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ORIGINAL ARTICLE

# Long-term variability of urinary salt excretion and blood pressure in hypertensive patients

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**We investigated the long-term trend and variability of urinary salt (sodium chloride) excretion in hypertensive patients. Subjects included 186 hypertensive patients (103 women and 83 men, mean age: 58.5 ± 10.5 years) who underwent 10 successful 24-h home urine collections over a mean observation period of 7.7 years. We measured 24-h urinary salt excretion and blood pressure (BP) sequentially at the time of each collection and monitored the long-term trend and variability of urinary salt excretion. BP significantly decreased from 145 ± 16/85 ± 11 mm Hg to 130 ± 12/70 ± 11 mm Hg and was associated with an increased use of antihypertensive drugs. The 24-h urinary salt excretion also decreased from 9.5 ± 3.6 g per day at the first measurement to 8.5 ± 3.2 g per day at the 10th measurement. Urinary salt excretion during the observation period ranged from a minimum value of 5.2 ± 1.8 g per day to a maximum value of 13.4 ± 3.6 g per day with a coefficient of variation of 29.2 ± 8.1%. When subjects were assigned to a low, medium and high salt group based on the tertiles of the first measurement of urinary salt excretion and the tertiles based on the mean value of 10 measurements during the observation period, only 56.2% remained in the same category, suggesting that a single measurement of urinary salt excretion can only predict long-term urinary salt excretion in approximately half of the individuals. In conclusion, urinary salt excretion shows large variability such that a single measurement may not be sufficient to assess salt intake in individuals.**
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**Keywords:** blood pressure; salt intake; urinary salt excretion; variability

## INTRODUCTION

Hypertension is a major risk factor for cardiovascular events and is also a cause of chronic kidney disease.[1] It is well-recognized that hypertension and excessive salt (sodium chloride) intake are closely linked,[2] and several studies have suggested that excessive salt intake *per se* is a cardiovascular risk factor independent of blood pressure (BP).[3] We have also reported that long-term high salt intake promotes a decline in renal function,[4] suggesting that salt restriction is important to prevent the decline of renal function in hypertensive patients. The guidelines of the Japanese Society of Hypertension (JSH 2009) recommend a salt intake of $<6$ g per day for the management of hypertension.[5] However, the average salt intake still exceeds 10 g per day in Japan,[6] and it has been reported that compliance with salt restriction is poor in Japanese hypertensive patients.[7]

The assessment of salt intake is essential for the guidance of salt restriction, and the measurement of urinary salt excretion is well-recognized as one of the methods used to evaluate an individual's salt intake.[8] However, salt intake may change from day-to-day, and it may also be influenced by a change in dietary habits or by interventions given by medical staff. Thus, a single or even a few measurements may not be sufficient to accurately evaluate an individual's salt intake.

The primary purpose of the present study was to investigate the long-term variability of urinary salt excretion in hypertensive patients. Because BP variability has also been reported to be a risk factor for cardiovascular events,[9] we also investigated the long-term changes and variability of BP.

## METHODS

This study was conducted in accordance with the institutional guidelines. Participants were recruited from hypertensive outpatients who visited the National Kyushu Medical Center, Fukuoka, Japan. We assessed urinary salt excretion by using a 24-h home urine collection. Urine samples were collected at 24-h intervals using a partition cup (proportional sampling method) that collects 1/50 of the urine over 24 h. If the 24-h creatinine excretion was within ± 30% of the estimated value, the urine collection was considered successful. BP was measured twice on each occasion with a sphygmomanometer by the doctors while the patients were quietly seated. Hypertension was considered to be present if the patients had a systolic and diastolic BP $\geqslant$140 mm Hg and 90 mm Hg, respectively, or they were taking antihypertensive medications.

The subjects included 186 hypertensive patients (103 women and 83 men) who underwent 10 successful 24-h home urine collections over an observation period of at least 3 years. We measured 24-h urinary salt excretion and BP sequentially at the time of each collection and monitored the long-term trend

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and variability of urinary salt excretion. The number of patients adhering to successful salt restriction of <6 g per day was also recorded. Nutritional guidance on salt restriction was provided by the doctors and nutritionists, if needed, based on the result of each 24-h urinary salt excretion.

