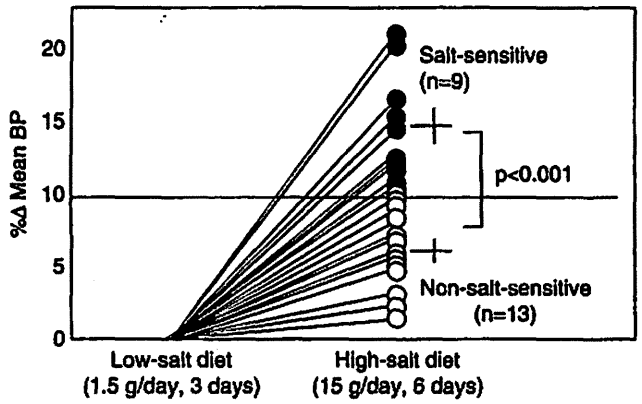


Figure 2 Increase in blood pressure (BP) on salt loading in patients with essential hypertension.[11] As the salt sensitivity of BP consecutively showed a normal distribution, the greatest number of values was distributed around the border of arbitrarily classified salt-sensitive and nonsalt-sensitive groups (10% in this study).

In particular, low salt intake markedly potentiated the antihypertensive effects of the renin-angiotensin (RA) system inhibitors.

Salt intake and diurnal changes in BP

A salt reduction-related decrease in BP was observed over 24 h.[22] Concerning diurnal changes in BP, a study reported that many salt-sensitive hypertensive patients showed a nondipper pattern, in which nocturnal BP fall was small, on a high-salt diet (12 to 15 g per day), whereas salt reduction (1 to 3 g per day) decreased the nocturnal BP, showing a dipper pattern.[23]

Mechanisms by which salt increases BP

Salt sensitivity is closely related to renal Na metabolism. Renal Na excretion depends on filtration, which depends on the glomerular filtration rate, and tubular reabsorption, which is influenced by various factors. Na reabsorption-promoting factors include the renin–angiotensin–aldosterone system (angiotensin II, aldosterone), sympathetic nervous system (α/β receptor stimulation), insulin and oxidative stress. Na reabsorption-inhibiting factors include atrial natriuretic peptide, prostaglandin, nitric oxide and dopamine. It is essential to induce Na retention for enhancing the salt sensitivity of BP. Na retention may occur when one of these factors is disturbed. Therefore, the salt sensitivity in patients with essential hypertension may be associated with multifactorial and complex etiologies.[7] The degree of salt sensitivity of BP shows a normal distribution, and the entity of salt-sensitive and nonsalt-sensitive groups was obtained by arbitrarily classifying the salt sensitivity using specific criteria (Figure 2).[10,11] In addition, the fact that an extremely excessive salt intake increases BP even in normotensive individuals in whom the renal Na-excreting function is normal[24] is also consistent with the viewpoint that salt sensitivity is related to the quantitative limit of the renal Na-excreting capacity. As various factors influencing renal Na reabsorption are influenced by lifestyle-related factors including diet, lifestyle changes may alter the salt sensitivity of BP, as described below (refer to the section 'Lifestyle-related factors affecting renal Na metabolism'). In addition, the salt sensitivity of BP may change even in the same individuals.

Na retention alone does not cause an increase in BP. To increase BP, it is necessary for retaining Na to increase the circulating blood volume, leading to an elevation of the cardiac output or (inappropriate) increase in vascular resistance.[7] For example, in the presence of edematous diseases, extravascular body fluid retention occurs, but does not lead to an increase in BP. Even when blood is pooled in veins, BP may not increase. Therefore, venous vasoconstriction mechanisms, such as the enhancement of the sympathetic nervous system, are also important. Generally, the cardiac output is normal in most hypertensive patients, with an increase in the vascular resistance. Therefore, several hypotheses regarding the mechanism by which Na retention causes an increase in the vascular resistance were proposed. For example, the autoregulation hypothesis proposed by Guyton[25] and intrinsic endogenous digitalis-like factor (EDLF)[26] are well-known candidates. EDLF, which enhances to excrete Na but to constrict vasculature, is proposed to be overproducted with salt loading in salt-sensitive hypertensive patients. Organ-specific vasoconstriction (sympathetic nerve stimulation) associated with central sympathoexcitation may be also important.[11,27] Some studies indicated that salt directly acted on the central nervous system, increasing the sympathetic nerve activity.[28,29] Furthermore, the association of EDLF with central sympathetic stimulation was proposed.[26] The involvement of these mechanisms by which Na retention increases the vascular resistance may differ among individual patients. The phenotype of salt-associated BP rise is considered to be formed based on complex, individual background factors.

Conclusion

- Dietary salt consumption is closely associated with the level of BP. Although the mechanisms of salt-induced BP elevation may be complex, impairment of renal Na excretion plays an important role.
- Dietary salt reduction decreases BP. When salt intake is lower, BP level reduces more markedly.
- There are marked individual differences in the salt sensitivity of BP. However, the antihypertensive effects of salt reduction may be achieved even in nonsalt-sensitive hypertensive patients and antihypertensive drug-administered hypertensives.

LIFESTYLE-RELATED FACTORS AFFECTING RENAL NA METABOLISM

Obesity and metabolic syndrome

In obese individuals and patients with metabolic syndrome, the salt sensitivity of BP is enhanced.[30–32] The results of a large-scale clinical trial[32] showed that in hypertensive patients with metabolic syndrome, there was a marked increase in BP on salt loading and marked decrease on salt reduction. In the TONE study, in which the effect of salt reduction, weight loss and their combination on end points regarding control of BP was investigated, the rate at which lifestyle goals were achieved was lower in the weight-loss + salt-reduction group than in the salt-reduction or weight-loss groups.[18] However, the improvement effects on BP-control end points in the combination group were 2 times more marked than in the salt-reduction or weight-loss groups,[15] suggesting that weight loss synergistically enhances the depressor effects of low salt intake. The mechanisms by which salt sensitivity of BP is enhanced in the presence of obesity or metabolic syndrome have been proposed to cause hyperinsulinemia,[33] the stimulation of the sympathetic nervous system,[27,34] enhancement of the renin–angiotensin–aldosterone system,[34] and an aldosterone-releasing factor produced by adipose cells.[35,36]

DASH diet

The DASH diet[37] primarily consists of vegetables, fruits and low-fat milk products, in which the levels of saturated fatty acids and cholesterol are restricted, and those of calcium, potassium (K), magnesium and dietary fiber are high. The results of additional

analysis of the DASH-Sodium study,[16] which investigated BP-lowering effect of a combination of the DASH diet and salt restriction, suggested that the DASH diet reduces the salt sensitivity of BP.[38] Dietary factors important for the natriuretic actions of the DASH diet may include high potassium and calcium intakes.

It is known that BP more markedly increases during not only high Na intake but also low K intake.[9] An interventional study involving humans also demonstrated that the urinary excretion of Na was enhanced by increasing K intake, inhibiting an increase in BP on salt loading.[39] A high concentration of K is contained in cells, but is lost by food processing. On the other hand, salt is an additive for food processing. Therefore, the Na/K ratio in processed foods is high. In a civilized society where processed foods are available, the harmful effects of excessive salt intake are likely to come out.[40] The suppression of the sympathetic nervous system[39,41] and antioxidant actions[42] may be involved in the natriuretic actions of K.

The antihypertensive effects of calcium are marked in patients with low-renin (salt-sensitive) hypertension, but weak in those with high-renin (nonsalt-sensitive) hypertension.[43] In addition, high dietary calcium inhibits an increase in BP on salt loading.[44] Sympatho-inhibiting and natriuretic actions[45] may be involved in this mechanism.

Exercise

Several studies reported that moderate exercise enhanced the urinary excretion of Na.[46,47] The kallikrein–kinin system, an increase in the dopamine level and suppression of the sympathetic nervous system may be involved in the mechanism.

Mental stress

Mental stress may inhibit the urinary excretion of Na through sympathetic nerve stimulation. A study indicated that a combination of salt loading and mental stress caused hypertension.[48] In contrast, dietary salt reduction may reduce sympathoexcitation in the presence of stress. There are individual differences in the mental stress-associated decrease in renal Na excretion. Among normotensive individuals, the inhibitory effects of mental stress on urinary Na excretion were marked in high-risk individuals with a family history of hypertension or high normal BP values.[49]

Conclusion

The improvement of obesity/metabolic syndrome, DASH diet, exercise and mental stress reduction may inhibit the salt-induced increase in BP. In contrast, dietary salt reduction may reduce the obesity- and stress-associated rise in BP.

SALT AND CARDIOVASCULAR DISEASES

Stroke

In the 1950s and 1960s, salt intake was very high in Japan, especially in the Tohoku District.[8] For example, salt intake in Akita Prefecture was ~27 g per day, being ~2 times higher than that in Okayama Prefecture (15 g per day). The mortality of stroke was 2 to 2.5 times higher.[50] However, salt intake was reduced rapidly thereafter. With this, the stroke mortality markedly decreased in Japan. In addition to the results based on such historical facts of salt reduction and a decrease in the mortality of stroke, a recent study indicated the association between salt intake and the incidence of stroke based on regional differences in salt intake. When reviewing the results from a national nutritional survey involving 12 areas in Japan (salt intake in these areas ranged from ~10 to 15 g per day) and those from a demographic survey conducted by the Ministry of Health, Labour and Welfare, there was a positive correlation between salt intake and mortality of stroke.[51]

As observational studies involving general populations in Japan, the Takayama (Nagata *et al.*[52]) and Japan Collaborative Cohort (JACC) (Umesawa *et al.*[53]) studies are known. In the Takayama study, the stroke mortality elevated with an increase in salt intake in males, and tended to increase in females. In the JACC study, the combined results from males and females showed an increase in stroke with elevating salt intake. Similarly, in an observational study performed of a general population in Finland by Tuomilehto *et al.*,[54] the incidence of strokes elevated with an increase in salt intake. These positive associations between salt consumption and stroke were significant after adjustment for hypertension status or the level of BP and other confounding factors. These studies involving general populations, and also a study conducted by O'Donnell *et al.*[13] in high-risk patients regarding cardiovascular diseases who participated in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND),[13] indicated that excessive salt intake increased the incidence of stroke. These observational studies are consistent with historical and regional facts that salt reduction decreased the incidence of stroke in Japan.

