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Effect of salt intake on blood pressure in patients receiving antihypertensive therapy: Shimane CoHRE Study

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Abstract

Background: Salt intake is recognized as an important risk factor for hypertension in the general population. On the other hand, the availability of various classes of antihypertensive drugs means that it is generally not considered crucial to control the salt intake of hypertensive patients. In this study, we evaluated whether blood pressure (BP) was correlated with 24-hour salt intake in patients receiving antihypertensive therapy.

Methods: A total of 1496 consecutive participants undergoing health screening examinations were recruited. Subjects were divided into two groups according to their antihypertensive medications checked on prescriptions: 1005 subjects without antihypertensive therapy (untreated subjects) and 491 subjects with antihypertensive therapy (treated subjects). The 24-hour urinary sodium excretion (24h-uNa), a surrogate marker for daily salt intake, was estimated with the formula proposed by Tanaka et al. in 2002.

Results: Univariate analysis indicated that 24h-uNa was positively correlated with the systolic BP of both untreated and treated subjects. This was confirmed by multiple linear regression analysis after adjustment for confounding factors (untreated subjects: partial regression coefficient $\beta=1.45\pm0.26$, $p<0.001$; treated subjects: $\beta=0.75\pm0.27$, $p=0.01$). Salt intake was also correlated with the pulse pressure in both treated subjects ($\beta=0.55\pm0.24$, $p=0.02$) and untreated subjects ($\beta=0.93\pm0.19$, $p<0.001$).

Conclusion: These results suggest the importance of reducing salt intake in hypertensive patients on pharmacotherapy, as well as in the general population. Further studies of

hypertensive patients employing 24-h urine collection are warranted to confirm the present findings.

Keywords: Salt intake, hypertension, antihypertensive treatment

Introduction

Hypertension is the most prevalent lifestyle-related disease in the world, with the number of hypertensive patients being one billion worldwide, including 40 million in Japan [1,2]. Hypertension is a well-known risk factor for stroke, cardiac disease, and kidney disease, all of which may reduce life expectancy [3,4]. Among young seniors (< 65 years old), elevation of blood pressure (BP) was reported to be a clear risk factor for cardiovascular disease and mortality [5]. In addition, it was recently found that hypertension is associated with deterioration of cognitive function [6]. These observations emphasize the importance of antihypertensive therapy for elderly persons to maintain healthy longevity. However, it has been reported that 50% of Japanese patients on antihypertensive drugs do not reach their target BP [7]. According to the guideline produced by the Japanese Society of Hypertension, stage I patients are recommended to try lifestyle modification before starting antihypertensive drugs [8]. Although lifestyle modification is also important for patients on antihypertensive therapy, patients may rely too much on their medication and disregard instructions about lifestyle modification, resulting in a low proportion of patients achieving an appropriate BP despite drug treatment.

The most important lifestyle factor with an influence on BP is salt intake [9,10]. Therefore, we hypothesized that salt intake could have a significant influence on BP, even among patients taking antihypertensive medications. In this cross-sectional study, we showed that salt intake (estimated from spot urine) was correlated with BP in patients on antihypertensive therapy.

Materials and Methods

Subjects

This study was a part of a cohort study (Shimane CoHRE Study) conducted by the for the Community-based Health Research and Education (CoHRE) of Shimane University. A total of 1501 consecutive participants (571 men and 930 women) were recruited from among persons undergoing health screening examinations in rural areas of Shimane Prefecture during 2012. Participants were limited to the age range between 40 and 74 years. Information about physical activity, smoking, drinking, and use of antihypertensive medications was obtained by interview, and the actual medications were confirmed by checking prescriptions. After excluding 5 subjects with a history of treatment for renal disease, the remaining1496 participants were divided into groups with or without antihypertensive medication. This yielded a group of hypertensive subjects on medication (treated subjects: N=491) and a group of normotensive or hypertensive subjects without medication (untreated subjects: N=1005). The International Standardized Physical Activity Questionnaire was employed to assess 24-hour physical activity and the exercise count (ex) was calculated according to the method reported previously [11,12]. Participants were categorized into two groups (low and high physical activity groups) based on the median exercise count (56 ex/week). Habitual smokers and habitual drinkers were defined as persons who smoked at least 1 cigarette/day and persons who drank at least 20g of ethanol/day, respectively. Written informed consent was obtained from each participant. The study protocol was approved by the ethics committee of Shimane University.

