Characteristics of Sodium Sensitivity in Korean Populations

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INTRODUCTION

Epidemiologic studies and interventional trials have revealed various risk factors related to hypertension. Among the risk factors, sodium is an important and well-known risk factor that can be modified by dietary intervention. A large observational follow-up study demonstrated that a reduction in dietary sodium intake leads not only to a reduction in blood pressure (BP), but also a reduction in the long-term risk of cardiovascular events by 25% over a period of 10-15 yr (1, 2). Moreover, recent systematic reviews and meta-analyses have shown that there is a significant relationship between a high sodium intake and an increased risk of morbidity and mortality related to stroke and cardiovascular events (3).

However, the BP responses to a low or high sodium diet are not uniform. Some individuals show a dramatic response to dietary sodium intake, with an increase in BP by ingesting a diet high in sodium or decreasing BP by a diet low in sodium. However, other individuals show no response or a negative response to diets low and high in sodium. This phenomenon has been defined as sodium sensitivity (SS) and sodium resistance (SR) (4, 5). Many studies have reported around a 20% prevalence of SS in non-hypertensives, and around a 50% prevalence in hypertensives (4-7). However, there appears to be ethnic differences in the prevalence of SS, showing a high prevalence in African-Americans (5). In addition, there are limited data for SS of non-hypertensives in Asians (8).

Considering the clinical importance, it is necessary to know the characteristics of subjects with SS to make a proper plan to improve public health. However, there are no studies that have evaluated Korean subjects with SS. Thus, this dietary interventional study was aimed to demonstrate the existence of subjects with SS, and to evaluate the characteristics of Korean subjects with SS.

Sodium sensitivity (SS) is a variable response of blood pressure (BP) to changes in sodium intake. The present study evaluated the existence and the characteristics of subjects with SS in Koreans. One hundred one subjects with (n = 31, 57.7 ± 9.8 yr) or without hypertension (n = 70, 40.8 ± 16.5 yr) were given a low-sodium dietary approach to stop hypertension (DASH diet (LSD) for 7 days and a high-sodium DASH diet (HSD) for the following 7 days. The prevalence of SS in the present study population was 27.7% (17.6% in the non-hypertensive subjects and 51.6% in the hypertensive subjects). Analysis of the non-hypertensive subjects showed that systolic BP, diastolic BP, and mean arterial pressure at baseline and after HSD were higher in the subjects with SS than the subjects without SS, and there were no differences after LSD. In the hypertensive subjects, there was no difference in the BP at baseline and after HSD whether or not the subjects had SS. However, the systolic BP of hypertensive subjects with SS was lower than hypertensive subjects without SS after LSD. In the present study population, subjects with SS have distinctive BP features unlike to subjects without SS.

Key Words: Hypertension; Sodium Sensitivity; DASH Diet

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This research was supported by a grant (08082KFDA999) from the Korea Food & Drug Administration in 2009.
MATERIALS AND METHODS

Subjects
We studied 101 volunteers, 18-65 yr of age (mean ± SD, 46.0 ± 16.6 yr). We excluded the volunteers with stage 2 hypertension (BP ≥ 160/100 mmHg) at the time of entry into the study, secondary hypertension, angina pectoris, myocardial infarction, congestive cardiac failure, stroke, diabetes mellitus, or chronic kidney disease (estimated GFR by the MDRD equation < 60 mL/min/1.73 m²). The volunteers who were taking medications affecting blood pressure and urinary electrolyte excretion were excluded if they could not quit during the study period. Pregnant or breastfeeding women were also excluded. Hypertension was defined as follows: 1) a previous diagnosis of hypertension with or without the current use of antihypertensive medications; or 2) a systolic blood pressure (SBP) ≥ 140 mmHg, or a diastolic blood pressure (DBP) ≥ 90 mmHg at the office (9). The result for the evaluation of the genetic variations associated with SS in the present population has been published, presenting part of the subject characteristics and baseline metabolic parameters (10).

Study protocol
After the eligibility of each subject was confirmed, all of the participants were asked to maintain their usual dietary pattern and physical activity for 2 weeks. Any medications that affect BP or urinary electrolyte excretion, such as antihypertensive medications, were asked to be discontinued at least 2 weeks before the study commenced. Other medications that did not interfere with the present study were permitted throughout the study. After 2 weeks, participants satisfying the enrollment criteria were hospitalized and confined to their ward during the study period.