On the other hand, Kagan *et al.*[55] examined Japanese males living in Hawaii, and reported that there was no significant relationship between salt intake and the new onset of stroke. Cohen *et al.*[56] reported similar results based on the National Health and Nutritional Survey II (NHANES II) in the United States. In an observational study (Stolarz-Skrzypek *et al.*[12]) in which adult males and females without cardiovascular diseases were selected from individuals who were enrolled in two cohort studies involving residents in Europe, the Flemish Study on Genes, Environment and Health Outcomes (FLEMENGHO) and European Project on Genes in Hypertension (EPOGH), there was also no association between salt intake and onset of stroke. Similarly, there was no association in another observational study involving hypertensive patients (Alderman *et al.*[57]). Thus, some investigators emphasized that there was no influence of salt on the onset of stroke.

However, He *et al.*[59] separately analyzed the obese and nonobese subjects of the NHANES I cohort study, and indicated that morbidity and mortality of stroke was elevated with increasing salt intake/energy ratio in the obese subjects, whereas there was no significant relationship in the nonobese subjects. Thus, the relationship between the frequency of stroke and salt intake may vary in different characteristics of a population. Strazzullo *et al.*[58] conducted a meta-analysis of prospective cohort studies involving 3.5- to 19-year follow-up surveys in 19 cohorts[52–57,59–62] including some of the above studies, consisting of 177 025 subjects, and reported that the incidence of stroke was high in subjects with a high salt intake (Figure 3). Therefore, the results suggest that excessive salt intake causes and salt restriction prevents stroke.

When comparing the findings that excess salt increased the morbidity and/or mortality of stroke with the results that there was no influence, the latter were tended to be published earlier, as indicated by Strazzullo *et al.*[58] Furthermore, the number of patients who developed or died from stroke was too small to provide sufficient statistical power in some negative studies.[12,57] In addition, salt intake was estimated to be low in most studies, concluding that salt intake did not affect the morbidity and/or mortality of stroke, excluding a study by Stolarz-Skrzypek *et al.*,[12] which is criticized because of methodological problems such as analysis of two populations of different times and the inaccuracy of assessment of salt intake.[63]

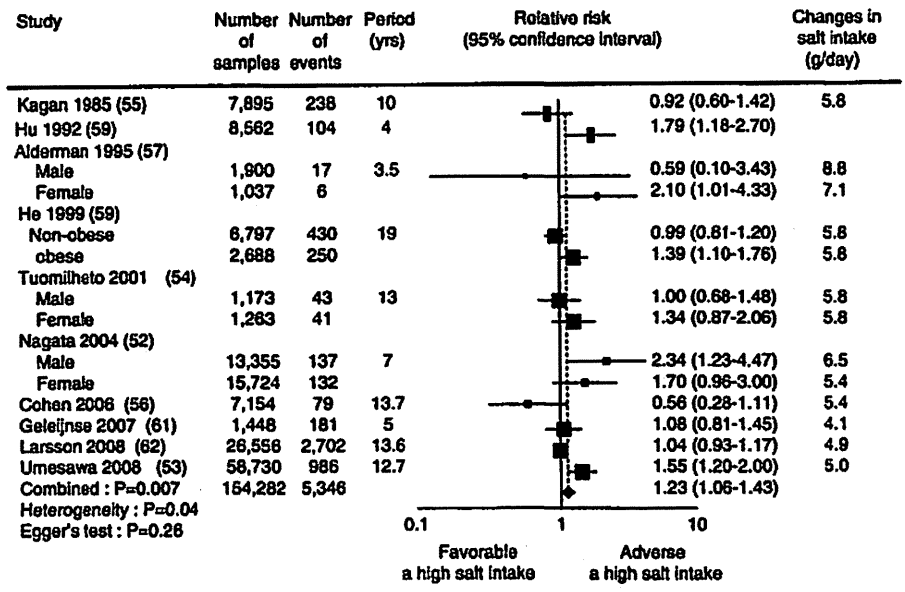


Figure 3 Meta-analysis of the relationship between salt intake and stroke.[58] An increase in salt intake elevates the risk of stroke.

According to a study by O'Donnell *et al.*,[13] the data from the population with high salt intake showed the relationship between salt and the morbidity and mortality of stroke, but those from the population with low salt intake did not suggest similar relationship. On the other hand, in the NHANES I data-based results by He *et al.*,[59] there was a significant relationship between salt intake and the morbidity/mortality of stroke in obese patients, although salt intake was estimated to be rather low. They were possibly obtained for the following reasons: salt reduction may prevent stroke in accordance with its grade. Low salt intake potently reduces the risk of stroke through marked improvement in hypertension of subjects with high salt intake, whereas its effects are weak in patients with low salt intake possibly because of slight decrease in BP. Thus, the relationship between salt intake and stroke in population with low salt intake may be impossible to detect in an observational study.

Overall, the inhibitory effects of salt reduction on the risk of stroke were apparently demonstrated. Therefore, salt restriction may be important for stroke prevention in Japan, in which salt intake exceeds 10 g per day.

Heart disease

Left ventricular hypertrophy. Many small-scale studies have suggested that excessive salt intake leads to the deterioration of left ventricular hypertrophy.[64] In observational studies, salt intake was weakly and positively correlated with the left ventricular wall thickness and left ventricular weight in not only hypertensive patients[65,66] but also normal adults.[66] On the other hand, in another study, when dividing subjects into two groups with a systolic BP of <121 and 121 mm Hg or more, salt intake was positively correlated with the left ventricular weight in only the high-BP group.[67] The inhibitory effects of salt reduction on cardiac hypertrophy may be mediated by its influence on BP. In addition to these observational studies involving a small number of patients, intervention studies also showed the inhibitory effects of salt reduction on cardiac hypertrophy. For example, a 12-week combination therapy with a diuretic (chlorthalidone at 25 mg per day) and salt reduction at 2.5 g per day decreased the left ventricular weight in patients with mild to moderate hypertension.[68] In another study, slight decreases in the left ventricular weight and posterior wall thickness after 1 year were observed in the salt-reduction group, whereas there was no improvement in the heart weight in nonsalt-reduction group.[69] In these intervention studies,[68,69] treatment involving salt restriction decreased BP. A fall of BP may be important for the mechanism of the salt restriction-induced decrease in left ventricular weight.

Ischemic heart disease. The effects of salt reduction on the risk of ischemic heart disease are less marked than those on the risk of stroke. Of the four studies indicating that the risk of stroke elevated with an increase in salt intake,[13,53,54,59] the coronary artery disease or myocardial infarction elevated with an increase in salt intake in only two studies: the studies by Tuomilehto *et al.*[54] in Finland and by O'Donnell *et al.*[13] in high-risk patients (ONTARGET/TRANSCEND). There was no significant relationship in the JACC study (Umesawa *et al.*[53]). On the other hand, the NHANES I-based results regarding obese patients by He *et al.*[59] showed that excessive salt intake increased the mortality but not morbidity of coronary artery disease. In an observational study by Stolarz-Skrzypek *et al.*,[12] there was no association between the morbidity/mortality of coronary artery disease and salt intake, as demonstrated for stroke. Yang *et al.*[70] analyzed the influence of salt intake on cardiovascular diseases using the NHANES III cohort, and reported that there was no significant relationship between the salt intake and the mortality of ischemic heart disease. Thus, in many studies, it was impossible to verify that the incidence of ischemic heart disease elevates with an increase in salt intake, excluding some studies involving populations consuming a considerably excess level of salt. This tendency may reflect the fact that salt restriction is useful for decreasing BP, but the effects of changes in BP are greater in stroke than in ischemic heart disease.

In an observational study by Alderman *et al.*[57] in patients with hypertension, the incidence of myocardial infarction was higher in males in whom the salt intake was lower (there was no significant relationship in females). Cohen *et al.*[56] also reported a similar weak tendency based on the NHANES II results (involving a general population). To explain this, Alderman *et al.*[71] hypothesized that the salt reduction-induced enhancement of the RA system might be an important risk factor for ischemic heart diseases. However, there are

marked individual differences in plasma renin activity (PRA). For example, not only salt intake but also antihypertensive treatment and other factors influence PRA level. Therefore, it is impossible to conclude the presence of a causal relationship based on this result. Furthermore, there was no inverse correlation between salt intake and ischemic heart disease in other observational studies involving general populations; therefore, these results[56,57] may be due to the indirect influence by other factors.

Heart failure. It is recognized that salt restriction is essential in the treatment of heart failure. However, there is small number of evidence supporting this. In a study involving a 3-year follow-up of a small number of patients with stable systolic heart failure,[72] the number of acute noncompensatory heart failure and heart failure-related hospitalization was smaller in patients in whom the salt intake was lower. In addition, in an observational study involving high-risk patients in the ONTARGET and TRANSCEND cohorts,[13] the number of heart failure-related hospitalization also elevated with an increase in salt intake. In this report, even when the salt intake decreased, the number of heart failure-related hospitalization increased; salt intake showed a J-shaped relationship to the risk of heart failure. However, the subjects in whom salt intake was low may have been high-risk patients with regard to the exacerbation of heart failure. In an intervention study on salt reduction for heart failure,[73] salt restriction was done under excessive-dose diuretic administration and strict water-intake restriction; therefore, the study is not appropriate for estimating the effect of salt reduction on heart failure. Thus, salt restriction may improve heart failure, although the evidence level is not high.

Kidney disease

Urinary protein or albumin. Several studies involving a small number of patients showed that salt reduction decreased the urinary protein or albumin excretion.[74] For example, slight salt reduction significantly decreased the urinary protein level (22% of decrease from 3.8 g per day) in patients with nondiabetic nephropathy.[75] Short-term salt reduction in hypertensive patients also reduced the urinary albumin level.[76,77] In addition, moderate salt restriction (9.7 to 6.5 g per day) decreased urinary albumin from 10.2 to 9.1 mg per day in untreated hypertensive individuals.[78] As these urinary protein/albumin-decreasing effects of salt reduction are associated with BP-lowering effects in many cases,[75–78] a fall of BP may be important.

