Hypertension Research (2013) 36, 172–176

www.nature.com/hr

ORIGINAL ARTICLE

# High salt intake promotes a decline in renal function in hypertensive patients: a 10-year observational study

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**We investigated the influence of long-term salt load on renal function in hypertensive patients. The subjects were 133 hypertensive patients (80 women and 53 men, mean age 60 ± 9 years) who underwent at least five successful 24 h home urine collections during the 10-year observation period. Blood pressure (BP) and 24-h urinary salt and creatinine excretion levels were measured. BP decreased from 143 ± 12/85 ± 8 to 129 ± 14/68 ± 11 mm Hg during the 10.5-year observation period, and this decrease was associated with patients taking an increased number of antihypertensive drugs (1.3 ± 1.0 to 2.2 ± 1.1). The estimated glomerular filtration rate (eGFR) also significantly decreased from 71.7 ± 14.6 to 64.7 ± 16.5 ml min$^{-1}$ ($P<0.01$), and the change in eGFR was −0.68 ml min$^{-1}$ per year on average. The average salt excretion was 8.6 ± 2.2 g per day and showed a significant negative correlation with the change in eGFR ($r=-0.21$, $P=0.02$). Subjects with an average salt excretion < 8 g per day showed a significantly slower decline in renal function than those with an average salt excretion ⩾ 8 g per day (the change in eGFR: −0.41 ± 1.10 *vs.* −0.83 ± 1.19 ml min$^{-1}$ per year, $P<0.05$). In the multivariate analysis, the average salt excretion (partial $r=-0.19$, $P=0.03$) and baseline eGFR (partial $r=-0.23$, $P=0.01$) were significantly associated with the change in eGFR. This association was independent of BP change or an increased number of antihypertensive drugs. The results suggest that long-term salt load promotes a decline in renal function in hypertensive patients; thus, salt restriction is encouraged, to prevent renal damage.**
*Hypertension Research* (2013) **36,** 172–176; doi:10.1038/hr.2012.155; published online 11 October 2012

**Keywords:** eGFR; hypertensive patients; renal function; salt load; urinary salt excretion

## INTRODUCTION

The number of patients with end-stage renal disease (ESRD) is increasing in Japan and it is well recognized that hypertension and chronic kidney disease (CKD) are closely related.[1] CKD, in which patients have low glomerular filtration rate (GFR), is not only the cause of ESRD but also a risk factor for cardiovascular disease. Thus, the control of blood pressure (BP) has been emphasized as a strategy for preventing ESRD.

Inappropriate lifestyle habits, such as obesity and excessive salt intake, also accelerate kidney damage through BP-dependent and -independent mechanisms. Several studies have suggested a role for salt intake in the pathophysiology of the progressive decline in renal function.[2–4] The importance of salt restriction is well recognized, and JNC-7 and the guidelines of the Japanese Society of Hypertension (JSH 2009) recommend a salt intake of <6 g per day for the management of hypertension.[5,6] However, average salt intake still exceeds 10 g per day in Japan, and we have previously reported that Japanese hypertensive patients are poorly compliant with long-term salt restriction.[7] The failure to reduce salt intake may lead to the deterioration of renal function. In the present study, therefore, we investigated the effect of long-term salt load on renal function in Japanese hypertensive patients.

## METHODS

Participants were recruited from hypertensive outpatients who visited the National Kyushu Medical Center, Fukuoka, Japan. We assessed urinary salt excretion through 24 h home urine collection, which is one of the methods recommended for evaluating salt intake by the working group for dietary salt reduction of the Japanese Society of Hypertension.[8] Urine samples were collected at 24-h intervals using a partition cup (proportional sampling method[9]), which collects 1/50 of the urine over 24 h. If the 24 h creatinine excretion was within ± 30% of the estimated values, the urine collection was considered successful. The subjects included 133 patients (80 women and 53 men, mean age 60 ± 9 years) who underwent more than five successful 24 h home urine collections during the follow-up period. The first examination was performed between 1998 and 2000, and the last examination was performed between 2008 and 2010. Urinary salt and creatinine excretion levels were measured. The urinary protein concentration was measured with a pyrogallol red molybdate protein assay, and the sensitivity of this method was 2.58 mg dl$^{-1}$.