A statistical software package (SAS, version 9.2, SAS Institute Inc., Cary, NC, USA) was used for analysis. The data are presented as the mean ± s.d. unless otherwise stated. A paired *t*-test and a one-way analysis of variance were used for analysis. *P*-values <0.05 were considered statistically significant.

## RESULTS

A total of 186 subjects (mean age 58.5 ± 10.5 years at baseline) underwent 10 successful 24-h home urine collections over a mean observation period of 7.7 ± 2.1 years. The characteristics of the subjects are shown in Table 1. BP decreased from 145 ± 16/85 ± 11 mm Hg at the first visit to 130 ± 12/70 ± 11 mm Hg at the 10th visit ($P<0.01$) and was associated with an increased use of antihypertensive drugs (from 1.1 ± 0.8 to 1.9 ± 0.9 drugs, $P<0.01$), especially an increase in the use of angiotensin II receptor blockers (from 25 to 75%). The s.d. of BP was 11.4 ± 3.8/8.5 ± 3.1 mm Hg during the observation period, and the BP change from the first to the 10th visit was significantly correlated with the s.d. of BP during the observation period (systolic BP: $r=0.47$, $P<0.01$; diastolic BP: $r=0.58$, $P<0.01$), suggesting that the decrease in BP was the major determinant of BP variability.

**Table 1 Characteristics of the subjects**

| | |
|---|---|
| N *(men:women)* | 186 (83:103) |
| Age at baseline (years) | 58.9 ± 10.5 |
| Follow-up period (years) | 7.7 ± 2.1 |
| *Body weight* | |
| Baseline (kg) | 59.8 ± 10.7 |
| Last visit (kg) | 60.0 ± 10.5 |
| *BP* | |
| Baseline (mm Hg) | 145 ± 16/85 ± 11 |
| Last visit (mm Hg) | 130 ± 12**/70 ± 11** |
| *Number of antihypertensive drugs* | |
| Baseline | 1.1 ± 0.8 |
| Last visit | 1.9 ± 0.9** |
| Mean of BP during the observation period (mm Hg) | 135 ± 8/74 ± 8 |
| s.d. of BP during the observation period (mm Hg) | 11.4 ± 3.8/8.5 ± 3.1 |
| CV of BP during the observation period (%) | 8.4 ± 2.8/11.6 ± 4.7 |
| *Urinary NaCl* | |
| 1st try (g per day) | 9.5 ± 3.6 |
| 10th try (g per day) | 8.5 ± 3.2** |
| Mean urinary NaCl (g per day) | 8.9 ± 2.2 |
| Max urinary NaCl (g per day) | 13.4 ± 3.6 |
| Min urinary NaCl (g per day) | 5.2 ± 1.8 |
| Range (g per day) | 8.2 ± 3.1 |
| CV (%) | 29.2 ± 8.1 |
| *Urinary protein* | |
| 1st try (g per day) | 0.29 ± 0.63 |
| 10th try (g per day) | 0.15 ± 0.37** |
| *Estimated glomerular filtration rate* | |
| 1st try (ml min$^{-1}$ per 1.73 m$^2$) | 71.2 ± 16.4 |
| 10th try (ml min$^{-1}$ per 1.73 m$^2$) | 67.5 ± 21.5** |
| Chronic kidney disease (%) | 41.9 |
| Diabetes mellitus (%) | 14.0 |
| Dyslipidemia (%) | 55.4 |

Abbreviations: BP, blood pressure; CV, coefficient of variation; Max, maximum; Min, minimum. Values are mean ± s.d., **$P<0.01$ *vs.* baseline.

