Hypertension Research (2013) 36, 1009–1019

www.nature.com/hr

REVIEW

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

(1) Role of salt in hypertension and cardiovascular diseases

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Dietary salt consumption is closely associated with the level of blood pressure (BP); stricter salt reduction more markedly decreased BP. Obesity/metabolic syndrome, Dietary Approach to Stop Hypertension (DASH) diet, exercise and mental stress influence the BP-elevating effect of high-salt diet. Observational and intervention studies suggested that salt restriction improved the risk of cardiovascular diseases. However, the effects may differ among the types of the hypertensive complications; salt reduction may decrease the risk of stroke more than that of ischemic heart disease. Small-scale studies demonstrated that excess salt increased the risk of the left ventricular hypertrophy, heart failure, the urinary protein/albumin levels and end-stage renal failure. These diverse beneficial effects of salt reduction are probably because low-salt diet is an effective strategy to decrease BP and body fluid volume but is less effective to ameliorate the other cardiovascular risk factors. A mean salt intake 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.
Hypertension Research (2013) **36,** 1009–1019; doi:10.1038/hr.2013.102; published online 24 October 2013

Keywords: blood pressure; heart disease; kidney disease; sodium chloride; stroke

INTRODUCTION

Excessive salt intake has been known to be an important environmental factor in the pathogenesis of hypertension. Not only many animal experiments but also epidemiological and interventional human studies demonstrated that high salt intake increased blood pressure (BP), and that salt reduction exhibited antihypertensive effects.[1] Therefore, it is clear that excessive salt consumption is one of the major factors for BP rise. In many guidelines for the management of hypertension, salt restriction is recommended as a lifestyle modification. In the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009),[2] the target level of salt intake is set as <6 g per day. As the salt intake in the Stone Age is estimated to have been 0.5 to 3 g per day,[3] humans may have been adapted to such a low salt intake. There has been a marked increase in salt intake during the past 1000 years.[4] Considering human history, this increase has been very rapid. In the modern society, in which the number of aged and obese people is greater than in the past, however, the effects of excessive salt intake in human health may be altered.

Many animal experiments showed the inhibitory effects of salt reduction on the onset and progress of cardiovascular diseases. However, it may remain controversial whether low salt intake is beneficial to suppression of cardiovascular diseases in humans. Salt reduction lowers BP but enhances the renin–angiotensin–aldosterone system.[5] Some studies have indicated that low salt intake stimulated the sympathetic nervous system and exacerbated the risk factors for metabolic syndrome.[6] As most studies regarding salt intake and cardiovascular diseases in humans have been epidemiological, some conflicting results may reflect the fact that the accurate assessment of dietary salt intake is difficult and that changes in salt consumption alters the dietary pattern. Furthermore, the increased risk for cardiovascular diseases with reducing salt intake in a few studies may simply indicate that high-risk patients with cardiovascular

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Received 4 July 2013; accepted 24 July 2013; published online 24 October 2013

diseases are more positively performing salt-reducing strategies as compared with low-risk patients.

The purpose of this report is to validate evidence on the relationship of dietary salt intake to hypertension, cardiovascular diseases and the risk factors for cardiovascular diseases, and to clarify whether dietary salt reduction is beneficial in subjects with hypertension and/or cardiovascular diseases.

SALT AND HYPERTENSION

Salt intake and BP level

Many experimental, epidemiological and interventional studies demonstrated that high salt intake was associated with the onset and progress of hypertension.[1,7] According to a classical epidemiological study by Dahl and Love,[8] there was a positive correlation between salt intake and incidence of hypertension in the studied population, and hypertension was noted in ~30% of residents in the Tohoku District (1950s), with a salt intake of ~25 to 30 g per day. In Japan, the incidence of hypertension has rapidly decreased with a recent, marked reduction in salt intake. In the International Study on Salt and Blood Pressure (INTERSALT),[9] in which the relationship between salt intake and BP was investigated through a survey involving various areas of the world, including Yanomamo in South America (dietary salt intake: <0.1 g per day) and Tianjin in China (~15 g per day), there was a positive correlation between the salt intake estimated from the urinary excretion of sodium (Na) and BP. In particular, the mean BP was markedly low in a population with a very low salt intake (<3 g per day). In addition, there was no aging-related increase in BP in such a population with a very low salt intake. As there are individual differences in the salt-induced increase in BP (salt sensitivity),[10,11] it is difficult to identify the relationship between salt intake and BP in epidemiological studies involving a single population or populations with a similar lifestyle (salt intake). However, even such studies indicated the positive relationship between salt intake and BP.[12,13]