BP was measured with a sphygmomanometer by the doctors while the patients were quietly seated. Hypertension was considered to be present if the patients had a systolic BP ⩾ 140 mm Hg and/or diastolic BP ⩾ 90 mm Hg or the patients were on antihypertensive medication. CKD was considered to be present if the patient had either a decreased estimated GFR (eGFR) (<60 ml min$^{-1}$ per 1.73m$^2$) or persistent proteinuria, which was defined as

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Received 23 March 2012; revised 14 June 2012; accepted 28 July 2012; published online 11 October 2012

dipstick proteinuria greater than +1 for more than 3 months. eGFR was calculated using the Modification of Diet in Renal Disease formula (for men, $0.741 \times 175 \times$ serum creatinine levels $-1.154 \times$ age $-0.203$; for women, $0.741 \times 175 \times$ serum creatinine levels $-1.154 \times$ age $-0.203 \times 0.742$,[10]). This study was performed in accordance with institutional guidelines and approved by the ethical committee.

### Statistical analysis

The values are presented as mean ± s.d. The differences in the variables were compared with a one-way analysis of variance. A chi-square test was also utilized when appropriate. *P*-values less than 0.05 were considered significant.

## RESULTS

During the average period of 10.5 years, 133 subjects (80 women and 53 men, mean age 60 ± 9 years at the first visit) underwent urine collection an average of 11.7 times. The characteristics of the subjects are shown in Table 1. BP decreased from 143 ± 12/85 ± 8 to 129 ± 14/68 ± 11 mm Hg during the 10.5-year observation period, and this decrease was associated with patients taking an increased number of antihypertensive drugs (1.3 ± 1.0 to 2.2 ± 1.1) and with a decrease in body weight (59.8 ± 9.9 to 58.7 ± 10.6 kg). In addition, eGFR decreased significantly from 71.7 ± 14.6 to 64.7 ± 16.5 ml min$^{-1}$ per 1.73m$^2$ and the average change in eGFR was −0.68 ml min$^{-1}$ per year. The frequency of CKD higher than stage 3 increased from 21.8 to 34.6% during the observation period. The urinary salt excretion at the last visit was significantly lower than at the first visit (7.8 ± 3.1 *vs.* 9.4 ± 3.5 g per day, respectively, $P<0.01$), and the average salt excretion during the observation period was 8.6 ± 2.2 g per day (Figure 1). The average salt excretion showed a significant negative correlation with the change in eGFR ($r = -0.21$, $P = 0.02$, Figure 2).

Table 2 compares the profiles of hypertensive patients whose average salt excretion was less than 8 g per day and those with ⩾8 g per day. Patients with an average salt excretion <8 g per day were more frequently female and had a lower body weight, diastolic BP, number of antihypertensive drugs and urinary protein excretion than those with an average salt excretion more than 8 g per day. Subjects with an average salt excretion <8 g per day showed a significantly slower decline in renal function than those with an average salt excretion ⩾8 g per day (the change in eGFR: −0.41 ± 1.10 *vs.* −0.83 ± 1.19 ml min$^{-1}$ per year, $P<0.05$). Similarly, male subjects with an average salt excretion <9.5 g per day showed a significantly slower decline in renal function than those with an average salt excretion ⩾9.5 g per day (the change in eGFR: −0.43 ± 0.83 *vs.* −1.03 ± 1.14 ml min$^{-1}$ per year, $P<0.05$, Figure 3a), and female subjects with an average salt excretion <8 g per day showed a significantly slower decline in renal function than those with an average salt excretion ⩾8 g per day (the change in eGFR: −0.33 ± 1.21 *vs.* −0.91 ± 1.25 ml min$^{-1}$ per year, $P<0.05$, Figure 3b). The frequency of patients with new-onset CKD (eGFR <60 ml min$^{-1}$ per 1.73m$^2$) during the 10-year observation period was 21.9%. Male subjects with an average salt excretion <9.5 g per day showed a significantly lower frequency of new-onset CKD than those with an average salt excretion ⩾9.5 g per day (7.7 *vs.* 37.1%, $P<0.05$). Similarly, the frequency of new-onset CKD tended to be lower in female patients with an average salt excretion <8 g per day than in those with an average salt excretion ⩾8 g per day, although the difference was not statistically significant (15.8 *vs.* 22.8%).