The 24-h urinary salt excretion also decreased from 9.5 ± 3.6 g per day at the first measurement to 8.5 ± 3.2 g per day at the 10th measurement (Figure 1). Urinary salt excretion during the observation period ranged from a minimum value of 5.2 ± 1.8 g per day to a maximum value of 13.4 ± 3.6 g per day with a coefficient of variation of 29.2 ± 8.1%. We investigated the characteristics of the patients who demonstrated a large variability of urinary salt excretion. When these subjects were defined based on the range of urinary salt excretion (8 g per day or more), they were more likely to be male ($P<0.05$) and have a significantly lower estimated glomerular filtration rate and higher body mass index ($P<0.01$) than those with a small variability (<8 g per day). Moreover, the frequency of diuretic use was significantly higher in the subjects with a large variability of urinary salt excretion than in those with a small variability at the 10th collection (18.4% *vs.* 8.1%, $P<0.05$), even though there was no difference in the use of antihypertensive drugs (1.97 ± 1.0 *vs.* 1.86 ± 0.9 drugs). There was also no difference in the prescription of diuretics at the first collection (2.3% *vs.* 3.0%). When the subjects with a large variability of urinary salt excretion were defined based on the coefficient of variation of urinary salt excretion (30% or more), they had significantly higher urinary protein excretion ($P<0.05$), lower estimated glomerular filtration rate ($P=0.08$) and significantly larger BP variability ($P<0.05$) than those with a small variability (<30%). Again, there were no differences in the prescription of diuretics either at the first or the last collection.

The rate of urinary salt restriction to a level <6 g per day is shown in Figure 2. Only 14% (men: 7%, women: 19%) achieved this successful level of salt restriction on five or more occasions, and 79% (men: 92%, women: 69%) achieved it on three or less occasions. We investigated the characteristics of the patients who achieved a salt restriction of <6 g per day on several occasions. Those who achieved a urinary salt restriction of <6 g per day on five or more occasions were more likely to be female ($P<0.05$) and to have a significantly lower body mass index ($P<0.05$) than those who achieved it on fewer than five occasions. We also investigated the characteristics of the patients who eventually achieved a successful level of salt restriction in spite of failing at the initial collection. Urinary salt excretion at the initial collection was 9 g per day or more in 92 subjects. When the successful level of salt restriction was defined based on the mean value of 10 measurements during the observation period with <9 g per day, the subjects who succeeded ($n=24$) had a significantly lower body mass index ($P<0.01$) than those who failed ($n=68$).

The initial level of urinary salt excretion was significantly correlated with average salt excretion for 10 measurements ($r=0.62$, $P<0.01$) (Figure 3). When subjects were assigned to a low, medium and high salt group based on the tertiles of the first measurement of urinary salt excretion and then compared with the group based on the tertiles of the mean value of 10 measurements during the observation period, 56.2% of the subjects remained in the same category, suggesting that a single measurement at baseline can only predict the long-term urinary salt excretion in approximately half of the individuals (Figure 4).

Mean urinary salt excretion correlated with the changes in systolic ($r=0.14$, $P=0.06$) and diastolic BP ($r=0.15$, $P<0.05$) during the observation period, indicating that lower long-term salt intake leads to a greater BP reduction. In the multivariate analysis, the change in systolic BP during the observation period tended to be associated with the mean urinary salt excretion (partial $r=0.08$, $P=0.08$) and was