Data collection

Systolic BP and diastolic BP (SBP and DBP) were measured twice in the sitting position using an automatic sphygmomanometer after a 15-min rest and the lower of the 2 measurements was used. Pulse pressure was calculated as SBP-DBP. A venous blood sample was collected from each subject after an overnight fast. Triglycerides (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 spot urine collected at the health screening examination, and 24-hour urinary sodium excretion was estimated with the formula proposed by Tanaka et al. [13]. Because most of the salt (sodium) ingested is thought to be excreted in the urine when renal function is normal, we defined 24-hour urinary sodium excretion as the daily sodium intake. While 24-hour urinary sodium excretion estimated from a spot urine sample using Tanaka's formula only has a modest correlation with actual sodium excretion measured by 24-hour urine collection [14-16], this method is considered useful for evaluation of salt intake in epidemiological studies with a large population because of its simplicity [13-15].

Statistics

Results are expressed as the mean ± S.D. Because several parameters were highly skewed, logarithmic transformation was done before analysis. Correlations between BP and other continuous variables were analyzed by calculating Spearman's rank correlation coefficients. The influence of categorical parameters on BP was determined by Student's t-test. Multiple regression analysis was performed to assess the influence

of each variable on BP. The partial regression coefficient (β), its 95% confidence interval (95% CI), and the standardized β are reported for each independent variable in the tables with t-statistics and P values. All statistical analyses were performed with SPSS statistical software (ver. 21) and $P<0.05$ was taken to indicate statistical significance.

Results

Demographic data of the subjects are summarized in Table S1. There was no significant difference of estimated salt intake between the untreated and treated subjects. As expected, the treated subjects were significantly older and had a higher BP and higher body mass index (BMI) compared with the untreated subjects. Treated subjects also had higher LDL-C and TG levels than untreated subjects, as well as lower HDL-C levels, probably due to their larger BMI. Low physical activity was slightly, but significantly, more prevalent among the treated subjects, but there were no significant differences of smoking and drinking habits between the two groups.

Twenty-three of the treated subjects were using diuretics. Since these drugs could cause overestimation of the salt intake if they were prescribed temporally, we compared the estimated salt intake between subjects with and without diuretics. The estimated salt intake of the subjects using diuretics was 10.5±3.1 g/day (N=23), which was not significantly different from that of subjects without diuretics (9.6±2.5 g/day; N=305, p=0.1). Therefore, we included all of the treated subjects in the following analyses.

Table 1 lists the correlations of various parameters with SBP and DBP in the two groups.

Salt intake showed a significant positive correlation with SBP and DBP in both treated and untreated subjects. The correlation between salt intake and SBP is shown in Fig. 1. Multiple linear regression analysis was performed using the parameters showing a significant correlation with BP in univariate analysis to find variables with an independent influence on SBP and/or DBP. As shown in Table 2(A), the salt intake was independently associated with SBP and DBP in the untreated subjects. Even in the treated subjects, salt intake had an independent association with SBP together with age and BMI [Table 2(B)]. This result seemed to be robust because analysis after excluding the 23 subjects using diuretics also revealed a positive correlation between salt intake and SBP (β=0.72±0.28, p=0.01, Table S2).

Female sex had a significant negative influence on DBP despite no significant effect on SBP (Table 2), so we assessed the effect of sex on pulse pressure by multiple linear regression analysis. As expected, female sex had a significant positive influence on pulse pressure in both the treated and untreated subjects (Table 3). The effect of salt intake on pulse pressure was also significant.

Discussion

In the present study, we showed that salt intake estimated from the sodium concentration in spot urine was positively correlated with SBP in subjects on antihypertensive therapy. Accordingly, it may be important to control the salt intake of hypertensive patients receiving pharmacotherapy to ensure that their treatment is effective.

On the other hand, it is of note that the estimated salt intake did not differ between the untreated and the treated subjects (9.6±2.0 and 9.7±2.5 g, respectively, see Table S1). This observation implies the difficulty of controlling salt intake as well as BP itself in some patients.

An unexpected finding was that sex did not have a significant influence on SBP in both the untreated and treated subjects (Table 2). A possible reason for this finding was the relatively high age of the population studied (an average age of 66.4 years). In fact, it was previously reported that the increase of SBP due to aging was greater in elderly women than in elderly men [1,17-19]. In contrast, female sex showed a significant negative influence on DBP in both the treated and untreated subjects (Table 2). These observations regarding SBP and DBP implied that pulse pressure was larger in women, and multiple linear regression analysis confirmed that female sex had a strong positive influence on pulse pressure (Table 3). This observation is interesting when we consider the relationship of pulse pressure to arterial stiffness in the elderly [20,21]. However, multiple factors are known to influence pulse pressure, so further evaluation will be necessary to clarify the pathophysiological significance of the larger pulse pressure in women from our study population [22].

While the present study provided epidemiological evidence of a positive correlation between salt intake and BP in subjects on antihypertensive therapy, it has limited clinical applicability because the method of estimating salt intake used in this study is not reliable enough to assess the salt intake of individual patients [13]. Probably because of this limitation, the correlation between SBP and estimated salt intake was

only modest (Fig. 1). Therefore, it would be necessary to confirm the present results by using 24-hour urine data before clinical application could be considered.