Serum and urinary uric acid levels were available for 104 patients. As shown in Table 1, uric acid clearance at the last visit was significantly lower than that at the first visit (6.4 ± 2.2 *vs.* 7.5 ± 2.7 ml min$^{-1}$, $P<0.01$), and there was a significant difference in serum uric acid levels during this period (5.5 ± 1.1 *vs.* 5.7 ± 1.5 mg dl$^{-1}$, n.s.). In the multivariate analysis, eGFR at the first

**Table 1 Characteristics of the subjects ($N = 133$)**

| | *First visit* | *Last visit* |
|---|---|---|
| Age (years) | 59.7 ± 8.6 | 70.2 ± 8.7 |
| Body weight (kg) | 59.8 ± 9.9 | 58.7 ± 10.6** |
| Systolic blood pressure (mm Hg) | 143 ± 12 | 129 ± 14** |
| Diastolic blood pressure (mm Hg) | 85 ± 8 | 68 ± 11** |
| Number of antihypertensive drugs | 1.3 ± 1.0 | 2.2 ± 1.1** |
| Urinary salt excretion (g per day) | 9.4 ± 3.5 | 7.8 ± 3.1** |
| Urinary protein excretion (g per day) | 0.19 ± 0.37 | 0.10 ± 0.22** |
| Serum total cholesterol (mg dl$^{-1}$) | 207 ± 30 | 201 ± 27† |
| Serum triglyceride (mg dl$^{-1}$) | 146 ± 99 | 122 ± 64** |
| Serum HDL cholesterol (mg dl$^{-1}$) | 62 ± 15 | 59 ± 16* |
| Plasma glucose (mg dl$^{-1}$) | 106 ± 17 | 105 ± 25 |
| Blood urea nitrogen (mg dl$^{-1}$) | 16 ± 4 | 16 ± 5 |
| Serum creatinine (mg dl$^{-1}$) | 0.76 ± 0.22 | 0.83 ± 0.35 |
| eGFR (ml min$^{-1}$ per 1.73m$^2$) | 71.7 ± 14.6 | 64.7 ± 16.5** |
| Serum uric acid (mg dl$^{-1}$), $n = 104$ | 5.7 ± 1.5 | 5.5 ± 1.1 |
| Uric acid clearance (ml min$^{-1}$), $n = 104$ | 7.5 ± 2.7 | 6.4 ± 2.2** |

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.
Values are means ± s.d., †$P<0.1$, *$P<0.05$, **$P<0.01$ *vs.* first visit.