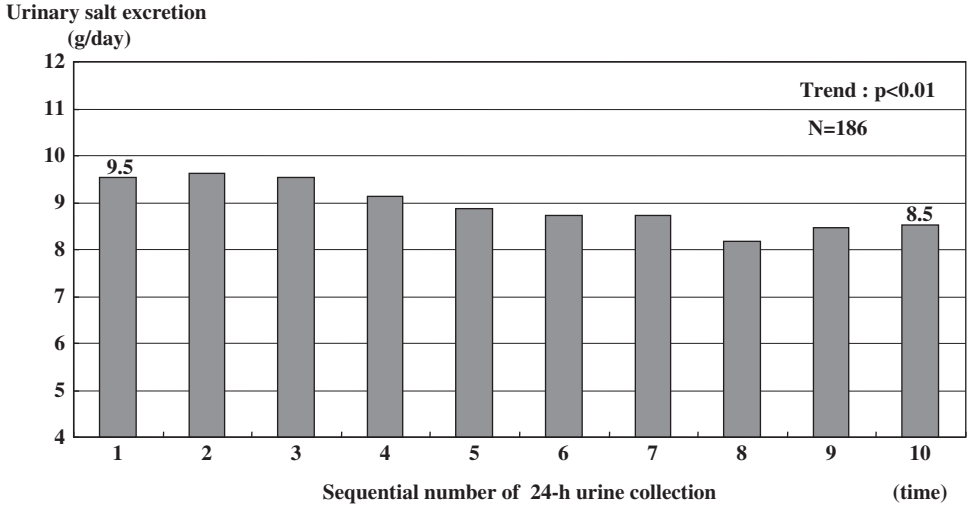


**Figure 1** Changes in 24-h urinary salt excretion determined by 10-times-measurements during the observation period of 7.7 years in 186 hypertensive patients.

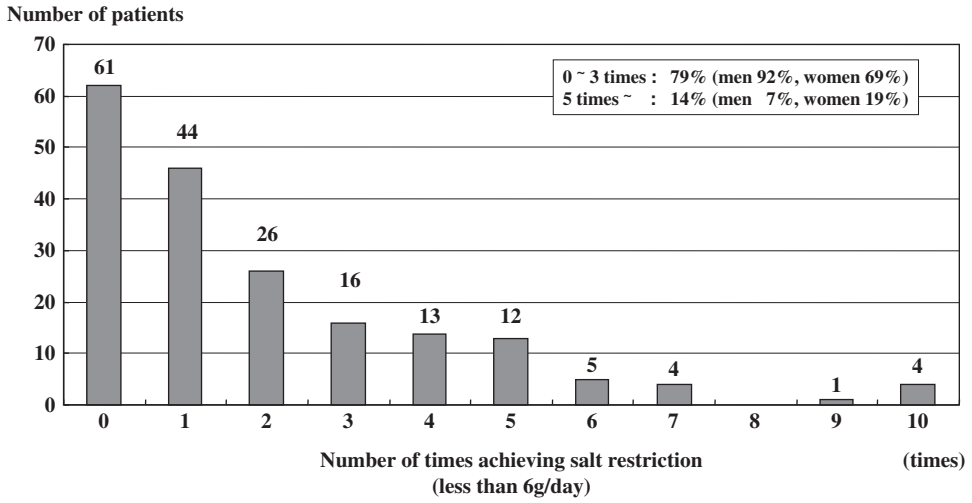


**Figure 2** Achievement rate of urinary salt restriction of <6 g per day in hypertensive patients.

independent of the addition of antihypertensive drugs (Table 2). In the patients taking three or more antihypertensive drugs ($N=40$), at the 10th collection, urinary salt excretion was higher ($9.3\pm3.6$ *vs.* $8.3\pm3.0$ g per day, $P<0.10$), estimated glomerular filtration rate was significantly lower ($58.0\pm20.9$ *vs.* $70.1\pm20.9$ ml min$^{-1}$ per 1.73 m$^2$, $P<0.01$) and urinary protein was significantly higher ($0.28\pm0.55$ *vs.* $0.12\pm0.29$ g per day, $P<0.05$) compared with those taking two antihypertensive drugs or less ($N=146$). There were no significant differences in body weight, body mass index or BP at the 10th collection. Moreover, in the patients taking diuretics at the 10th collection, urinary salt excretion was significantly higher both at the first ($11.0\pm3.4$ *vs.* $9.3\pm3.6$ g per day, $P<0.05$) and 10th collection ($10.2\pm3.7$ *vs.* $8.3\pm3.0$ g per day, $P<0.01$) compared with those not taking diuretics, suggesting that diuretics may be needed to manage patients with long-term high salt intake.