In Japan, there has been no large-scale, interventional study in which the antihypertensive effects of salt reduction were evaluated. In studies in Europe and the United States, such as the Trials of Hypertension Prevention (TOHP)-I,[14] Trial of Nonpharmacologic Interventions in the Elderly (TONE)[15] and Dietary Approaches to Stop Hypertension (DASH)-Sodium,[16] significant antihypertensive effects of salt reduction were observed. The achieved salt intake in these studies was lower than in the TOHP-II study,[17] in which there were no significant BP-lowering effects. Therefore, to obtain significant decrease in BP, salt intake should be reduced to some extent. For example, in the TONE study, the level of salt restriction effective for maintaining a normal BP after the discontinuation of an antihypertensive drug was ~5.6 g per day or less.[18] However, this value was obtained in Europe and the United States, in which the average salt intake in general public is lower than in Japan. A significant decrease in BP may be achieved in Japan even if salt intake is not reduced to the level that has been reported in Europe and the United States.

A meta-analysis of intervention studies,[19] in which the antihypertensive effects of moderate salt reduction were investigated, showed that when salt intake was reduced from 9.5 to 5.1 g per day (median) in hypertensive patients (4.6 g per day of decrease), there was a 5.0/2.7 mm Hg of mean decrease in BP (Figure 1). In other words, the systolic BP decreased by 1.2 mm Hg per 1.0 g per day salt reduction in hypertensive patients. In normotensive individuals, a 4.4 g per day decrease in salt intake led to a 2.0/1.0 mm Hg decrease in BP. Another meta-analysis indicated that a 5.6 g per day decrease in salt intake resulted in a 3.7/0.9 mm Hg decrease in BP in hypertensive patients, and that a 7.4 g per day decrease in salt intake resulted in a 1.0/0.1 mm Hg decrease in BP in normotensive individuals.[20] Although the decrease in BP varied among studies, a reduced salt intake linearly lowered BP in accordance with its extent of decrease. Slight salt reduction could contribute to a decrease in BP, even though the BP decrease is small.

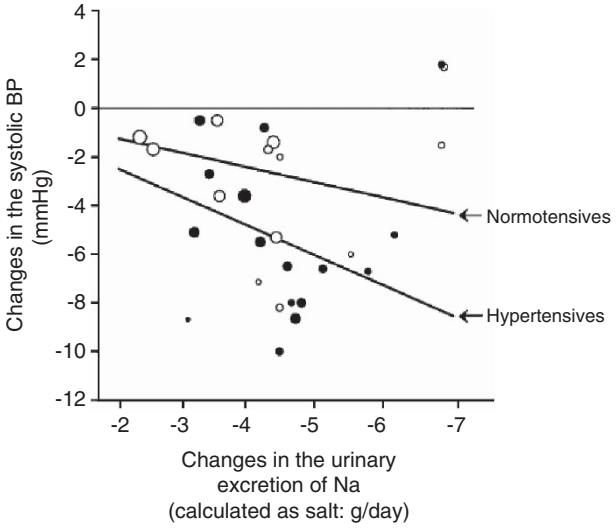

Figure 1 Meta-analysis of the antihypertensive effects of salt reduction.[19] In both hypertensive and normotensive individuals, the relationship between the grade of salt reduction estimated by urinary sodium (Na) excretion and blood pressure (BP) decrease was linear. Salt reduction may exhibit antihypertensive effects in accordance with its grade.