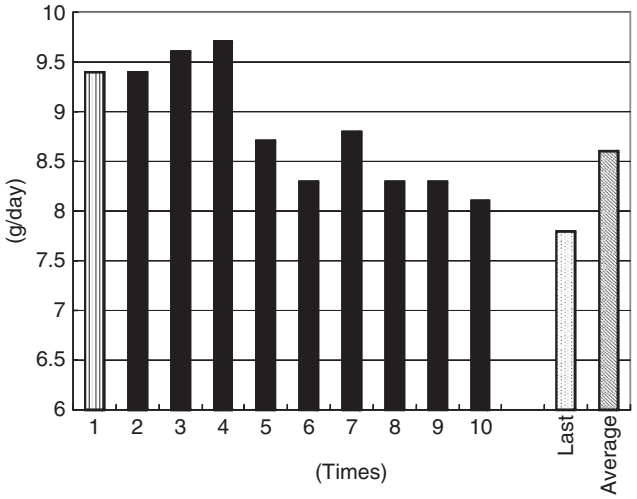


**Figure 1** Trend in the urinary salt excretion during the observation period.

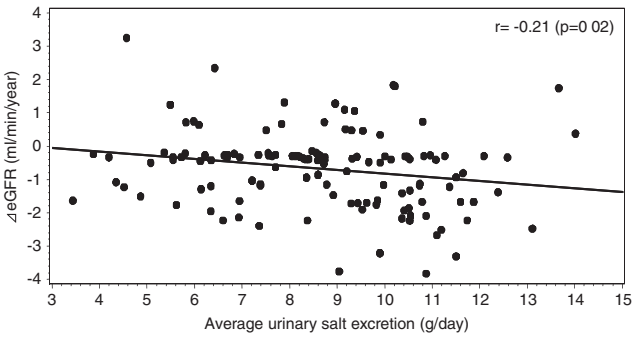


**Figure 2** Correlation between the change in eGFR and average urinary salt excretion in all subjects.

**Table 2 Comparison of the characteristics between patients with high and low urinary salt excretion**

| | *More than 8 g per day (N = 85)* | | *Less than 8 g per day (N = 48)* | |
|---|---|---|---|---|
| *Average urinary salt excretion* | *First visit* | *Last visit* | *First visit* | *Last visit* |
| Male (%) | 51 | | 21$^{\#\#}$ | |
| Age (years) | 58.7 ± 8.6 | 69.2 ± 8.8 | 61.5 ± 8.3 | 72.0 ± 8.3 |
| Body weight (kg) | 62.7 ± 9.6 | 62.0 ± 9.9 | 54.7 ± 8.2$^{\#\#}$ | 52.9 ± 9.3$^{*\#\#}$ |
| SBP (mm Hg) | 143 ± 12 | 129 ± 14$^{**}$ | 143 ± 13 | 129 ± 14$^{**}$ |
| DBP (mm Hg) | 85 ± 8 | 69 ± 11$^{**}$ | 84 ± 8 | 68 ± 11$^{**\#}$ |
| Number of antihypertensive drugs | 1.4 ± 1.1 | 2.4 ± 1.2$^{**}$ | 1.2 ± 0.8 | 2.0 ± 0.9$^{**\#}$ |
| Average urinary salt excretion (g per day) | 10.9 ± 3.3 | 8.9 ± 3.1$^{**}$ | 6.8 ± 2.2$^{\#\#}$ | 6.0 ± 2.2$^{\#\#}$ |
| Urinary protein excretion (g per day) | 0.23 ± 0.44 | 0.13 ± 0.26$^{*}$ | 0.12 ± 0.13 | 0.04 ± 0.06$^{**\#}$ |
| Serum total cholesterol (mg dl$^{-1}$) | 202 ± 30 | 199 ± 26 | 217 ± 28$^{\#\#}$ | 206 ± 27$^{8}$ |
| Serum triglyceride (mg dl$^{-1}$) | 160 ± 101 | 129 ± 67$^{*}$ | 121 ± 89 | 108 ± 57 |
| Serum HDL cholesterol (mg dl$^{-1}$) | 59 ± 15 | 56 ± 12$^{*}$ | 67 ± 15 | 66 ± 19 |
| Plasma glucose (mg dl$^{-1}$) | 109 ± 18 | 108 ± 29 | 102 ± 14 | 98 ± 15 |
| Blood urea nitrogen (mg dl$^{-1}$) | 16 ± 4 | 17 ± 6$^{*}$ | 16 ± 4 | 16 ± 4 |
| eGFR (ml min$^{-1}$ per 1.73m$^2$) | 72.7 ± 15.9 | 64.3 ± 18.2$^{**}$ | 69.9 ± 12.2 | 65.5 ± 13.0$^{*}$ |

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic blood pressure.
Values are means ± s.d.
$^{*}P<0.05$, $^{**}P<0.01$ *vs.* first visit, $^{\#}P<0.05$, $^{\#\#}P<0.01$ *vs.* more than 8 g per day.