Salt reduction-induced decreases in the urinary protein/albumin levels are also observed in normal adults. In an observational study involving a portion of the Prevention of Renal and Vascular End Stage Disease (PREVEND) cohort,[79] the urinary excretion of albumin (within the normal range) elevated with an increase in salt intake. In Takayama study that consisted of a large number of general population in Japan, salt intake was greater in subjects with higher levels of urinary albumin/creatinine ratio.[80] In another study, the urinary albumin level significantly decreased from 7.6 to 6.0 mg per day within 7 days when the salt intake was strictly reduced in normal young males.[81] Excessive salt intake induces glomerular hyperfiltration in both hypertensive patients[74,77] and normal adults.[81] Salt reduction inhibits the urinary protein/albumin levels possibly through hyperfiltration-improving effects.

In addition, salt reduction potentiates the urinary protein-reducing effects of the RA system inhibitors. In an observational study involving nondiabetic chronic kidney disease patients receiving angiotensin-converting enzyme inhibitors in the Ramipril Efficacy in Nephropathy (REIN) study,[82] the urinary protein/creatinine ratio elevated with an increase in the salt intake. When the salt intake was increased in patients with nondiabetic nephropathy, the inhibitory effects of angiotensin-converting enzyme inhibitors on proteinuria was suppressed.[83] Furthermore, salt restriction enhanced the urinary protein-reducing effects of angiotensin receptor antagonists as well as angiotensin receptor antagonists plus thiazide diuretic therapy in patients with nondiabetic nephropathy.[75] Thus, salt reduction may inhibit the urinary protein/albumin levels and potentiate the urinary protein-reducing actions of the RA system inhibitors.

End-stage renal failure. In a large number of women participating in the Nurses' Health Study, higher salt intake was associated with more rapid decline of estimated glomerular filtration rate.[84] However, few studies have examined the influence of excessive salt consumption on the deterioration of end-stage renal failure. Thomas *et al.*[85] analyzed the relationship between salt intake and incidence of end-stage renal failure in subgroups consisting of a small number of patients with microalbuminuria from a cohort consisting of patients with type I diabetes based on the Finnish Diabetic Nephropathy (FinnDiane) study, and showed that the risk of end-stage renal failure was higher when the salt intake was extremely lower. However, in the study, the profiles of the subgroups are not presented. On the other hand, in the observational study involving nondiabetic chronic kidney disease patients receiving angiotensin-converting enzyme inhibitors in the REIN study,[82] the incidence of end-stage renal failure elevated with an increase in the salt intake. Despite the small-sized study in patients undergoing therapeutic intervention, there were no differences in BP among the subjects. Concerning the preventive effects of salt restriction on the deterioration of end-stage renal failure, its usefulness may be suggested, although the evidence level is not so high.

Cardiovascular diseases

Cardiovascular diseases (due to arteriosclerosis) are defined as a disease entity involving ischemic heart disease, coronary artery disease, cerebrovascular disorder, aortic and arterial diseases and peripheral vascular diseases.[86] Regarding the influence of salt intake on overall cardiovascular diseases, He *et al.* (obese subjects),[59] Tuomilehto *et al.*[54] and Umesawa *et al.*[53] suggested that salt reduction prevented the onset of cardiovascular diseases. In a study by O'Donnell *et al.*,[13] the tendency of an excessive salt intake-induced increase in the incidence of cardiovascular diseases was also observed. On the other hand, Alderman *et al.*[57] and Cohen *et al.*[56] suggested that salt reduction increased the incidence of cardiovascular diseases. A few other studies also showed that there was a reverse correlation between salt intake and the morbidity and mortality of cardiovascular diseases.[12,87,88] Strazzullo *et al.*[58] performed a meta-analysis of prospective cohort studies[53,54,56,57,59,61,89–91] and reported that excessive salt consumption tended to increase the incidence of cardiovascular diseases (Figure 4).[58] Therefore, salt reduction may be useful for preventing cardiovascular diseases.

It may be difficult to detect whether an increase in salt intake significantly elevates the risk of cardiovascular diseases in populations in whom salt intake is low, and salt reduction might result in exacerbation of cardiovascular diseases in some populations. Alderman[92] hypothesized that the relationship between salt intake and the risk of cardiovascular diseases is J-shaped and that salt intake at 5 to 6 g per day might be characterized by the lowest risk of cardiovascular diseases. However, in most studies supporting the fact that salt reduction increases the risk of cardiovascular diseases, methodological problems have been indicated,[12,63] or study subjects were high-risk patients[13,57,91] (the possibility cannot be ruled out that therapeutic intervention may reverse the causal relationship). In addition, He

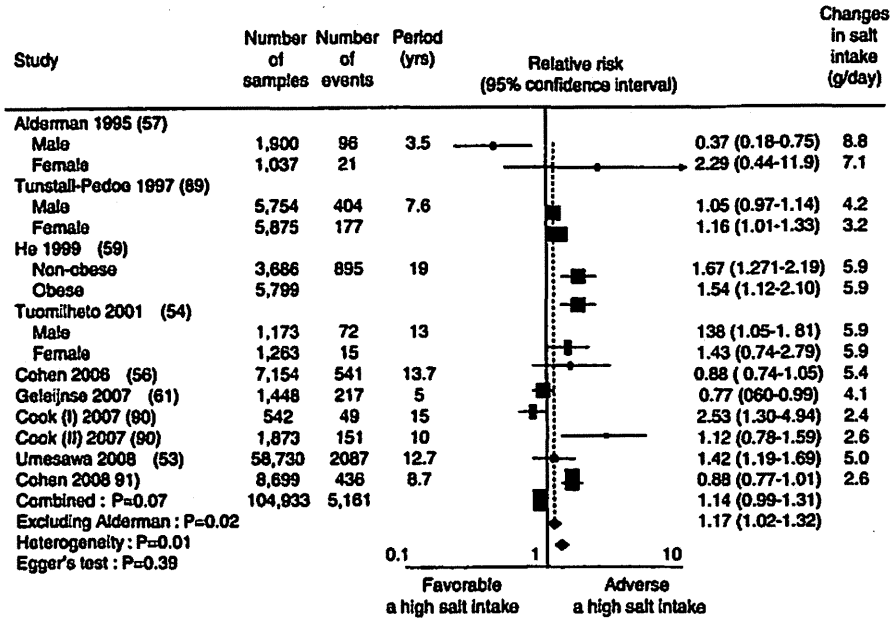


Figure 4 Meta-analysis of the relationship between salt intake and cardiovascular diseases.[58] Overall, excessive salt intake tended to increase the risk of cardiovascular diseases ($P=0.07$). There was a significant increase ($P=0.02$), excluding the study by Alderman *et al.*[57]

et al.[59] reported that excessive salt intake increased the incidence of cardiovascular diseases in a population consisting of obese subjects consuming a relatively low level of dietary salt. Thus, the hypothesis that there is a J-shaped relationship between salt intake and the risk of cardiovascular diseases is not always reliable.

A study involving the follow-up of normotensive subjects for >10 years after the completion of the TOHP I intervention[14] and II intervention[17] studies showed the preventive effects of salt restriction on cardiovascular diseases.[90] In the TOHP I/II studies, the subjects were randomly assigned to salt-reduced and nonsalt-reduced groups. In 77% of these subjects, a follow-up survey after 10 to 15 years was done. As a result, there was a significant (25%) decrease in the incidence of cardiovascular diseases with salt reduction, although there are no data on salt intake during the follow-up survey.

Taylor *et al.*[93] published the results of a meta-analysis of intervention studies regarding salt reduction. This meta-analysis involved randomized, control studies of salt reduction in which follow-up was continued for ⩾6 months; three of these studies involved normotensive individuals, two hypertensive patients and one normotensive and hypertensive combined subjects. Of these, hypertensive and normotensive individuals were separately analyzed. In both hypertensive and normotensive individuals, salt reduction slightly decreased the incidence of cardiovascular diseases, although there was no significant difference. In contrast, He *et al.*[94] simultaneously analyzed normotensive individuals and hypertensive patients from the same studies including Taylor's meta-analysis. They reported that salt reduction at 2.0 to 2.3 g per day significantly decreased the risk of cardiovascular diseases (20% of decrease; Figure 5). Intervention studies regarding salt reduction have several limitations: it is impossible to conduct a blind study; it is difficult to separate salt from other nutrients; and a large-scale, long-term study must be performed in low-risk patients. However, the results of the meta-analysis of intervention studies[94] suggest the protecting actions of salt restriction on the cardiovascular system.

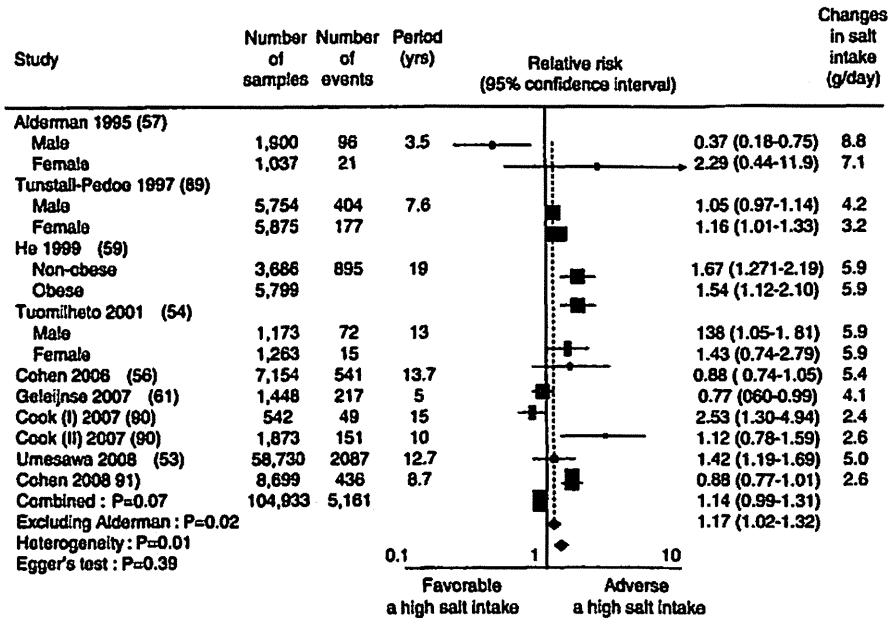
To investigate the target value of salt intake based on evidence, it is necessary to review the degree of salt reduction in intervention studies quoted in the meta-analyses conducted by Taylor *et al.*[93] and He *et al.*[94] (Figure 5). In the corresponding intervention studies, the TOHP I,[14] TOHP II,[17] TONE[15] and the trial by Morgan *et al.*,[95] salt intake in the salt reduction group ranged from 6.5 to 9.2 g per day. When comparing the data from these studies, the cardiovascular disease risk-reducing effects in the TOHP I study[14] and the TONE study[15] in which the salt intake could be more markedly decreased, may be more potent than in the TOHP II study[17] and the study by Morgan *et al.*,[95] in which the salt intake was less decreased (Figure 5). Thus, these intervention studies supported the preventive effects of moderate salt reduction on cardiovascular diseases. The effects on the risk of cardiovascular disease with salt reduction may be more potent in individuals in whom salt intake is lowered more greatly.