Diet
On the first day, the usual diet without control of sodium content was given and baseline measurements were performed. Participants were put on a low-sodium dietary approaches to stop hypertension (DASH) diet (LSD; 100 mM NaCl/day) during the next 7 days and a high-sodium DASH diet (HSD; 300 mM NaCl/day) during the following 7 days. The DASH diet (2,300 kcal/day) was selected, which encourages the consumption of whole grains, fish, nuts, fruits, and vegetables with lowering of the intake of total and saturated fats, red meats, sweets, and sugar-containing beverages (11). Fourteen different diet types were used for all of the subjects. All three meals were cooked by trained dieticians based on the dietary plan for the present study in the hospital kitchen. The amount of sodium in the diets was calculated according to the food composition tables reported by the Rural Nutrition Institute and Rural Development Administration, the Government of the Republic of Korea (12).

Measurements
At each of two screening visits at least 1 week apart, BP was measured by a trained staff member using a random-zero sphygmomanometer, 2 times in a 5-min interval after the participants rested for 10 min in a seated position.

Twenty-four-hour ambulatory BP monitoring (24-hr ABPM) was measured during the first day of hospitalization and the last day of each diet period using an automated, non-invasive oscillometric device (P6 Pressurometer; Del Mar Reynolds, Inc., Irvine, CA, USA), which was attached to the left upper arm. Ambulatory blood pressures were measured at 30-min intervals for 24 hr. SS was defined as an increase in the MAP of > 4 mmHg (P < 0.05) in response to a HSD (10, 13). The mean arterial pressure (MAP) was calculated according to the following equation: MAP = (2DBP + SBP)/3.

A 24-hr urine specimen was collected to measure the amount of excretion of creatinine, sodium, and potassium during the first day of hospitalization and the last day of each diet period. Fasting blood samples were obtained 2 weeks prior to the study period, and at the last day of each diet period of the LSD and HSD. The complete blood cell count, total protein, albumin, calcium, phosphorus, bilirubin, glucose, BUN, creatinine, sodium, potassium, chloride, triglycerides, HDL-cholesterol, LDL-cholesterol, and total cholesterol levels were measured.

Statistical analysis
All statistical tests were two-sided, and the level of significance was set at 0.05. Continuous variables were expressed as the mean ± SD and categorical variables were described by number and percent in parentheses. Demographic and clinical characteristics were expressed by descriptive statistics for the 101 subjects. The summary statistics are presented by the SS and SR groups and also stratified according to all, hypertensive, and non-hypertensive patients. We performed an independent two-sample t-test to test the mean differences between SS and SR. To compare SS and SR, all categorical data were analyzed using Pearson’s chi-square test. All outputs were produced using SPSS (version 18; SPSS Inc., Chicago, IL, USA).

Ethics statement
The study was conducted according to the Declaration of Helsinki. The Dongguk University Institutional Review Board reviewed and approved the study protocol (2008-1-9). Informed consent was obtained from all participants.

RESULTS

Demographic and clinical characteristics of the studied subjects
One hundred one volunteers (51 men and 50 women) completed the present study (Table 1). Among the studied subjects, 31
Table 1. Baseline demographic and clinical characteristics of all participants

| Variables        | Values         |
|------------------|----------------|
| Numbers          | 101            |
| Age (yr)         | 46.0 ± 16.6    |
| Gender           |                |
| Male (%)         | 51 (50.5)      |
| Female (%)       | 50 (49.5)      |
| Hypertension (%) | 31 (30.7)      |
| Current smoker (%) | 25 (14.9)   |
| Body weight (kg) | 65.7 ± 13.1    |
| Body mass index (kg/m²) | 24.5 ± 3.7 |
| Fasting glucose (mg/dL) | 93.7 ± 11.1 |
| Serum creatinine (mg/dL) | 0.7 ± 0.1    |
| Serum Na (mM/L)  | 140.2 ± 1.9    |
| Serum K (mM/L)   | 4.1 ± 0.3      |
| Total cholesterol (mg/dL) | 192.5 ± 37.8 |
| Urinary Na (mM/day) | 204.7 ± 65.8 |
| Urinary K (mM/day) | 55.2 ± 17.5   |
| 24 hr SBP (mmHg) | 116.2 ± 11.5   |
| 24 hr DBP (mmHg) | 73.9 ± 9.5     |
| 24 hr MAP (mmHg) | 88.0 ± 9.8     |
| 24 hr PP (mmHg)  | 42.3 ± 6.9     |
| 24 hr HR (bpm)   | 66.0 ± 7.9     |

Data are expressed as the mean ± SD for continuous variables and described by numbers (%) for categorical variables. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate; bpm, beats per minute.