In conclusion, we showed that the salt intake estimated from a spot urine sample had an independent influence on SBP and pulse pressure in patients on antihypertensive therapy. Careful control of salt intake may be important to achieve better therapeutic outcomes in treated hypertensive patients.

Learning points

- In patients on antihypertensive therapy, the daily salt intake estimated from spot urine was positively correlated with systolic blood pressure and pulse pressure after adjustment for confounders.
- The salt intake did not differ significantly between subjects with and without antihypertensive treatment, implying the difficulty of controlling salt intake in some patients.
- Careful control of salt intake may be required to achieve better therapeutic outcomes in hypertensive patients on pharmacotherapy.

Conflict of interest; none

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Figure legend

Fig. 1. Correlation of the estimated salt intake with SBP

(A) Untreated subjects. (B) Treated subjects.

Spearman's ρ was 0.22 ($p<0.0001$) and 0.17 ($p=0.0002$) for the untreated and treated subjects, respectively.

Highlights [each highlight should have 85 characters or less (including spaces)]

- Deleterious effect of high salt intake on blood pressure is well established.
- No evidence is available yet for hypertensive patients treated pharmacologically.
- The epidemiological evidence on the treated subjects is provided in this study.

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Discussion

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Learning points

- In patients on antihypertensive therapy, the daily salt intake estimated from spot urine was positively correlated with systolic blood pressure and pulse pressure after adjustment for confounders.
- The salt intake did not differ significantly between subjects with and without antihypertensive treatment, implying the difficulty of controlling salt intake in some patients.
- Careful control of salt intake may be required to achieve better therapeutic outcomes in hypertensive patients on pharmacotherapy.

Conflict of interest; none

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Figure legend

Fig. 1. Correlation of the estimated salt intake with SBP

(A) Untreated subjects. (B) Treated subjects.

Spearman's ρ was 0.22 ($p<0.0001$) and 0.17 ($p=0.0002$) for the untreated and treated subjects, respectively.

Table(s)

Table 1. Correlations of variables with blood pressure

(A) Untreated subjects

	SBP		DBP	
	ρ or t*	*P*	ρ or t*	*P*
Age	0.17	＜0.001	0.02	0.54
BMI	0.21	＜0.001	0.23	＜0.001
Salt intake	0.22	＜0.001	0.17	＜0.001
HDL-C	-0.10	0.002	-0.11	0.001
LDL-C	0.07	0.03	0.02	0.60
TG	0.19	＜0.001	0.21	＜0.001
Sex, male vs. female	3.36	0.001	8.47	＜0.001
Physical activity, low vs. high	-1.50	0.14	-2.23	0.03
Habitual smoker, yes vs. no	1.97	0.05	4.08	＜0.001
Habitual drinker, yes vs. no	4.48	＜0.001	6.64	＜0.001

(B) Treated subjects

	SBP		DBP	
	ρ or t*	*P*	ρ or t*	*P*
Age	0.05	0.23	-0.15	0.001
BMI	0.14	0.001	0.06	0.19
Salt intake	0.17	＜0.001	0.12	0.01
HDL-C	-0.08	0.07	-0.03	0.56
LDL-C	0.04	0.44	0.01	0.89
TG	0.19	＜0.001	0.10	0.03
Sex, male vs. female	-0.65	0.52	4.33	＜0.001
Physical activity, low vs. high	0.31	0.75	0.94	0.35
Habitual smoker, yes vs. no	-0.12	0.90	1.01	0.31
Habitual drinker, yes vs. no	-0.36	0.72	4.29	＜0.001

*: Correlations with SBP/DBP were examined by calculating Spearman's ρ value and by Student's t-test for continuous and categorical variables, respectively

Salt intake was estimated from the sodium and creatinine concentrations in a spot urine sample using the formula proposed by Tanaka et al. (see Methods)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides

Low physical activity: ＜56 ex/week, Habitual smoker: ≥ one cigarette/day, Habitual drinker : 20 g of ethanol/day

Table(s)

Table 2. Multiple linear regression analysis of the influence of variables on blood pressure