All-cause mortality

The results of observational studies regarding the relationship between the all-cause mortality and salt intake varied.[54,56,59,85,87,88] A meta-analysis of intervention studies by Taylor *et al.*,[93] in which hypertensive and normotensive subjects were separately analyzed, could not verify the inhibitory effects of salt reduction on the all-cause mortality. He *et al.*[94] performed a meta-analysis in combined normotensive and hypertensive individuals using the same studies, but could not detect a significant relationship between the salt intake and all-cause mortality. The all-cause mortality is associated with more complex factors in comparison with cardiovascular diseases, and therefore it may be difficult to obtain apparent association of salt intake.

Conclusions

- Observational studies showed that the risk of stroke was higher when the salt intake was higher.
- Small-scale observational and intervention studies demonstrated reducing effects of salt reduction on the left ventricular hypertrophy.



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Conclusions

- Observational studies showed that the risk of stroke was higher when the salt intake was higher.
- Small-scale observational and intervention studies demonstrated reducing effects of salt reduction on the left ventricular hypertrophy.

blood sugar and insulin levels with the high-salt diet were higher than those in salt-resistant group and that salt reduction improved the insulin sensitivity in the salt-sensitive group, but deteriorated it in the salt-resistant group. Raji *et al.*[107] indicated that there was no influence of changes in the salt balance on the homeostasis model assessment ratio (HOMA-R) in normotensive subjects, in patients with low-renin hypertension or in those with modulator-type hypertension, whereas salt reduction increased the HOMA-R in patients with nonmodulator-type hypertension, in whom the salt sensitivity of the BP is enhanced.[114] The results by Sharma *et al.*[105] are not always consistent with those reported by Raji *et al.*[107] Such different types of responsiveness may be mixed in different characteristics of hypertension, leading to conflicting results.

Others

Some studies reported that salt reduction elevated inflammation parameters.[115] On the other hand, others indicated that salt restriction increased the nitric oxide level.[116] However, these are short-term studies involving a small number of patients. In the future, the reliability of the results of these studies must be elucidated.

Conclusions

- Salt reduction enhances the renin–angiotensin–aldosterone system that may not damage the cardiovascular system, with the exception of specific cases.
- Salt reduction activates the sympathetic nervous system in a short period, influencing metabolic risk factors. However, its influence on these factors may not be marked over a long period.

USEFULNESS OF DIETARY SALT REDUCTION

Concerning BP control, it was demonstrated that stricter salt reduction more markedly decreased BP. There is evidence for the antihypertensive effects of strict salt reduction.[16] With respect to cardiovascular diseases, improvement may also be achieved by salt reduction. However, the effects may differ among individuals and diseases. Salt reduction may decrease the risk of stroke more than that of ischemic heart disease. Although there is insignificant evidence, the effects of salt reduction on inhibition of left ventricular hypertrophy, a decrease in the risk of heart failure, a decrease in the urinary protein and prevention of progress to end-stage renal failure were reported. A mean salt intake exceeding 10 g per day in Japan is markedly high. Considering the present condition, salt reduction is essential for the prevention and treatment of hypertension and for the prevention of cardiovascular diseases. A salt-reduction target level of <6 g per day, described by JSH2009,[2] is appropriate. This should be established as a target level in not only hypertensive patients but also normal adults.

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REVIEW

[Scientific Statement] Report of the Salt Reduction Committee of the Japanese Society of Hypertension

(2) Goal and strategies of dietary salt reduction in the management of hypertension

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In this section of the Report of the Salt Reduction Committee of the Japanese Society of Hypertension, the target level of dietary salt reduction and its scientific evidence, present status of salt consumption in Japan, salt-reducing measures/guidance methods in individuals and population strategies to reduce salt intake are introduced. In the Dietary Reference Intake for the general population in Japan (2010 version), the target levels of salt restriction in men and women were established as less than 9.0 per day and 7.5 g per day, respectively. The Japanese Society of Hypertension Guidelines for the Management of Hypertension 2009 recommended the target level of dietary salt restriction in patients with hypertension as less than 6 g per day. However, the National Health and Nutrition Survey of Japan in 2010 reported that the mean salt intake in adults was 10.6 g per day (men: 11.4 g per day and women: 9.8 g per day). To effectively decrease salt intake in Japan, it is necessary to reduce the consumption of high-salt foods (especially traditional foods) and replace high-salt seasonings (soy sauce and so on) with low-salt alternatives. Health-care professionals must effectively perform salt-reduction guidance for hypertensive patients in hospitals/administrative organizations. To promote population strategies for salt reduction in the whole society of Japan, social strategies, such as administrative policies, companies' cooperation and educational staff's cooperation, are necessary.
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INTRODUCTION

Many studies have shown that almost all people in the modern world consume an excess level of sodium and that excessive salt intake is one of the most important etiological factors for hypertension and the onset of cardiovascular diseases. Evidence on a reduction in blood pressure (BP) and the risk of cardiovascular diseases by dietary salt restriction has been accumulated. Consequently, a tendency to establish a stricter target level of salt intake in nutrient intake standards and dietary guidelines has become marked in the world. On the other hand, salt intake markedly differs among regional diets. Previously, salt intake in Japan was the highest in the world, and it is still relatively high; therefore, establishment of effective dietary salt-reducing measures is needed in our modern dietary habits. Moreover, it is also necessary to promote salt-intake reduction in the whole society as a population strategy.

In this section, we introduce the target level of dietary salt reduction and its scientific evidence, present status of salt consumption in Japan, salt-reducing measures/guidance methods in individuals and population strategies to reduce salt intake.

TARGET LEVEL OF DIETARY SALT RESTRICTION

Sodium loss unavoidable in adults without massive sweating is 500 mg per day or less. Considering inter-individual variation (coefficient of variation: 10%), it is 600 mg per day (volume

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corresponding to salt: 1.5 g per day). On the basis of this evidence, the estimated average requirement of sodium in adults (both sexes) is established as 600 mg per day in the 'Dietary Reference Intake in Japanese (2010)'.[1] However, salt intake in ordinary Japanese diet is very rarely lower than 1.5 g per day.

The INTERSALT study showed that the mean systolic BP was 90–100 mm Hg in Yanomamo Indians living in the Amazon area, in whom the urinary excretion of sodium was very close to zero, and there was no hypertensive patient. Furthermore, their BP did not increase with age.[2] A strict feeding trial in the United States, the DASH (Dietary Approaches to Stop Hypertension)-Sodium trial, showed that sodium restriction at 2300 mg (volume corresponding to salt: 5.8 g per day) decreased BP, and that the attainment of sodium restriction at 1500 mg (volume corresponding to salt: 3.8 g/ per day) further reduced BP safely.[3] On the basis of the results of many other intervention studies to confirm a salt reduction-related BP decrease, the Institute of Medicine in the United States established an adequate intake of sodium in adults as 1500 mg and a tolerable upper intake level as 300 mg in the Dietary Reference Intake in 2005.[4] The US Dietary Guidelines and the American Heart Association Guidelines further recommended that the target sodium intake should be less than 2300 mg for healthy adults and less than 1500 mg for high-risk individuals (hypertensives, Blacks, middle-aged to elderly).[5–7] According to the American Heart Association Guidelines, the high-risk individuals account for 69% of the total population in the United States. The World Health Organization/Food and Agriculture Organization (WHO/FAO) Report on diet, Nutrition and the Prevention of Chronic Diseases, which was published in 2003, described that salt intake should be restricted to less than 5 g to decrease BP, and that sodium ingestion from sodium glutamate should also be considered.[8]

In 2007, the European Society of Hypertension-European Society of Cardiology (ESH-ESC) established a target salt intake of less than 5 g per day, although salt intake of less than 3.8 g/day was considered to be ideal.[9] In the first version (2000) of the Japanese Society of Hypertension Guidelines for the Management of Hypertension, the target level of dietary salt restriction in patients with hypertension was established as less than 7 g per day. However, considering the subsequent scientific evidence and target levels of dietary salt restriction established in the world, the target value was tightened to less than 6 g per day in the 2004 and 2009 versions[10] (Table 1).

On the other hand, in the Dietary Reference Intake for the general population in Japan (2010 version), the target levels of salt restriction to be achieved within coming 5 years in men and women were established as less than 9.0 g per day and 7.5 g per day, respectively, being lower than those previously established (men: less than 10 g per day and women: less than 8 g per day).[1] These were established as targets that can be achieved, because the median salt intake in men aged 50–69 years in the National Health and Nutrition Surveys in 2005 and 2006 was 12.2 g per day, and because the intermediate value between this value and 6 g per day, which was recommended by the Japanese Society of Hypertension, was 9.1 g per day (value for women 1.5 g per day lower than for men). The target values for children aged 1–11 years were established through extrapolation with the body-surface area ratio, regarding the values for adults (18–29 years) as references. The same values as established for adults were used for children aged 12–17 years.

CURRENT STATUS OF SALT CONSUMPTION IN JAPAN

The National Health and Nutrition Survey in 2010 reported that the mean salt intake in adults was 10.6 g per day (men: 11.4 g per day and women: 9.8 g per day) (Figure 1).[11] There was an ~4 g decrease in comparison with that in 1972 (14.5 g), when salt intake was investigated for the first time in the National Nutrition Survey. According to surveys in the 1950s, the mean salt intake was 27 g per day in the Tohoku district and 17 g per day in the Kinki district; therefore, it may have more markedly decreased during the past 60 years.[12] This was possibly associated with improvement in salt-free food processing/storage technologies, extended-area fresh food transportation related to the development of transport facilities, the widespread use of refrigerators and a Western-style diet in addition to the effects of salt-reduction strategies/policies developed throughout Japan.