(30.7%) had hypertension and 25 (14.9%) were current smokers. All laboratory data were in the normal range. The baseline 24-hr urinary sodium excretion was 204.7 ± 65.8 mM/day, and the 24-hr urinary potassium excretion was 55.2 ± 17.5 mM/day. The 24-hr average SBP, DBP, and MAP were 116.2 ± 11.5, 73.9 ± 9.5, and 88.0 ± 9.8 mmHg, respectively, and the 24-hr average pulse pressure was 42.3 ± 6.9 mmHg.

Demographic and clinical characteristics of subjects between subjects with SS and SR

In the studied population, 28 subjects (27.7%) were determined to have SS, and the remainder (n = 73, 72.3%) had SR (Table 2). Subjects with SS were older than subjects with SR (54.4 ± 12.9 vs 42.8 ± 16.9 yr, P < 0.001), and had a higher prevalence of hypertension (57.1% vs 20.5%, P < 0.001). Twenty-two subjects with SS were > 50 yr of age (78.6%) and 32 subjects with SR were > 50 yr of age (43.8%). There was no significant difference in gender and cigarette smoking status between subjects with SS and SR. Among the non-hypertensive subjects, 12 (17.6%) had SS and 56 (82.3%) had SR. However, in the hypertensive subjects, 16 (51.6%) had SS. There was also no gender difference between subjects with SS and SR in the hypertensive and non-hypertensive groups.

Comparison of blood and urinary biochemical analysis between subjects with SS and SR

At baseline, there were no significant differences in the fasting blood glucose level, level of serum creatinine, sodium, potassium, and total cholesterol levels, whether or not the participants had SS or SR (Table 3). The 24-hr urinary excretion of sodium and potassium showed no marked differences from the baseline levels. After 1 week of a LSD, no significant difference was observed in biochemical data, with the exception of the fasting blood glucose level. The fasting blood glucose level of subjects with SS was higher than the subjects with SR. However, this difference was not considered to be a clinically significant finding because the level of fasting blood glucose in subjects with SS was not in the range of diabetes. For non-hypertensive patients, serum creatinine was significantly different between groups after 1 week of a HSD (P = 0.036). However, this difference was also not considered to be clinically significant finding because the level of serum creatinine was in the normal range.

After 1 week of a LSD, urinary sodium excretion was decreased from 193.3 ± 43.0 mM/day to 65.8 ± 14.5 mM/day in subjects with SS, and from 209.0 ± 72.4 to 61.8 ± 24.2 mM/day in subjects with SR. Urinary potassium excretion in subjects with SS was increased from 58.0 ± 15.9 mM/day to 63.3 ± 14.6 mM/day, but this was an insignificant finding (P = 0.254). However, urinary potassium excretion in subjects with SR was increased significantly from 54.1 ± 18.0 mM/day to 64.7 ± 17.6 mM/day. After 1 week of a HSD, urinary sodium excretion was increased to 205.2 ± 51.1 mM/day in SS and 193.2 ± 45.2 mM/day in SR (P = 0.393). Urinary potassium excretion was 74.0 ± 19.1 in subjects with SS and 76.1 ± 15.4 in subjects with SR (P = 0.561).

Urinary potassium excretion after 1 week of a HSD was significantly increased from baseline and 1 week of a LSD (P < 0.001). Subgroup analysis for the subjects with or without hypertension showed similar blood and urinary biochemical changes.
Comparison of blood pressure between subjects with SS and SR

The baseline SBP (P < 0.001), DBP (P = 0.001), and MAP (P < 0.001) of the subjects with SS were significantly higher than the subjects with SR (Table 4). This difference in SBP, DBP, and MAP disappeared after 1 week of sodium LSD. However, after 1 week of a HSD, all parameters of SBP, DBP, and MAP were elevated, and the significant difference in these parameters reappeared be-
tween subjects with SS and SR \( (P < 0.001) \).

