.001
Habitual smoker, yes vs. no	1.11	(-1.47, 3.68)	0.03	0.84	0.40
Habitual drinker, yes vs.no	2.47	(0.35, 4.60)	0.08	2.28	0.02

(B) Hypertensives under medication

Variable	pulse pressure				
	B	(95% CI)	standardized β	t	*P*
Age	0.54	(0.30, 0.77)	0.20	4.5	＜0.001
BMI	0.46	(0.08, 0.83)	0.11	2.29	0.02
Salt intake	0.55	(0.08, 1.03)	0.10	2.28	0.02
TG	0.02	(-0.002,0.04)	0.08	1.73	0.09
Sex, male vs. female	-4.34	(-7.12, -1.56)	-0.16	-3.07	0.002
Habitual drinker, yes vs. no	-1.82	(-5.08, 1.45)	-0.06	-1.10	0.27