However, the National Health and Nutrition Survey in 2009 showed that, in ~70% of both men and women, salt consumption exceeded the target level described in the Dietary Reference Intake (men: less than 9 g per day and women: less than 7.5 g

Table 1 Recommendations of salt/sodium intake established by Japanese/overseas/international societies/organizations

Society/organization (year)	*Target population (name of recommendation)*	*Recommendation*
Japanese Society of Hypertension (2009)	Hypertensives (target of salt reduction)	Salt: less than 6 g per day
Dietary Reference Intake, Japan (2010)	Adults (estimated average requirement)	Sodium: 600 mg per day (salt: 1.5 g per day)
	Adult men (dietary goal)	Salt: less than 9 g per day
	Adult women (dietary goal)	Salt: less than 7.5 g per day
WHO/FAO (2003)	Adults (dietary goal)	Salt: less than 5 g per day
Dietary Reference Intake, IOM, USA (2005)	Adults (adequate intake)	Sodium: 1500 mg per day (salt: 3.8 g per day)
	Adults (tolerable upper intake level)	Sodium: 2300 mg per day (salt: 5.8 g per day)
US Dietary Guidelines (2005)/American Heart Association (AHA) Dietary Recommendations (2006)	Adults (dietary goal)	Sodium: less than 2300 mg per day (salt: less than 5.8 g per day)
	High-risk persons (hypertensives, Blacks, middle-aged and elderly) (dietary goal)	Sodium: less than 1500 mg per day (salt: less than 3.8 g per day)
European Society of Hypertension-European Society of Cardiology (ESH-ESC) (2007)	Hypertensives (dietary goal)	Salt: less than 5 g per day
JNC7, USA (2003)	Hypertensives (dietary goal)	Sodium: less than 2400 mg per day (salt: less than 6 g per day)

Abbreviations: IOM, Institute of Medicine; WHO/FAO, World Health Organization/Food and Agriculture Organization.

per day). Furthermore, salt intake was the highest in both men and women aged 60–69 years (men: 12.4 g per day and women: 10.5 g per day).

In the INTERMAP study, two-timed 24-h urine collection and a 4-day nutritional survey by the 24-h recall method were conducted in 4680 participants (men and women) aged 40–59 years in 17 populations (8 in the USA, 2 in the UK, 3 in China and 4 in Japan) between 1996 and 1999.[13,14] Mean salt intake, which was evaluated based on the 24-h urinary sodium excretion, among the 4 countries, was 12.3 g per day and 10.9 g per day in Japanese men and women, respectively, being 2–3 g per day higher than in the USA and the UK (Figure 2). On the basis of the results of 24-h recall dietary survey, the sources of salt consumption in Japan consisted of soy sauce (20%), pickled vegetables (10%), *miso* soup (10%), fish (including salted, dried fish) (9%), salt as a seasoning (9%) and soup (7%). These six foods accounted for more than 60% (Figure 3).[15] Regarding soy sauce and miso paste as processed foods, ~90% of salt was estimated to be ingested from processed foods in Japan.

Gender difference in salt intake disappears when corrected with the body weight; therefore, this may reflect differences in dietary intake related to differences in body size.[16]

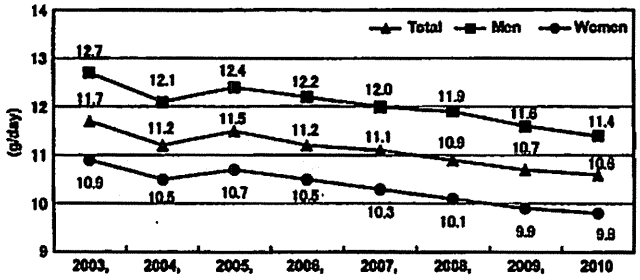

Figure 1 Changes in the mean salt intake of Japanese (20 years or older) (National Health and Nutrition Surveys in 2003–2010).

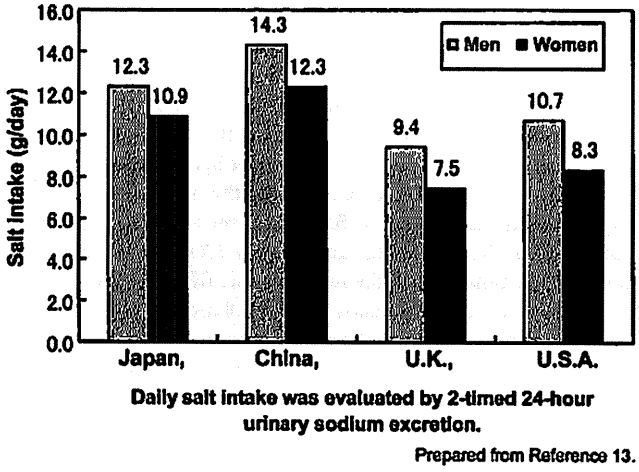

Figure 2 Comparison of salt intake among four countries (INTERMAP study, men and women aged 40–59 years, 1996–1999).

SALT-REDUCTION STRATEGIES IN INDIVIDUALS

Techniques to reduce salt intake

As described above, there is a Japan-specific traditional diet-related source of salt consumption. On the other hand, the new sources of salt consumption related to the introduction of a Western diet and an increase in processed foods/eating-out/daily dishes appeared. To effectively decrease salt intake, it is necessary to reduce the consumption of high-salt foods and replace seasonings with low-salt alternatives.

High-salt foods, as sources of salt consumption important in the Japanese diet, are presented in Table 2.[17] Many processed foods derived from marine products and meat contain high-level salt. Furthermore, eating-out menus such as a bowl of rice with food on top/noodles also contain high-level salt. When eating noodles with soup, 5 g or more of salt per meal is ingested. Eight dietary behaviors effective for salt reduction, 'techniques for dietary salt restriction', are shown in Table 3[17]: leaving the soup of noodles; and the utilization of low-salt seasonings, vinegar and spices instead of soy sauce or salt. Dietary salt restriction may be effectively achieved by performing these dietary behaviors and techniques.

In Japan, the sodium content (mg) is labeled as a nutrient composition in most processed foods. In some products, the volume corresponding to salt (g) is simultaneously described. When only the sodium content is presented, it must be converted using the following formula:

Volume corresponding to salt (g) = sodium content (mg) × 2.54/1000.

However, this can be used as a reference when selecting low-salt foods.

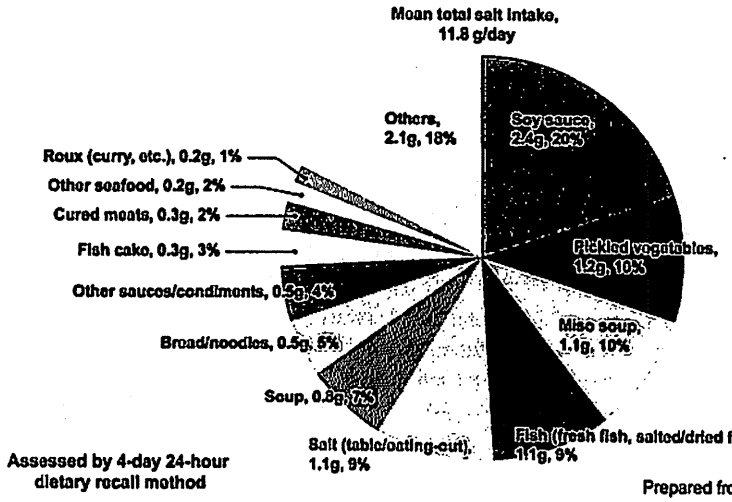

Figure 3 Sources of salt consumption in Japan and their proportions (INTERMAP Japan, 1145 men and women aged 40–59 years, 1996–1999).

Table 2 Representative high-salt foods/dishes in Japan

Food/dish	*Standard volume*	*Salt content*
Yellow pickled radish	Two pieces (20g)	1.5g
Pickled plum	One plum (10g)	2.0g
Potage	One cup	1.2g
Miso soup	One cup	1.5g
Horse mackerel	Small, one slice (60g)	1.2g
Ham	Three slices (60g)	1.5g
Salted salmon	One slice (40g)	3.5g
Curry rice	Dish for one person	3.3g
Bowl of rice with *tempura* on top	Dish for one person	4.1g
Hand-rolled *sushi*	Dish for one person (including soy sauce)	5.0g
Udon with deep-fried *tofu*	Dish for one person (including soup)	5.3g
Cup noodle	Dish for one person (including soup)	5.5g

The salt content is expressed as an approximate value. It differs among products or cooking methods.
Cited from Ueshima.[17]

Table 3 Representative dietary behaviors effective for salt reduction: '8 techniques to reduce salt intake'

1. Avoid pickled vegetables.	(Eat a small amount of lightly pickled vegetables, if you want.)
2. Leave the soup of noodles.	(2–3g of salt can be restricted by leaving the whole volume of soup.)
3. Use fresh food materials.	(Enjoy the tastes of food materials by light-taste cooking.)
4. Prepare *Miso* soup containing a lot of vegetables.	(Salt reduction can be achieved with the same taste.)
5. Use seasonings carefully.	(They should be used after confirming the taste.)
6. Use low-salt seasonings.	(Vinegar, tomato ketchup, mayonnaise, and dressing should be effectively utilized.)
7. Use spices, spicy vegetables, and fruit acidity.	(Combination of pepper, spices, ginger, and citrus fruit acidity can be a good choice.)
8. Avoid eating-out and processed foods.	(A large volume of invisible salt is contained.)

Cited from Ueshima.[17]

On the other hand, several studies reported that the use of dietary salt in which a portion of sodium chloride was substituted for potassium chloride (potassium salt) led to a BP fall related to a decrease in sodium intake and increase in potassium intake.[18,19] In persons in whom the kidney function is normal, the utilization of potassium salt is also effective.

It is necessary to educate the nation with correct knowledge on foods and techniques to reduce salt consumption.

Guidance/support for salt reduction

In the Guidelines for the Management of Hypertension, it is described that guidance for lifestyle modification to decrease BP is essential for all patients with hypertension, and that grade I hypertension patients without risk factors should be guided before the start of drug therapy.[10] In patients with hypertension, nutritional guidance to restrict dietary salt intake to less than 6g per day is necessary. In 'the Specific Health Guidance' started from 2008 in Japan, guidance for salt restriction must also be conducted when BP level is 'high-normal' level or higher. On an initial interview of this guidance, a physician, public health nurse and dietitian assist clients to set their goals.[20] As there are few cases in which salt intake from ordinary Japanese diet is less than 6g per day, guidance for salt restriction may be necessary in all persons.