In non-hypertensive subjects, a significantly higher level of SBP, DBP, and MAP at baseline and after 1 week of a HSD was maintained in subjects with SS, but the difference between subjects with SS and SR disappeared after 1 week of an LSD.

However, in hypertensive participants, SBP, DBP, and MAP at baseline, and after 1 week of an HSD was not different whether or not the participants were with SS or SR. After 1 week of an LSD, only the SBP in subjects with SS was lower than subjects with SR \( (P = 0.023) \).

**DISCUSSION**

This is the first study to demonstrate the existence and characteristics of SS in Koreans. In the present study population, 18% of non-hypertensive and 52% of hypertensive subjects were shown to have SS based on the study criteria.

After the first report of Kawasaki et al. (6), several investigators have reported the characteristics of SS in humans. SS is an independent risk factor of cardiovascular events. Morimoto et al. (14) showed a more frequent occurrence of cardiovascular events in hypertensive patients with SS. Moreover, Weinberger et al. (15) reported a long-term deleterious effect of SS on cardiovascular disease morbidity and total mortality, which was independent of hypertension. In the study by Kawasaki et al. (6), 50% of hypertensive patients had SS. Weinberger et al. (5) demonstrated that SS existed not only in hypertensive individuals, but also in individuals with a normal BP; SS was observed in 26% of non-hypertensive subjects and 51% of hypertensive subjects.

Measurement of the exact prevalence of SS in the general population is much difficult because of the difficulty in method involved, and the arbitrary definition of SS. Various methods and definitions have been used in the studies of SS. A rapid sodium loading and depletion method involves administering sodium by the administration of 2 L of saline intravenously over a 4-hr period, followed by a 10 mM sodium diet daily plus 40 mg of furosemide orally every 8 hr (5, 15, 16). Dietary approaches have used more different methods. The amount of sodium loaded, the duration of dietary loading, and the sequences of high and low sodium diets were varied (5, 16-18). Morning BP was measured by a mercury sphygmomanometer or automated devices, or the 24-hr ambulatory BP was measured (17, 18). Using these various sodium loading and BP measurement methods, investigators have also used arbitrarily defined criteria of SS. For example, Kerstens et al. (19) used an increase in MAP \( \geq 3 \) mmHg as a criterion of SS. Sullivan (20) used an increase in MAP exceeding 5%. However, Weinberger et al. (5) adopted an increase in MAP \( \geq 10 \) mmHg.

Although there are various methods and criteria defining SS, the reported prevalence of SS in various studied population is similar (approximately 50% in hypertensive patients). Our study population also showed a similar prevalence of SS in hypertensive subjects. However, reports in non-hypertensives are limited, and little data are available for Asians. The reported prevalence of SS in the studies of non-hypertensive subjects is 16%-34% (4, 5). In the present study, the prevalence of SS in non-hypertensive subjects was 18%, which was similar to that reported by Sullivan and Ratts (4), but lower than that reported by Weinberger et al. (5). This difference between the results of the present study and the study of Weinberger et al. (5) may be due to the discrepancies in methods of sodium loading and depletion, BP measurements, ethnicity, and study diets used.

Akita et al. (21) reported the changes in SS to SR through the diuretic action of the DASH diet. The DASH diet used in our study as a background diet may contribute to further lowering of BP by changing SS into SR through diuretic action. However, Akita et al. (21) gave the DASH diet for 30 days, which was longer than the duration of our study. The change in SS was also confined to African-Americans. The studied population of the present study was Asians, and little is known for the effect of DASH diet on the change of SS. The DASH diet can reduce BP within 2 weeks of starting a diet plan (22). In the present study, all participants were in a 2-week course of the DASH diet with an elevation of urinary potassium excretion at the end of the study. Subjects with SS showed elevation of BP after 1 week of a high-sodium DASH diet, although the subjects were maintained on the DASH diet for 2 weeks. Although it is difficult to conclude whether or not the DASH diet has changed the prevalence of SS in our study population, the findings of the present study indicates that the DASH diet only approach is not sufficient for lowering of BP if the sodium content is not reduced (11).