Thus, BP rises in accordance with increase in salt intake. Based on the results of the above interventional study,[14–18] salt intake must be reduced to ~6 g per day or less to obtain a significant decrease in BP in a population with the same salt intake as reported in Europe and the United States. Considering this, the target salt intake was established as <6 g per day in many guidelines for hypertension treatment. In addition, in the INTERSALT[9] study, the mean BP was markedly lower in a population with a salt intake of <3 g per day. In the DASH-Sodium[16] study, salt reduction at 3.8 g per day (period of 30 days) resulted in a marked decrease in BP without causing adverse events. Therefore, a salt intake of <6 g per day has been considered to be reasonable.

Individual differences in the BP response to salt reduction

There are marked individual differences in the BP response to changes in salt intake.[10,11] Clinically, the antihypertensive effects of salt reduction are large in elderly individuals, obese subjects, patients with metabolic syndrome, diabetics, hypertensives with kidney dysfunction and low-renin hypertensives.[7] However, as many factors are involved in the salt sensitivity of BP in a complex manner, it is difficult to predict the salt sensitivity based on clinical characteristics in individual patients. The salt sensitivity of BP is consecutively distributed,[10,11] and antihypertensive effects may be achieved in many patients by reducing salt intake (Figure 2). Furthermore, a study reported that in resistant hypertensive patients, salt reduction from 15 to 3 g per day led to a decrease in BP even during the administration of antihypertensive drugs.[21] Actually, it was established that salt restriction enhanced the effects of several antihypertensive drugs.

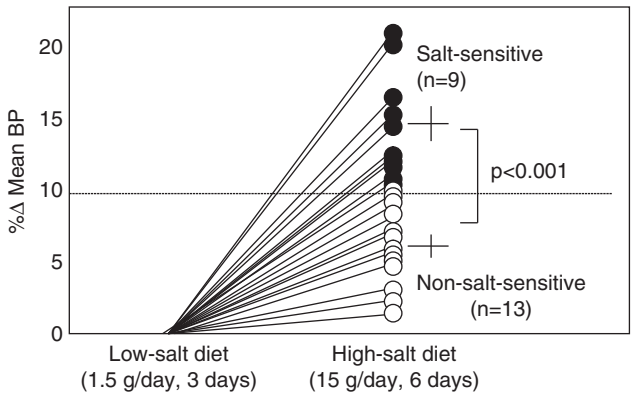

Figure 2 Increase in blood pressure (BP) on salt loading in patients with essential hypertension.[11] As the salt sensitivity of BP consecutively showed a normal distribution, the greatest number of values was distributed around the border of arbitrarily classified salt-sensitive and nonsalt-sensitive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

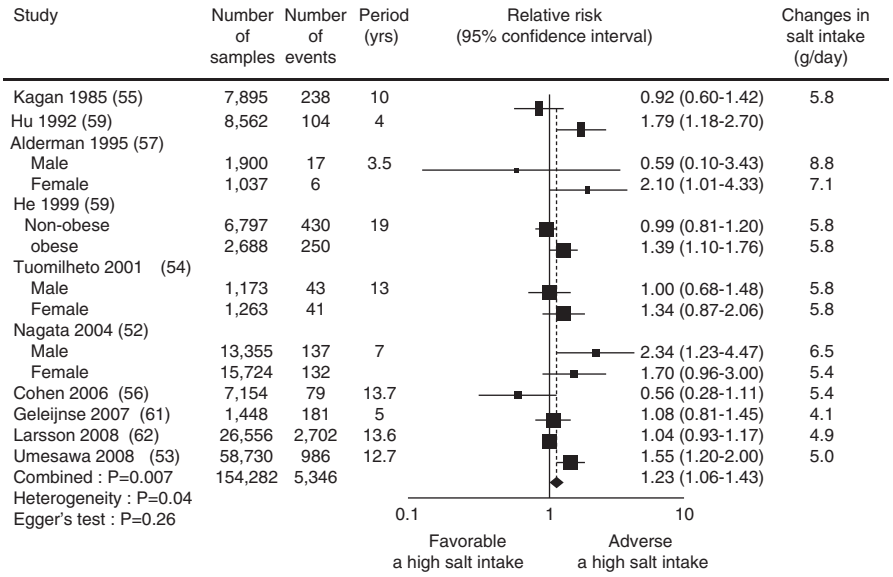

Figure 3 Meta-analysis of the relationship between salt intake and stroke.[58] An increase in salt intake elevates the risk of stroke.