When guiding/supporting dietary correction, behavioral scientific procedures to achieve behavioral changes in daily living are necessary.[17] Personal interview, group assistance and communication support should be repeatedly conducted using procedures/teaching materials such as goal-setting, behavioral-change stage theory, self-monitoring, operant intensification and group dynamics. In addition in 'the Specific Health Guidance' in Japan, standard programs for 6 months are prepared.[20]

Furthermore, individual goal-setting can be established by conducting a survey regarding the present status of diet habits/salt intake before the start of guidance and clarifying dietary problems. A detailed survey on diet or objective salt-intake assessment with urine is useful for guidance (Refer to the Scientific Statement (3)).

POPULATION STRATEGIES FOR SALT REDUCTION

Since the 1990s, the entity of the population strategy whereby dietary salt reduction is necessary in a population consisting of hyper- and normotensive persons has been emphasized in the guidelines for the prevention of hypertension in the USA.[21,22] This entity was initially proposed by Rose.[23] The hypotensive effects of salt intake reduction are observed in both hyper- and normotensive persons. Therefore, when salt reduction is conducted in the whole population, BP distribution in the population shifts to the left and the mean BP decreases. Consequently, the prevalence of hypertension also reduces. Stamler *et al.*[24] estimated that, when the mean salt intake in a population is decreased by 5.8g (100mmol) per day, the mean systolic BP in the population decreases by 2.2mm Hg. A recent study in the USA estimated that the mean systolic BP reduces by 3.6mm Hg in hypertensive/elderly persons and by 1.8mm Hg overall with a 3g per day decrease in salt intake in the nation, and that, with this, the number of ischemic heart disease patients would decrease by 60000–120000 persons per year and annual health expenditure would decrease by 100–240 hundred million dollars.[25] In Japan, it was also estimated that a 3mm Hg decrease in the mean systolic BP in the nation might lead to a 10% reduction in the stroke mortality rate, and that a 5mm Hg decrease might lead to a 16% reduction in the stroke mortality rate, using the NIPPON DATA80 datas et on the preparation of the 'Kenko Nippon 21 (Health Japan 21)'.[26]

As population strategies for the primary prevention of hypertension, including salt reduction, the following methods were proposed[21] (Table 4). One of these is education for the general public. The mass media has an important role: to widely disseminate accurate, simple messages regarding the influence of salt on health using various broadcast and print media. The second method is to promote salt reduction in processed foods to food manufacturers. It is also necessary to obligate them to label the salt content of a processed food and conduct legal actions/administrative guidance regarding the salt-content limit. The third method is to promote salt reduction in meals provided at school, work sites, hospitals and when eating out, such as restaurants. It is necessary to achieve dietary salt reduction and allow individual persons to be able to select their meals by indicating the level of salt and establishing salt-restricted menus. The fourth method is to obtain all health/medical specialists' (physicians'/nurses'/health nurses'/school nurses'/dietitians'/pharmacists') cooperation. In health/medical practice, it is necessary to instruct all persons to reduce salt intake, as described for guidance regarding

Table 4 Population strategies for salt reduction (US High Blood Pressure Education Program Working Group, 1993)

1. Mass media-mediated education for the general public	>Providing accurate, simple messages regarding the influence of salt on health widely using various broadcast and print media
2. Salt reduction in processed foods by food manufacturers	>Spontaneous promotion of salt reduction by food manufacturers
	>Enforced labeling of the salt content of a processed food/legal actions regarding the salt-content limit/ administrative guidance
3. Salt reduction on cooking in lunch-providing/ eating-out industries	>Promotion of salt restriction in schools/work sites/hospitals
	>Promotion of salt restriction in the eating-out industry such as restaurants
	>Indication of salt content in menus
	>Establishment of salt-reduced menus
4. Guidance/education by health/medical specialists	>All health/medical specialists' (physicians'/nurses'/health nurses'/school nurses'/dietitians'/pharmacists') cooperation
	>Guidance for salt reduction in all persons in health/medical practice
	>Dietary/health education in the field of education

Prepared from National High Blood Pressure Education Program Working Group.[21]

body weight management/physical activities/smoking cessation. In the USA, more detailed strategies were announced in 2010.[27]

MacGregor *et al.*[28] indicated commercial reasons why food and eating-out industries have a negative view of salt reduction in processed foods. First, there is a dependence on salty taste, and desires to eat more salty foods lead to an increase in profits. Secondly, high-salt diet-related thirst results in an increase in the consumption of beverages, elevating profits. Third, an increase in the water content related to the high osmotic pressure of high-salt products leads to a low-cost increase in the weight, again elevating the profits. Therefore, to correct this, legal actions and administrative guidance are required.

The nationwide salt reduction movement from the 1960s in Japan is a population-based strategy to be internationally introduced.[29] The establishment of the 'Kenko Nippon 21', health-promoting laws and basic laws for dietary education after 2000 have further promoted this. The HIPOP-OHP study developed procedures for population strategies including salt reduction in work sites.[30,31] On the other hand, the sodium content (unit: mg) is expressed in the food composition label in Japan. However, as described above, the indication of the volume corresponding to salt is voluntary; the calculation of volume from the sodium content is difficult for individual persons. In 2010, the Japanese Society of Hypertension submitted a request to force manufacturers to express the volume corresponding to salt in the food composition table, to relevant agencies including the Consumer Affairs Agency, with 55 groups agreeing to this, so that individual persons might utilize the food composition label for the prevention and management of hypertension.

CONCLUSION

Internationally, the target of salt reduction is being established to further lower the level. As salt intake in Japanese is still higher than the international level, the target level is established as a slightly higher value. However, it is necessary to continuously make efforts to reduce salt intake not only in hypertensive patients but also in the whole nation. In addition to education for the widespread use of salt-reducing techniques for Japanese, health-care professionals must effectively perform salt-reduction guidance for hypertensive patients in hospitals/administrative organizations. To promote population strategies for salt reduction, social strategies, such as administrative policies, companies' cooperation and educational staff's cooperation, are necessary.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REVIEW

[Scientific Statement] Report of the Salt Reduction Committee of the Japanese Society of Hypertension

(3) Assessment and application of salt intake in the management of hypertension

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Salt-reduction guidance to hypertensive patients should be performed by evaluating salt intake of the individuals. However, each method to assess salt intake has both merits and limitations. Therefore, evaluation methods must be selected in accordance with the subject and facility's environment. In special facilities for hypertension treatment, measurement of sodium (Na) excretion with 24-h pooled urine or a survey on dietary contents by dietitians is recommended. In medical facilities in general, measurement of the levels of Na and creatinine (Cr) using second urine samples after waking-up or spot urine samples is recommended. The reliability of this method improves by using formulae including a formula to estimate 24-h Cr excretion. A method to estimate salt intake based on the Na excretion per gram Cr using the Na/Cr ratio in spot urine is simple, but not reliable. The method to estimate the daily excretion of salt from nighttime urine using an electronic salt sensor installed with a formula is recommended to hypertensive patients. Although its reliability is not high, patients themselves can measure this parameter simply at home and thus useful for monitoring salt intake and may intensify consciousness regarding salt reduction. Using these methods, salt intake (excretion) should be evaluated, and salt-reduction guidance targeting <6 g (Na: 100 mmol) per day should be conducted in the management of hypertension.
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INTRODUCTION

The relationship between salt and hypertension is clear. However, excessive salt intake may cause not only hypertension but also various diseases, such as stroke, heart failure, nephropathy and gastric cancer. Therefore, dietary salt restriction must be promoted not only in hypertensive patients but also in general population. The salt intake in Japanese is still higher than in various countries. According to the National Health and Nutritional Survey in 2010, the mean salt intake in males and females aged 20 years or older was 11.4 and 9.8 g per day, respectively.[1] In the 'Dietary Intake Standards in Japanese (2010 version)' issued by the Ministry of Health, Labor and Welfare, it was proposed that the target levels of salt intake in males (12 years or older) and females (10 years or older) at the national level should be <9 and 7.5 g per day, respectively.[2] However, the attainment rates in male and female adults in 2009 were 31.6 and 29.8%, respectively.[1] On the other hand, a target salt-restriction level of <6 g per day in hypertensive patients was proposed in the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009).[3] However, the target attainment rate is extremely low.[4,5]

It is commonly recognized that, among lifestyle modifications for hypertension, salt reduction is most important. However, a study reported that there was only a slight difference in the urinary salt

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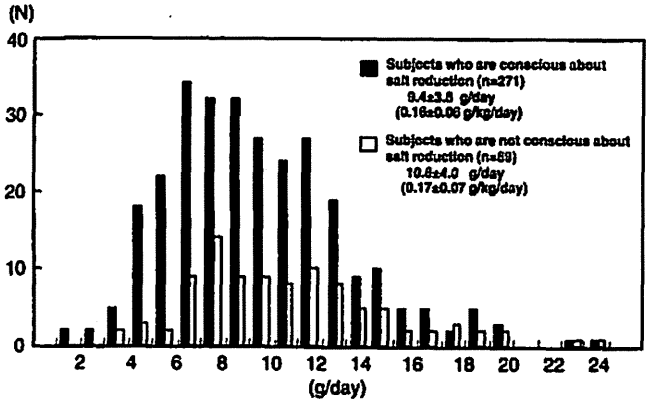

Figure 1 Consciousness regarding salt reduction and actual salt excretion (quoted from Ohta *et al.*[6]).

excretion related to the presence or absence of consciousness regarding salt reduction, suggesting that consciousness regarding salt reduction does not always contribute to actual salt restriction (Figure 1).[6] Thus, it is essential to evaluate salt intake in individuals for salt-reduction guidance. In other words, guidance to achieve the target should be conducted after the assessment of salt intake, and effective salt-reduction guidance may be accomplished by evaluating the response. The assessment of salt intake is classified into two types: dietary surveys by dietitians and monitoring of the urinary sodium (Na) level. Various procedures are used in accordance with environments, such as clinical practice regarding hypertension treatment or clinical/epidemiological studies. However, reliable assessment methods are generally difficult to perform.

The Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension (current name: Salt Reduction Committee) published a report on the 'Assessment of Salt Intake in the Management of Hypertension' in 2006.[7] In this article, we introduce the type and characteristics of methods to assess salt intake, which are available, based on the subsequent study results, and propose their application in hypertension treatment.