In the present study, the interesting finding is that in the non-hypertensive subjects, the baseline BP of subjects with SS was higher than the subjects with SR. After 1 week of LSD, the higher baseline BP in non-hypertensive subjects with SS was lowered and the BP level was not different from non-hypertensive subjects with SR. This finding demonstrates that a HSD may be an important factor in the elevation of BP in non-hypertensive participants with SS. Persons with high normal BP are known to have a higher chance of developing hypertension and a greater risk for cardiovascular events than persons with normal BP (23, 24). Although we did not evaluate subjects with high normal BP, a higher baseline BP indicates that non-hypertensive individuals with SS may have an increased possibility of developing hypertension in the future if they continue on a HSD. This is consistent with the previous study in which normotensive subjects with SS had a cumulative mortality that was similar to that of hypertensive patients (15). Although hypertensive subjects showed no difference in the baseline BP between subjects with SS and SR, hypertensive subjects with SS had a significantly lower level of BP than hypertensive subjects with SR after LSD. Higher baseline BP of non-hypertensive subjects with SS, and a marked de-
crease in BP after 1 week of LSD in all subjects with SS indicates that the reduction in dietary sodium intake is an important dietary approach for the prevention of developing hypertension and the management of hypertension.

The present study was performed under controlled conditions. Two trained nutritionists always checked the remainders of each meal. The dietary compliance was 99.8% (data not shown). There was no difference in the urinary sodium excretion between subjects with or without SS, indicating a similar amount of sodium intake. A similar amount of sodium intake and excretion suggests that BP elevation in individual with SS by HSD is not simply explained by sodium retention. Many mechanisms have been suggested regarding the development of the sodium sensitive hypertension, including inappropriate production of nitric oxide in response to sodium intake (25), dysregulated tissue renin-angiotensin system activity (26), and subtle acquired renal injury and inflammation (27).

The present study had several limitations. First, the present study was performed over a short-term period, and the data was only obtained at the end of each dietary intervention. Thus, it could not be interpreted that this effect could be maintained consistently in a long-term period, because studies have demonstrated the limited long-term effect of sodium restriction on the BP (28). Second, the present study was not performed in the representative cohort, not reflecting the general population of Korean. Thus, it is difficult to estimate the exact prevalence of SS in the general population of Korean. However, the known prevalence of SS was also not derived from the representative cohort, but by an extrapolation from the studied populations. Despite of this limitation, the prevalence of SS from the present study is similar to that of the previous reports (4-6, 14, 29). Third, the present study investigated individuals with normotension and stage 1 hypertension. Thus, the results can not be applicable to those with more severe hypertension. Fourth, it is well-known that the prevalence of SS increases with increasing age (16, 30). Also, in this study, the ages of subjects with SS were higher than that of subjects with SR. Further studies for the prevalence of SS in an age-matched population are needed.

In the present study, we have reported the existence of SS in Koreans and their characteristics. The characteristics of subjects with SS include a higher baseline BP in normotensive subjects, a higher prevalence of hypertension, and a higher age. Although a reduction of sodium intake is more important and effective in the persons with SS, the diagnosis of SS is difficult and expensive. Detection of persons with SS may be cost-ineffective in general practice. Moreover, the SS increases with increasing age (16, 30). Thus, dietary intervention of sodium reduction targeting to individuals with SS is impractical. Instead, targeting to a general public irrespective of SS might be a good strategy. To reduce sodium intake, strong commitment of individuals, healthcare professionals, voluntary organizations, communities, and government is necessary.

ACKNOWLEDGMENTS

We thank the dieticians (Hye-Jin Yun and Kyung-Hee Cho) for the preparation of meals.

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AUTHOR SUMMARY

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This is the first study to demonstrate the existence of sodium sensitivity and the effect on blood pressure in Koreans. The research showed that 18% of non-hypertensive and 52% of hypertensive subjects had sodium sensitivity. In the non-hypertensive at baseline and after a high-salt DASH diet, arterial blood pressures of sodium sensitive subjects were higher than those of the subjects without sodium sensitivity. Such difference disappeared after a low-salt DASH diet. In the hypertensive group, however, there was no difference between salt-sensitive and –insensitive subjects. Albeit with several limitations, this study might provide valuable information for future investigation on hypertension.