(A) Untreated subjects

Variables	SBP					DBP				
	β	(95% CI)	standardized β	t	*P*	β	(95% CI)	standardized β	t	*P*
Age	0.52	(0.38, 0.66)	0.22	7.34	＜0.001	0.12	(0.03, 0.20)	0.08	2.68	0.01
BMI	0.93	(0.56, 1.30)	0.17	4.89	＜0.001	0.66	(0.43, 0.89)	0.19	5.6	＜0.001
Salt intake	1.45	(0.93, 1.96)	0.17	5.54	＜0.001	0.52	(0.20, 0.83)	0.10	3.19	0.001
HDL-C	0.03	(-0.04,0.11)	0.03	0.91	0.36	0.04	(-0.01,0.08)	0.06	1.66	0.10
LDL-C	0.02	(-0.01,0.06)	0.04	1.18	0.24	0.01	(-0.01,0.03)	0.02	0.71	0.48
TG	0.02	(0.01,0.04)	0.09	2.48	0.01	0.02	(0.004,0.03)	0.09	2.61	0.01
Sex, male vs. female	-0.85	(-3.31,1.60)	-0.02	-0.68	0.50	3.21	(1.69, 4.73)	0.15	4.15	＜0.001
Physical activity, low vs. high	-0.34	(-2.34, 1.67)	-0.01	-0.33	0.74	-0.73	(-1.97, 0.51)	-0.03	-1.15	0.25
Habitual smoker, yes vs. no	2.64	(-0.93, 6.21)	0.05	1.45	0.15	1.52	(-0.70, 3.70)	0.04	1.35	0.18
Habitual drinker, yes vs.no	5.23	(2.26, 8.19)	0.12	3.46	0.001	2.81	(0.97, 4.65)	0.10	3.00	0.003

(B) Treated subjects

Variable	SBP					DBP				
	β	(95% CI)	standardized β	t	*P*	β	(95% CI)	standardized β	t	*P*
Age	0.3	(0.04, 0.57)	0.10	2.23	0.03	-0.24	(-0.40, -0.08)	-0.13	-2.90	0.004
BMI	0.54	(0.11, 0.97)	0.12	2.49	0.01	0.08	(-0.18, 0.34)	0.03	0.61	0.54
Salt intake	0.75	(0.21, 1.29)	0.12	2.74	0.01	0.20	(-0.13, 0.53)	0.05	1.20	0.23
TG	0.02	(0.00,0.05)	0.09	1.98	0.05	0.01	(-0.01,0.02)	0.04	0.77	0.44
Sex, male vs. female	-1.94	(-5.09, 1.21)	-0.06	-1.21	0.23	2.42	(0.51, 4.33)	0.13	2.49	0.01
Habitual drinker, yes vs. no	0.43	(-3.27, 4.12)	0.01	0.23	0.82	2.24	(0.003, 4.49)	0.10	1.97	0.05

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides, Habitual smoker: ≥ one cigarette/day, Habitual drinker : 20 g of ethanol/day, β: partial regression coefficient, CI: confidence interval

Salt intake was estimated from the sodium and creatinine concentrations in a spot urine sample using the formula proposed by Tanaka et al. (see Methods).

Table(s)

Table 3. Multiple linear regression analysis of the influence of variables on pulse pressure

(A) Untreated subjects

Variables	pulse pressure				
	β	(95% CI)	standardized β	t	*P*
Age	0.40	(0.30, 0.50)	0.24	7.87	＜0.001
BMI	0.27	(0.02, 0.54)	0.07	1.98	0.05
Salt intake	0.93	(0.56, 1.30)	0.16	4.94	＜0.001
HDL-C	-0.004	(-0.06,0.05)	-0.01	-0.16	0.88
LDL-C	0.01	(-0.01,0.04)	0.03	1.03	0.31
TG	0.01	(-0.01,0.02)	0.04	1.20	0.23
Sex, male vs. female	-4.17	(-5.84,-2.30)	-0.16	-4.51	＜0.001
Physical activity, low vs. high	0.40	(-1.05,1.84)	0.02	0.53	0.59
Habitual smoker, yes vs. no	1.12	(-1.45, 3.70)	0.03	0.86	0.39
Habitual drinker, yes vs.no	2.42	(0.28, 4.56)	0.08	2.22	0.03

(B) Treated subjects

Variable	pulse pressure				
	β	(95% CI)	standardized β	t	*P*
Age	0.54	(0.30, 0.77)	0.20	4.51	＜0.001
BMI	0.46	(0.08, 0.83)	0.11	2.40	0.02
Salt intake	0.55	(0.07, 1.03)	0.10	2.27	0.02
TG	0.02	(-0.003,0.04)	0.08	1.71	0.09
Sex, male vs. female	-4.36	(-7.14, -1.58)	-0.16	-3.08	0.002
Habitual drinker, yes vs. no	-1.82	(-5.08, 1.45)	-0.06	-1.09	0.27

BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglycerides,

Habitual smoker: ≥ one cigarette/day, Habitual drinker : 20 g of ethanol/day, β: partial regression coefficient, CI: confidence interval

Salt intake was estimated from the sodium and creatinine concentrations in a spot urine sample using the formula proposed by Tanaka et al. (see Methods).

Figure(s)
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