ASSESSMENT OF SALT INTAKE

The assessment of salt intake is classified into two types: assessment based on the dietary contents and the urinary excretion of Na. However, concerning the two procedures, simple methods are not reliable (Table 1). Furthermore, the whole volume of ingested salt is not excreted in urine, and ~10–20% is lost in the digestive tract or as sweat. Therefore, it must be considered that the urinary excretion of Na is lower than the actual salt intake. Na is an important factor for hypertension. Its greater portion is ingested as salt (sodium chloride: NaCl). One gram of salt corresponds to 17 mmol of Na (17 mEq), and 6 g of salt to ~100 mmol of Na. In the Health Promotion Law, it is described that the Na level should be expressed in the food composition. However, it must be considered that the actual salt level is 2.54 times higher (Na at 400 mg corresponds to ~1 g of salt).

Assessment based on the dietary contents

Analysis from a prepared meal. The daily salt intake can be calculated by preparing a surplus meal for one person and scientifically analyzing the Na content of this meal. This method is highly reliable if performed precisely. The accuracy of hospital and test meals for clinical research is sometimes confirmed using this method. However, specific procedures are required for sample preparation, and relatively high expenditure is required for analysis. Therefore, this method is not appropriate for long-term or large-scale strategies.

Table 1 Evaluation methods of salt intake

Evaluation method	*Reliability*	*Simplicity*
Evaluation based on the dietary contents		
Method to set a meal for an absent person	◎	×
Diet-recording method (weighing method, non-weighing method)	◎[a]	×
24-h recall method	◎[a]	Δ
Survey on the frequency of food intake, Dietary history method	○	○
Assessment with a salt sensor	×	◎
Evaluation by measurement of urinary Na excretion		
24-h pooled urine	◎	×
Nighttime urine	○	Δ
Second urine sample after waking-up	○	Δ
Spot urine	Δ(○)[b]	○
Assessment with test paper or a salt sensor	× (Δ)[c]	◎

◎: Excellent, ○: Good, Δ: Fair, ×: Poor.
[a]When the standardization of survey methods and adequate accuracy management can be maintained.
[b]When a formula for the estimation of the daily Cr excretion is used.
[c]When a salt sensor installed with the formula is used.

Diet-recording method. The weights and volumes of foods to be ingested are measured/recorded in scientific units using a balance and measuring cup/spoon, or values described on the container are recorded, and salt intake is calculated using the Food Composition Table. Among dietary survey methods, this is highly reliable. However, an interview by dietitians and calculation require much time; therefore, it is difficult to evaluate salt intake for a long period. This method is not always appropriate for frequent use in long-term intervention studies to verify the effects of salt-reduction guidance or clinical practice.

Twenty-four hour recall method. Foods ingested by each person the previous day or within the past 24 h are ascertained by an interviewer, and salt intake is calculated using the Food Composition Table. If adequate training for interviewers, standardization of survey procedures and accuracy of management are maintained, then the Na level obtained is similar to the actual analytical value, and is correlated with Na excretion in 24-h urine.[8,9]

Survey on the frequency of food ingestion and diet history. A questionnaire involving foods that are frequently consumed is prepared to investigate the frequency of consumption during a specific period (the past 1 month) and food intake per meal using writing or interview methods. This method is simpler than diet-recording and 24-h recall methods. However, it has some limitations: the assessment of salt intake is limited; and the same questionnaire cannot be used in a population in which the dietary habit markedly differs. According to several studies, the assessment of salt intake with the semi-quantitative, self-administered diet history questionnaire, in which dietary contents during 1 month are investigated using a questionnaire, and quantitative, brief-type, self-administered diet history questionnaire is correlated with assessment based on the 24-h urine/dietary records, suggesting that this assessment method is useful as a tool for salt-reduction guidance.[10,11]

Assessment with a salt sensor. It is possible to measure the concentration of salt in liquid foods to be ingested using a salt sensor at home, but it is difficult to assess salt intake unless the amount of food intake is simultaneously evaluated. However, this method may be available for strengthening/maintaining hypertensive patients' consciousness regarding salt reduction (for example, this method should be used for measurement of the *miso* soup concentration of salt to enhance motivation for salt reduction).

Measurement of urinary Na excretion

Twenty-four hour urine collection. The excretion of Na measured using 24-h urine is the most reliable among all methods to assess salt intake. This parameter is used in epidemiological (INTERSALT) and clinical studies.[12] There are two methods: methods with whole-urine collection and the collection using partition cup (Urinemate P, Sumitomo Bakelite Co., Ltd., Tokyo, Japan). The latter requires complex operations, but the collector can be easily taken on going-out or to the hospital. The assessment based on the 24-h urine is a gold standard to evaluate salt intake, but has some limitations: (1) this method is not simple, making repeated assessment difficult; (2) it is necessary to evaluate the validity of urine collection by assessing 24-h creatinine (Cr) excretion; and (3) urine collection may influence subjects' dietary contents and activities, and the results of one session of measurement do not always reflect their daily diet. As a portion of ingested Na is lost in stools or sweat, as described above, the salt intake calculated from the 24-h urinary excretion of Na is ~0.5–3 g lower than the actual intake.[13]

Nighttime urine. Measurement of Na excretion using urine collected at night or early morning urine, which consists of nighttime urine, is simpler than that using 24-h urine. It has been shown that there is a correlation between the nighttime and 24-h urinary excretions of Na. However, there are diurnal changes in Na excretion. As Na excretion at night is ~20% lower than that during the daytime,[14] it is necessary to estimate 24-h Cr excretion from the lean body mass, as well as 24-h Na excretion based on the nighttime urinary Na and Cr excretions using this value, for a more precise estimation.[15] Furthermore, a study indicated that sympathetic activity was reduced at night, and that pressure natriuresis became marked.[16] It must be considered that the nighttime urinary excretion of Na may have been influenced by blood pressure.

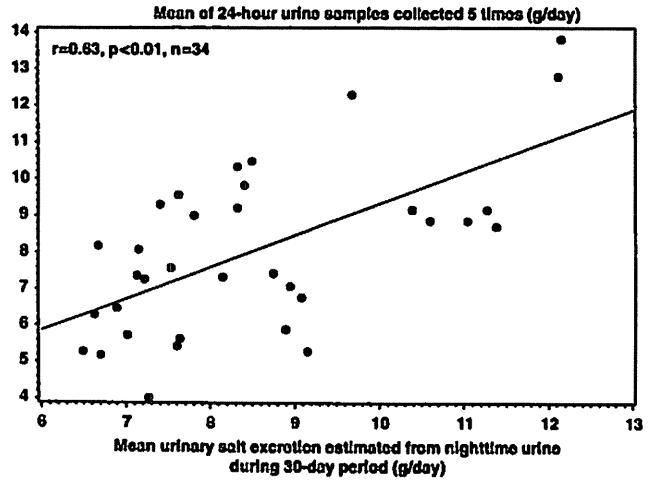

Figure 2 Relationship between the urinary salt excretion estimated from nighttime urine (mean during a 30-day period) and mean of 24-h urine samples collected five times (quoted from Ohta *et al.*[18]).

Recently, a 'salt monitor' to estimate 24-h salt excretion with an installed formula using 8-h nighttime urine was developed. It is applied in clinical practice as a method facilitating self-measurement.[17] A study reported that the mean salt excretion self-measured for 30 days using the salt monitor was correlated with that measured five times using 24-h urine (Figure 2).[18] The validity of values estimated using the salt monitor at various salt intake levels should be further investigated. However, it is possible to monitor the daily salt intake at home, and this method may be useful for motivating patients to reduce salt intake or maintain it.[19]

Second urine sample after waking-up. A study reported a method to measure the Na and Cr concentrations using a second urine sample after waking-up (within 4 h after waking-up, before eating breakfast), and estimate the 24-h urinary excretion of Na using a formula with the 24-h urinary excretion of Cr estimated from gender, height, body weight and age (Figure 3).[20] This method may be more reliable than the spot urine-based estimation described below. In particular, when adding a postural condition to maintain the sitting or standing position after waking-up, the correlation with 24-h urine is enhanced, and the daily salt intake is consistent with the value estimated using 24-h urine.[21] This assessment method may be useful in persons who can consult a physician early in the morning or in whom urine collection at home is possible.

Spot urine. For estimation with spot urine, in which there are no restrictions regarding the time of urine collection, an estimation formula prepared using the database from Japanese subjects who participated in the INTERSALT study is used (Figure 4).[22] The estimated 24-h urinary excretion of Na, which was calculated using a formula involving the estimated 24-h urinary excretion of Cr, was favorably correlated with the actual excretion of Na. Its simplicity is a merit. However, as described above, there are diurnal changes in urinary Na excretion, and the influence of the diet cannot be avoided; therefore, the relationship between estimated and actual values may vary according to the time of urine collection or salt intake (Figure 5).[23] Therefore, the reliability of the 24-h urinary Na excretion estimated using this procedure is limited.

Another method is to calculate Na excretion per gram Cr based on the spot urine levels of Na and Cr, and estimate the daily Na intake. Although its reliability is not high, this method is simple and clinically available as a parameter of motivation for salt-reduction or intensified guidance.

Test paper, salt sensor. A method to measure the spot or early morning urine concentrations of salt by detecting the concentration of chloride (Cl) using test paper or an electronic salt sensor, and estimate salt intake is the simplest.[24] Although self-measurement is possible, the quantitativity and reliability of this method are low. Therefore, this method is used only to intensify consciousness regarding salt reduction. However, the values measured using nighttime urine by a salt monitor, as described above, may be reliable to some extent.