## DISCUSSION

This study demonstrated that while urinary salt excretion in Japanese hypertensive patients decreased when measured by repeated 24-h home urine collection, there was a great deal of long-term variability. According to the National Health and Nutrition Survey Japan,[10] in 2011, the average salt intake decreased from 12.5 g per day in 1998 to 10.4 g per day (men: 11.4 g per day, women: 9.6 g per day), although levels were still higher when compared with those in western countries. Salt intake of Japanese hypertensive patients has also been reported to be high. Urinary salt excretion measured by a 24-h home urine collection prior to 2000 was 9.6 g per day in Fukuoka (an area with moderate salt intake)[7] and 11–13 g per day in Tohoku (an area with high salt intake).[11] In the present study, urinary salt excretion at the first collection was $9.5\pm3.6$ g per day and decreased to $8.5\pm3.2$ g per day over a mean observation period of 7.7 years. After 10 urine collections, only 14% (men: 7%, women: 19%) of the patients achieved salt restriction to less than 6 g per day on five or more occasions, suggesting that long-term compliance of salt restriction is difficult in Japanese hypertensive patients. However, the observation that the average salt excretion in 10 collections correlated with the change in BP during the observation period suggests that lower salt intake leads to the greater BP reduction.

Concerning the variability of salt intake, to address the methodological problems involved in estimating salt intake on a

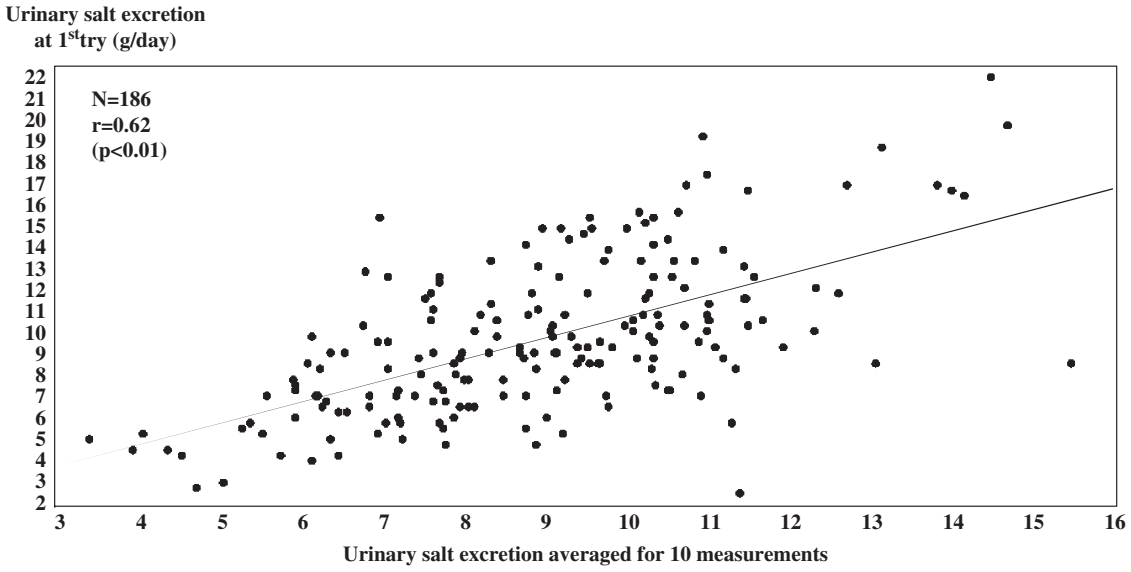


**Figure 3** Relationship between the first measurement of urinary salt excretion and the mean value of 10-times-measurements in hypertensive patients.

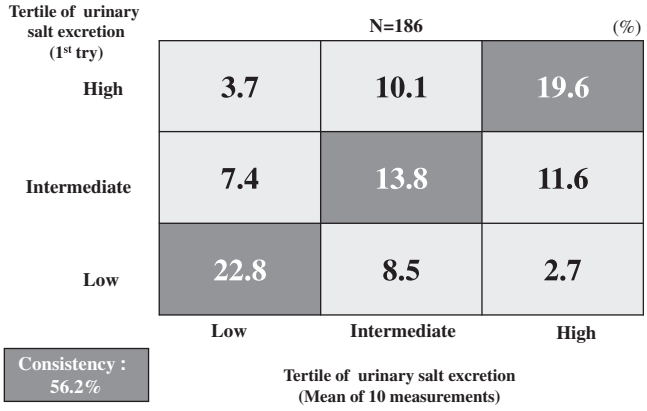


**Figure 4** Comparison between the patients who belonged to the tertile of the first measurement of urinary salt excretion and those who belonged to the tertile based on the mean value of the 10-times-measurements during the observation period.