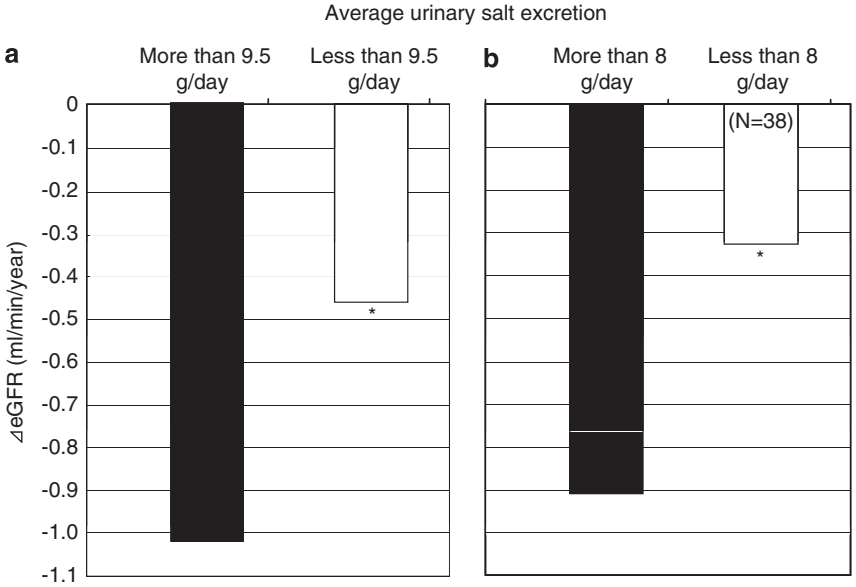


**Figure 3** The comparison of the change in eGFR between patients with high and low urinary salt excretion in male (**a**) and female (**b**) subjects. (**a**) $^{*}P<0.05$ *vs.* more than 9.5 g per day. (**b**) $^{*}P<0.05$ *vs.* more than 8.0 g per day.

visit and the average salt excretion during the observation period were significantly associated with the change in eGFR (Table 3a). Similarly, the change in serum uric acid was significantly associated with the change in eGFR in subjects for whom uric acid data were available ($N = 104$, Table 3b). These associations were independent of age, sex, BP change and increased number of antihypertensive drugs.

**Table 3 Clinical factors contributing to the change of eGFR ((a) $N = 133$ and (b) $N = 104$) (multivariate analysis)—**

| | *Partial* R | P |
|---|---|---|
| (a) | | |
| eGFR at the first visit (ml min$^{-1}$ per 1.73m$^2$) | −0.23 | 0.01 |
| Average urinary salt excretion (g per day) | −0.19 | 0.03 |
| (b) | | |
| Change in serum uric acid (mg dl$^{-1}$) | −0.34 | <0.01 |
| Average urinary salt excretion (g per day) | −0.32 | <0.01 |
| Body weight at the first visit (kg) | −0.16 | 0.06 |
| eGFR at the first visit (ml min$^{-1}$ per 1.73m$^2$) | −0.16 | 0.08 |

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate.
Independent variables: age, sex, first BP, last BP, change in body weight during observation period, change in BP during observation period, increased number of antihypertensive drugs.

## DISCUSSION

The present study demonstrates that long-term salt load promotes a decline in renal function in hypertensive patients.

Renal function declines with age, and GFR is usually considered to decrease at a rate of ~1 ml min$^{-1}$ per year.[11] However, age-associated decreases in the GFR estimated from Japanese health screening data have been reported to be small.[12] High BP is known to promote a decline in renal function.[13–15] The decrease in GFR has been reported

to be 4–8 ml min$^{-1}$ per year in hypertensive patients.[16] In our hypertensive subjects, the change in eGFR was −0.68 ml min$^{-1}$ per year on average. Body weight, BP and lipid levels decreased, and the use of angiotensin II receptor blockers increased significantly during the 10.5 years of the present study. Thus, improvements in risk factors, such as obesity, hypertension and dyslipidemia, and the increased use of new antihypertensive drugs during the observation period might be related to the smaller decline in renal function observed in our study than in previously published studies. Among antihypertensive drugs, renin–angiotensin system (RAS) inhibitors may influence changes in renal function. In the present study, however, the frequency of use of RAS inhibitors was comparable between high and low salt intake groups in both male and female patients, suggesting that the difference in the decline in renal function was not attributable to a difference in the use of RAS inhibitors.