ASSESSMENT OF SALT INTAKE FOR THE MANAGEMENT OF HYPERTENSION

As described above, there are many procedures to evaluate salt intake. However, there is no highly reliable, simple method; therefore, an adequate procedure must be selected in accordance with the purpose of assessment, subjects and facility environments. Although the diet-recording method and assessment of urinary Na excretion with 24-h pooled urine are the most reliable, salt intake on a specific day is

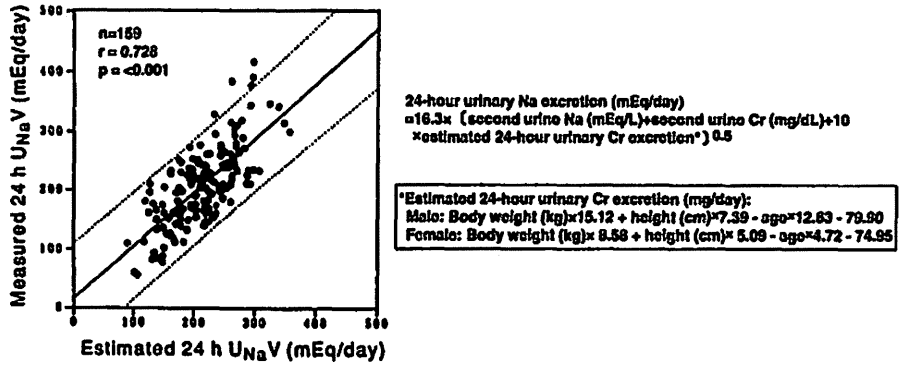

Figure 3 Estimation of 24-h urinary sodium excretion using second urine samples after waking-up (quoted from Kawasaki *et al.*[20] and partially modified).

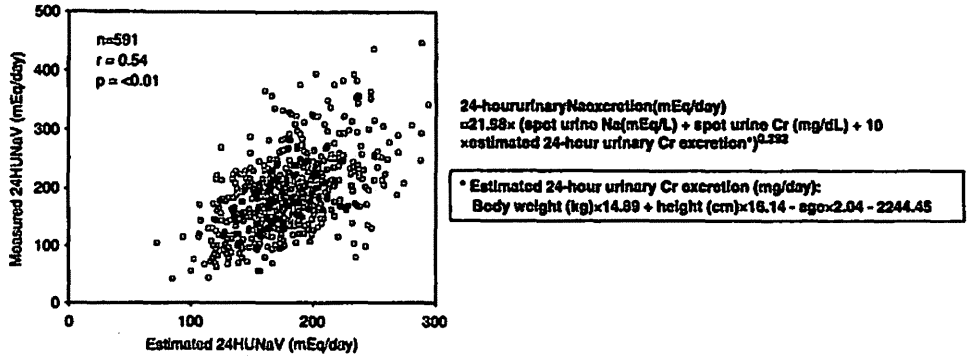

Figure 4 Estimation of 24-h urinary sodium excretion using spot urine (quoted from Tanaka *et al.*[22] and partially modified).

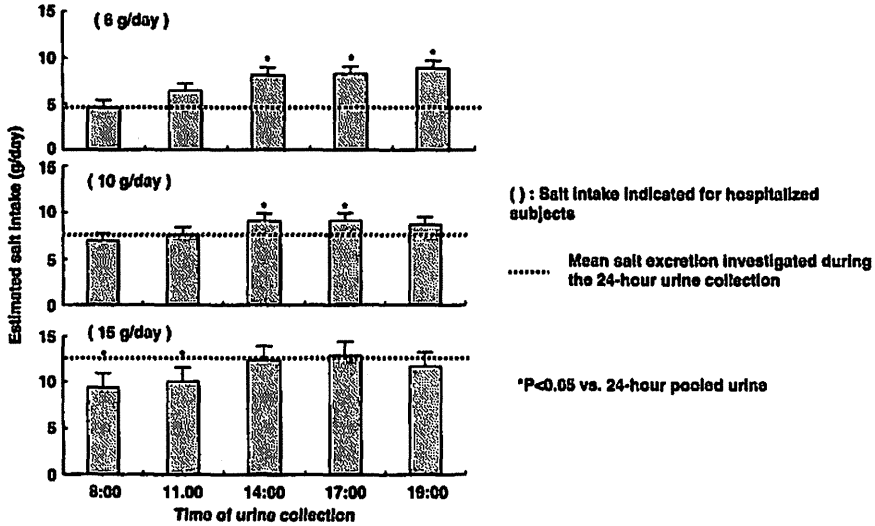

Figure 5 Relationship between the time of urine collection and estimated salt excretion with respect to various levels of salt intake (quoted from Kawamura *et al.*[23]).

evaluated, and the results may not always reflect daily changes in salt intake. In contrast, estimation using spot urine or self-measurement with early morning urine (nighttime urine) is less reliable, but repeated measurement is possible. These methods are appropriate for evaluating a trend in salt intake in individual persons. Furthermore, it must be considered that urinary Na excretion is lower than the actual salt intake calculated using the weighing method.

The Salt Reduction Committee of the Japanese Society of Hypertension proposes the guidelines presented in Table 2 with respect to the assessment of salt intake for the management of hypertension.

Special facilities for hypertension treatment

In facilities involving hypertension specialists and dietitians, measurement of urinary Na excretion with 24-h pooled urine and assessment using the weighing method or a questionnaire by dietitians are the most reliable and recommendable. When evaluating salt intake with 24-h pooled urine, the validity of urine collection should be investigated by measuring 24-h urinary Cr excretion. As shown in Figure 6 decrease in salt excretion in hypertensive patients can be confirmed by repeating the evaluation of urinary Na excretion using 24-h urine collection and nutritional guidance.[25] However, these

Table 2 Guidelines for the evaluation of salt intake

Conductor	*Evaluation method*	*Positioning*
Special facilities for hypertension treatment	Measurement of Na excretion in 24-h pooled urine Weighing by dietitians or dietary survey using the 24-h recall method	Although these methods are highly reliable and recommendable, they are complicated. They may be recommended if the patient's cooperation and facility's ability are secured
Medical facilities in general	Measurement of Na and Cr in second urine samples after waking-up or spot urine samples, survey on the frequency of food intake, dietary history method (Estimation with a formula involving the estimated 24-h urinary Cr excretion)	Although the reliability is slightly low, these methods are simple, and may be recommended as practical evaluation procedures
Self-monitoring by patients	Estimation based on the nighttime urine using an electronic salt sensor installed with a formula	Although the reliability is slightly low, the method is simple, and may be recommended as a self-monitoring tool

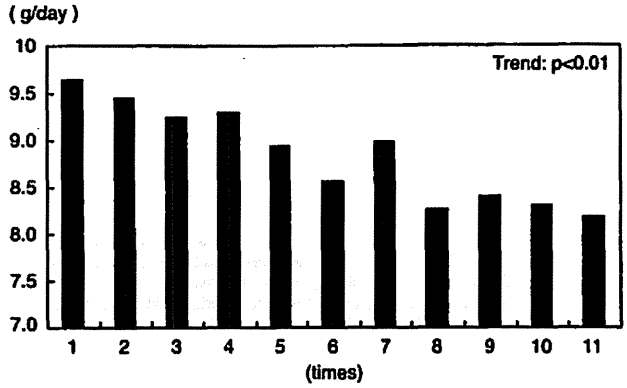

Figure 6 Changes in salt excretion repeatedly measured using 24-h pooled urine (quoted from Ohta *et al.*[25]) 103 hypertensive patients in whom 24-h urine collection was performed 11.4 times (mean), with a mean follow-up of 8.6 years.

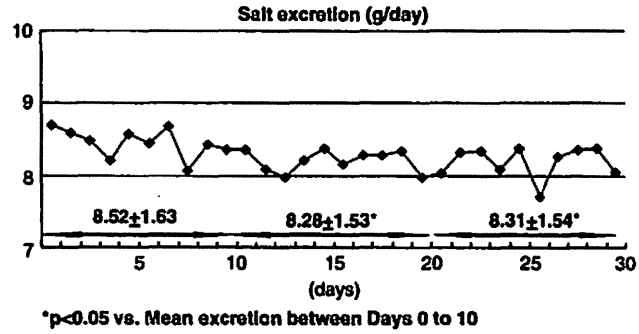

Figure 7 Changes in the self-measured values of 24-h urinary salt excretion estimated from nighttime urine (quoted from Ohta *et al.*[18]), hypertensive patients ($n=34$) and healthy adults ($n=25$), 59 subjects in total.

procedures are difficult to perform frequently, and thus it is recommended to combine these with assessment using simpler methods, such as measurement with spot or nighttime urine, as described below.

Medical facilities in general

In facilities or health checkup organizations in which it is difficult to conduct urine collection or a survey by dietitians, assessment with spot urine is simple, and can be readily performed. If conditions to collect urine can be specified, then assessment with second urine samples after waking-up (Figure 3) is recommendable. However, when it is difficult to establish conditions, assessment with spot urine should be carried out (Figure 4). To evaluate the effects of salt-reduction guidance in hypertensive patients, measurement under specific urine collection conditions is useful.

The estimation of Na excretion based on the Na/Cr ratio in spot urine is simple, but not reliable. The daily excretion of Cr in Japanese is ~1 g (~10 mmol).[12] If Na excretion per gram Cr is 100 mmol (100 mEq), then salt intake may be ~6 g. This may become a reference value for salt-intake screening or salt-reduction guidance. However, the urinary excretion of Cr depends on the age, gender and physical status; therefore, Na excretion estimated from the Na/Cr ratio may be overestimated in small females, and underestimated in large males. In this case, assessment using a formula to estimate 24-h Cr excretion should be considered.

Self-monitoring by patients

The reliability of a method to estimate the daily excretion of salt from nighttime urine using an electronic salt sensor installed with a formula is not high, but patients themselves can measure it simply. Therefore, this method is available for monitoring salt intake and intensifying consciousness regarding salt reduction. As shown in Figure 7, a study reported that serial measurement led to a decrease in salt excretion in the absence of special guidance or intervention.[18]

A method to measure the early morning/spot urine concentrations of salt using test paper is the simplest. However, its quantitativity is limited, and this method is not available for the evaluation of absolute values or the effects of salt-reduction guidance. Similarly, measurement of the food salt concentration using test paper or a salt sensor is also available as a tool for salt-reduction guidance, but not for the estimation of salt intake.

CONCLUSION

The salt intake-assessing methods have merits and limitations. Although there is no reliable, simple method, it is important to evaluate salt intake, for performing salt-reduction guidance. Therefore, evaluation methods must be selected in accordance with the subject and facility's environment. For the management of hypertension, it is strongly recommended to evaluate salt intake using one of the following methods:

(1) In special facilities for hypertension treatment, measurement of Na excretion with 24-h pooled urine or a survey on dietary contents by dietitians is recommended.
(2) In medical facilities in general, measurement of the levels of Na and Cr using second urine samples after waking-up or spot urine