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

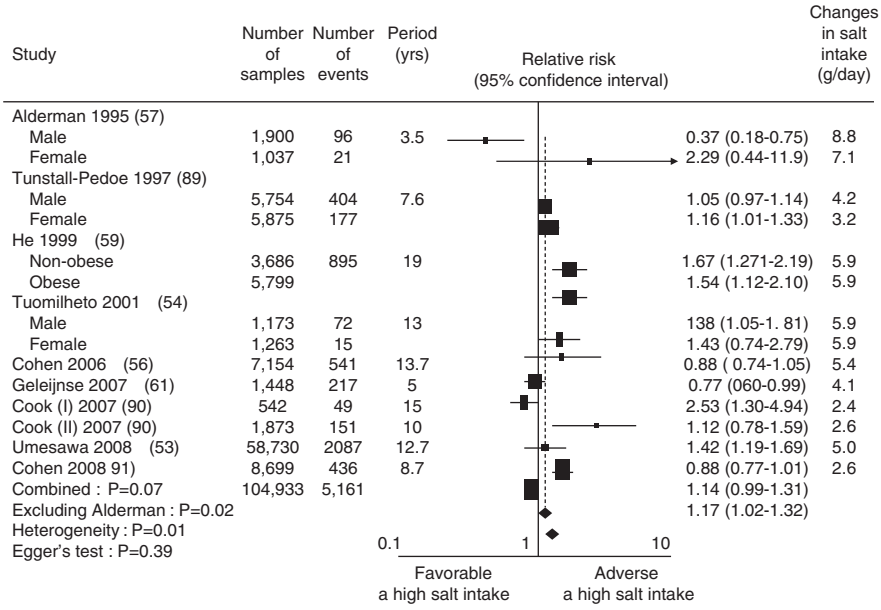

Figure 4 Meta-analysis of the relationship between salt intake and cardiovascular diseases.[58] Overall, excessive salt intake tended to increase the risk of cardiovascular diseases ($P=0.07$). There was a significant increase ($P=0.02$), excluding the study by Alderman *et al.*[57]

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 $\geqslant 6$ 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.

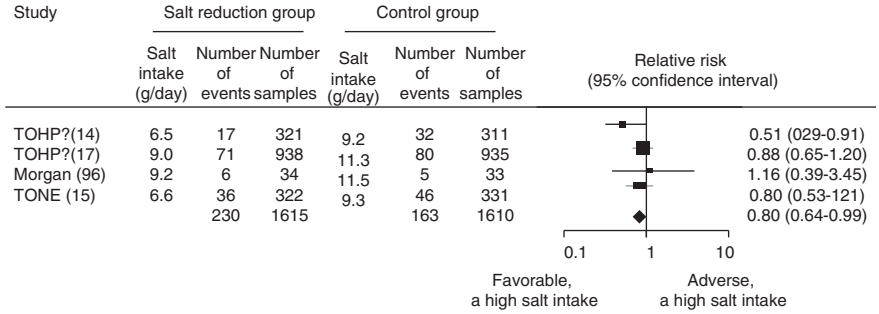

Figure 5 Meta-analysis of intervention studies regarding the effects of salt reduction on cardiovascular diseases in normotensive and hypertensive subjects (He *et al*.[94]). Salt reduction significantly decreased the risk of cardiovascular diseases. TOHP, Trial of Hypertension Prevention; TONE, Trial of Nonpharmacologic Intervention in the Elderly.

- According to observational studies, the relationship of salt with the risk of ischemic heart disease is weaker than that with the risk of stroke.
- Small-scale observational studies suggested the effects of salt reduction on heart failure.
- Small-scale observational and intervention studies indicated that salt restriction decreased the urinary protein/albumin levels.
- Small-scale observational studies suggested the reducing effects of salt reduction on the risk of end-stage renal failure.
- Observational and intervention studies suggested that salt restriction decreased the risk of cardiovascular diseases.