Glomerular hypertension and hyperfiltration are suggested to be risk factors for progressive renal damage.[17,18] Glomerular hyperfiltration results from several mechanisms, including increased postglomerular oncotic pressure and enhanced proximal tubular sodium reabsorption, and induces an increase in protein concentration in the postglomerular circulation. An increase in glomerular capillary pressure and elevation in GFR might be the consequence of a functional decrease in nephron number. The present finding that baseline eGFR was negatively associated with the change in eGFR may indicate that the decline in renal function was induced by glomerular hypertension and hyperfiltration. The regression to the mean phenomenon may be a possible alternative explanation.

In contrast, obesity accelerates kidney damage through BP-dependent and -independent mechanisms and leads to increased proximal sodium reabsorption independently of filtration fraction (FF).[18,19] The increased GFR in patients with an early stage of metabolic syndrome or hypertension is also associated with renal adiposity and microvascular proliferation, which precede the significant activation of oxidative stress and inflammation.[17,18] In contrast, weight reduction results in decreases in GFR, renal plasma flow, FF, arterial pressure and urinary protein excretion.[19] We have previously reported that body weight is a major determinant of salt intake.[20] Thus, the decrease in the body weight in the present study might be related, at least in part, to the decrease in GFR.

High salt intake has been reported to be associated with eGFR decline,[2–4] which is in accordance with the present finding that the change in eGFR was significantly associated with average salt excretion during the observation period. Salt intake not only elevates BP, glomerular capillary pressure and FF levels, leading to increased urinary protein excretion, but also increases oxidative stress within the renal cortex and promotes the progression of renal failure.[2,21,22] In animal models, high salt intake also promotes endothelial cell production of transforming growth factor (TGF)-β and produces interstitial fibrosis.[2,21,22] When nitric oxide production is impaired, such as with endothelial dysfunction, unopposed excess vascular TGF-β production results in reduced vascular compliance and augmented peripheral arterial constriction and hypertension. The increased vascular and glomerular production of TGF-β and decreased nitric oxide levels may contribute to the development of hypertensive nephrosclerosis. In addition, high salt intake stimulates nicotinamide adenine dinucleotide phosphate oxidase and reduces superoxide dismutase, thus increasing oxidative stress in the kidney. Considering that high salt intake leads to persistent alterations in vascular function and renal dysfunction, salt restriction is important to not only control BP but also prevent the progression of renal dysfunction. The National Nutrition Survey in Japan showed that the average salt intake decreased from 12.5 g per day in 1998 to 10.9 g per day in 2008. Urinary salt excretion in our subjects also decreased from 9.4 ± 3.5 g per day to 7.8 ± 3.1 g per day during a similar period; however, it still exceeded the target level recommended by JNC 7 and JSH 2009.[5,6] Dietary counseling focusing on salt restriction should be encouraged.

Recent studies have shown that uric acid is a causal risk factor for the development and progression of renal disease.[23,24] In the present study, we also demonstrated that the change in serum uric acid was significantly associated with the decline in eGFR. Uric acid is reported to have a key role in the development of renal microvascular disease, inflammation and the activation of RAS and cyclooxygenase-2, which aggravates renal disease and hypertension and induces endothelial dysfunction and cardiovascular disease.[23,25] Thus, the management of hyperuricemia may also be important to prevent the progression of CKD.

Another finding of the present study is that urinary protein excretion was significantly reduced during the observation period. Urinary protein excretion not only indicates glomerular or vascular damage but is also considered to exacerbate renal function. Indeed, decreases in urinary protein excretion have been reported to have a preventive effect on the progression of renal dysfunction, regardless of BP.[26,27] Treatment with RAS inhibitors ameliorates glomerular hypertension/hyperfiltration with a decrease in GFR and FF. The decrease in FF is also expected to lead to a reduction in proximal tubular sodium reabsorption and possibly provide an addition long-term advantage. The reduction in urinary protein excretion, along with the increased use of angiotensin II receptor blockers, may also have contributed to the modest decline in eGFR in the present study.

In conclusion, long-term salt load promotes a decline in renal function in hypertensive patients. The encouragement of salt restriction should be emphasized to prevent renal damage.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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