**Table 2 Determinants of blood pressure change—multiple regression analysis—**

| | *Partial* r | P-*value* |
|---|---|---|
| *Systolic BP change*[a] | | |
| Systolic BP at baseline | −0.79 | <0.01 |
| Age | 0.10 | 0.04 |
| Mean urinary salt excretion | 0.08 | 0.08 |
| *Diastolic BP change*[b] | | |
| Diastolic BP at baseline | −0.51 | <0.01 |
| Age | −0.32 | <0.01 |
| Body weight | 0.09 | 0.15 |

Abbreviation: BP, blood pressure.
[a]Adjusted variables: addition of antihypertensive drugs, body weight and diabetes mellitus.
[b]Adjusted variables: addition of antihypertensive drugs, mean urinary salt excretion and diabetes mellitus.

daily basis, the variability of urinary salt excretion has been previously evaluated in the general population.[12,13] To our knowledge, however, the variability of urinary salt excretion over the course of several years in treated hypertensive patients has not been reported. The present study demonstrated that the coefficient of variation of 10 measurements of urinary salt excretion was 29.2%, suggesting that there is a great deal of long-term variability in salt excretion. When the patients were assigned to a low, medium and high salt group based on the tertiles of the collection and compared with the tertiles based on the mean value of 10 measurements, 56.2% of patients remained in the same category. However, when the patients were categorized based on the tertiles of the average of the first and the second measurement of urinary salt excretion, this number increased to 64.3%. Moreover, the correlation coefficients between urinary salt excretion averaged for three (from the 1st to the 3rd), four (from the 1st to the 4th) and five (from the 1st to the 5th) measurements and the mean value of 10 measurements improved to 0.77, 0.82 and 0.89, respectively. These observations indicate that multiple measurements are clearly superior to a single measurement for the assessment of the long-term urinary salt excretion in individuals.

The assessment of salt intake is an important guide for determining the degree of salt restriction needed for hypertensive patients. The Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension proposed several methods to assess salt intake.[8] Each method has both merits and limitations. A 24-h urine collection is the most reliable of all methods to assess salt intake, and is recommended in special facilities for the treatment of hypertension. In the present study, we used a partition cup to collect the 24-h urine.[14] Estimation of urinary salt excretion using the first or the second morning urine, although practical and suitable for general medical facilities, is less reliable.[15,16] Recently, a 'salt monitor' was developed to estimate 24-h salt excretion with an installed formula using 8-h night-time urine. This method was applied in clinical practice in order to facilitate self measurement.[17] Although a reliable method is not easy to perform and a simple method is less reliable, the assessment of salt intake is strongly recommended for the management of hypertension. Based on our findings, individual salt intake should be repeatedly evaluated using one of the methods mentioned above for motivating patients to reduce salt intake.

Finally, some limitations of the present study should be noted. First, during the observation period, nutritional guidance by doctors or nutritionists was provided for each subject. However, we have not investigated the precise influence of nutritional guidance on urinary salt excretion, and are thus unable to address the possibility that dietary counseling may have led to an effective reduction of urinary salt excretion in some patients, and contributed to the variability or the inconsistency of long-term urinary salt excretion. Second, in the multivariate analysis for BP change, although we showed that the change in systolic BP during the observation period tended to be associated with mean urinary salt excretion independent of the addition of antihypertensive drugs, we did not specifically investigate whether the dose was increased or whether there was a change in the class of drugs used, both potential confounding factors. In addition, adjusted variables may be insufficient in the present analysis. We were unable to exclude the possibility that variables that were not examined such as a history of cardiovascular disease, smoking, alcohol intake or a family history of hypertension may have potentially contributed to the change in BP.

In conclusion, urinary salt excretion significantly decreased as measured by the repeated 24-h home urine collection. Because urinary salt excretion showed a large variability, a single measurement is insufficient for the assessment of long-term salt intake in individuals. Long-term compliance of salt restriction is important for the management of BP.

## CONFLICT OF INTEREST

TT received a research grant from MSD K.K., Japan. The remaining authors declare no conflict of interest.

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