SALT AND THE RISK FACTORS OF CARDIOVASCULAR DISEASE OTHER THAN BP

RA system

In spite of individual differences in PRA, many investigators indicated that PRA was reduced in individuals with a high salt intake, whereas it was elevated in those with a low salt intake.[5,71,96–98] A meta-analysis by Graudal *et al*.[6] also showed that salt restriction elevated PRA. Alderman *et al*.[57] explained the result of an observational study: salt reduction increased the incidence of myocardial infarction, probably because of the stimulation of the RA system.[71] However, the result of a reverse correlation between salt intake and ischemic heart disease is controversial, and this explanation is not applicable to the results of other observational studies. Some animal experiments demonstrated that a marked increase in the organ angiotensin II level in the absence of other risk factors of cardiovascular disease did not result in organ disorder.[99,100] The salt restriction-induced physiological stimulation of the RA system may lead to the risk of cardiovascular diseases only under specific circumstances.

Aldosterone

Graudal *et al*.[6] performed a meta-analysis involving all 51 series and examination of >2/4-week studies, and reported that salt reduction significantly increased the plasma aldosterone concentration. Therefore, salt restriction elevates plasma aldosterone concentration, as indicated for PRA. However, the excessive salt intake is necessary to cause aldosterone-induced organ injury.[101] A physiological increase in the aldosterone level on salt restriction cannot cause cardiovascular disease. Nonetheless, aldosterone may play an important role in the salt-induced cardiovascular lesion.

Sympathetic nervous system

It was shown that salt reduction increased the urinary and plasma levels of norepinephrine (NE) in a short period in healthy adults[96,97] and hypertensive patients.[98] Long-term (60 days) salt reduction increased plasma NE in patients with mild to moderate hypertension,[98] whereas plasma NE returned to the pretreatment values during long-term salt reduction in healthy adults.[97] A combination of salt reduction and weight loss in untreated patients with hypertension decreased the plasma NE level after 1 year, but there were no changes in the plasma NE level in the drug-therapy or time-control groups.[102] In this report, because weight loss was conducted, reducing effects on plasma NE may not be due to salt reduction alone. However, the results suggest that salt reduction does not cause a marked increase in the plasma NE level over a long period. A meta-analysis by Graudal *et al*.[6] reported that there was a significant increase in the plasma NE level in short-term studies, whereas there were no significant changes in plasma NE in long-term (>4 weeks) intervention studies. Thus, long-term salt reduction may not cause an increase in the plasma NE level.

Metabolic risk factors

Lipids. According to the meta-analysis by Graudal *et al*.,[6] the increase in the serum total cholesterol level (5.76 mg dl^{-1}) with salt restriction was not marked, but the change was significant. When analyzing >4-week studies alone, there were no significant changes. A meta-analysis of plasma low-density lipoprotein and high-density lipoprotein cholesterol showed that there were no significant changes. Plasma triglyceride significantly increased with salt reduction as a whole. However, in studies of >4 weeks, the change was not significant. A crossover study in Norway,[103] in which 3 g per day of salt capsules were administered to a small number of patients with hypertension with slight salt reduction (7.4 g per day) for 8 weeks, demonstrated that there were no significant changes in the serum cholesterol, low-density lipoprotein cholesterol or arteriosclerosis index (log(triglyceride/ high-density lipoprotein cholesterol)). Long-term salt reduction may not influence lipid metabolism.

Insulin sensitivity. Several intervention studies have been done to investigate the influence of salt reduction on insulin sensitivity, but most of these were short-term, small-scale studies, and the results varied.[96,103–113] Only a few studies reported that salt reduction improved insulin sensitivity. Although the level of salt reduction was slight, changes in the salt balance did not influence insulin sensitivity in an 8-week study by Meland *et al*.[103] Thus, long-term salt restriction may not markedly influence insulin sensitivity, as demonstrated for the influence on lipid metabolism.

However, it is suggested that the responsiveness of insulin resistance to changes in the salt balance may depend on the characteristics of subjects. Sharma *et al*.[105] showed that in salt-sensitive group, the

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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