Dietary Salt and Potassium Intake and Hypertension

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Evidence for a relationship between high sodium intake and high blood pressure comes from animal experimental studies, controlled clinical trials, and epidemiologic studies. Aanalyses from the International Co-Operative Study of Salt and Blood Pressure found estimates of systolic and diastolic blood pressure lower by 3 to 6 mmHg and 0 to 3 mmHg, respectively, for each lower daily sodium intake; the Dietary Approaches to Stop Hypertension-Sodium feeding trial showed that lower versus higher sodium reduced systolic blood pressure and diastolic blood pressure by 6.7 and 3.5 mmHg, respectively. Lowered sodium intake may help lower blood pressure and reduce or obviate the need for antihypertensive drugs. Most of studies suggest that potassium intake has inverse relationship on systolic and diastolic blood pressure; dietary potassium deficiency induces a salt sensitivity in the high incidence and prevalence of hypertension in African-Americans. Increased potassium intake reduces systolic and diastolic blood pressure; this effect is more enhanced in hypertensives compared to normotensives, and in those consuming a high intake of sodium. Increased potassium intake in combination with sodium restriction may provide the optimal means for prevention and treatment of hypertension. Increased potassium intake may reduce the risk of stroke independent of its effects on blood pressure

Key Words : Sodium, Potassium, Hypertension, Diet

Salt and Blood Pressure

1. Experimental Animal Studies

Wide variety of experimental animal models for salt-induced hypertension have been used to evaluate the relationship of sodium and hypertension. Several strains of rat develop hypertension and have strokes when given high doses of salt. In the spontaneously hypertensive rat, sodium intake restriction attenuates the severity of hypertension. Recently, a controlled study of added extra salt in chimpanzees showed that salt intake causes a progressive rise in blood pressure among the species closest to humans. In the wild world, the chimpanzee consumes a diet high in fruits and vegetables, high in potassium and low in salt. When up to 15 g of salt per day were added in their diets of the experimental group of chimpanzees over a 20-month period, systolic BP and diastolic BP rose 33 mmHg and 10 mmHg, respectively, and the elevated blood pressure resolved when the added salt was discontinued.

2. Early Clinical Observations

The addition of salt to the human diet is a relatively recent phenomenon. Humans evolved on a low-salt diet of no more than 20 to 40 mmol sodium per day, and became adapted to the physiologic conservation of the limited salt naturally present in foods and not for excretion of a sodium load some 10 to 20 times higher than the physiologic need (8 to 10 mmol/day). Current consumption of sodium in western countries averages around 140 to 150 mmol/day (8 to 9 g/day salt).

Although sodium reduction was advocated in the treatment of hypertension early in the twentieth century, it was not until the 1940s that it gained fa-

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vor when Kempner's low-sodium rice diet proved to be an effective treatment of malignant hypertension.

The introduction of diuretic therapy, which promotes sodium as well as water loss, revolutionized the management of hypertension and added support to the concept that sodium was important in the development and control of high blood pressure. A number of trials showed that low-sodium intake could reduce, or even obviate, the need for antihypertensive medications among people who had been treated for high blood pressure.

3. Epidemiologic Studies

In an overview by Elliott of 14 studies (16 populations) that reported blood pressure and 24 hour urinary sodium excretion date (excluding INTERSALT), a highly significant positive association of sodium with SBP and DBP was found, larger among women than men.

Salt and mortality

Several studies have investigated the association of sodium intake and subsequent mortality. In 2001, a group in Finland reported up to 14-years mortality follow-up of over 1,400 men and women from whom 24-hour urinary sodium excretion was obtained in the 1980s. There was a significant association between urinary sodium excretion and subsequent coronary heart disease, cardiovascular disease, and all cause mortality.

4. Controlled Clinical Trials

In well-controlled randomized trials up to 1997, overall impact of moderate sodium reduction is fall in blood pressure in hypertensives and normotensives of 4.8/2.5 and 1.9/1.1 mmHg, respectively.

Recent analysis of 40 randomized controlled trials published through 2001, an average reduction of sodium intake of 77 mmol/24 hr was associated with a -5.2/-3.7 mmHg decrease in blood pressure among hypertensives and a -1.3/-1.1 mmHg decrease among normotensives.

A interesting observations have been made concerning sodium reduction in newborns. This trial was conducted in The Netherlands in the early 1980s before no-added-salt baby formula was widely available. 231 new born infants randomly assigned to a low sodium diet for the first six months of life. With reduction in sodium intake by approximately two-thirds, SBP at 6 months was significantly lower than in the high sodium group by 2.1 mmHg. When 167 children from this cohort were examined 15 years later, the reduced sodium group continued to have

Table 1. International Study of Salt and Blood Pressure (INTERSALT)

	Estimated Difference in SBP (mmHg)			Estimated Difference in DBP (mmHg)		
Reliability Corrected†	Sample-Age-Se Adjusted	Multiple Adjustment*		Sample-Age-Se Adjusted	Multiple Adjustment*	
		With BMI	Without BMI		With BMI	Without BMI
Men and Women (N=10.074)						
No	1.6 (0.2)	1.0 (0.3)	2.1 (0.3)	0.7 (0.2)	0.04 (0.2)	0.9 (0.2)
Yes	4.3 (0.8)	3.1 (0.9)	6.0 (1.1)	1.8 (0.5)	0.1 (0.6)	2.5 (0.7)
Men (N=5.042)						
No	1.2 (0.3)	0.6 (0.3)	1.5 (0.3)	0.6 (0.2)	0.08 (0.3)	0.8 (0.3)
Yes	3.2 (0.9)	1.8 (1.2)	4.6 (1.2)	1.5 (0.6)	10.2 (0.9)	2.3 (0.9)
Women (N=5,032)						
No	2.2 (0.4)	1.3 (0.4)	2.6 (0.4)	0.9 (0.3)	0.09 (0.3)	0.9 (0.3)
Yes	5.7 (1.2)	4.0 (1.4)	7.5 (1.5)	2.3 (0.7)	0.3 (0.9)	2.8 (0.9)

Abbreviations : BMI, body mass indes; DBP diastolic blood pressure; SBP, systolic bolld pressure
*Adjusted for sample, age, sex, 24-hour urinary potassium excretion, alcohol intake.
†Multivariate correction tor reliability (regression dilution bias); standard error estimated approximately by bootstrap sampling.

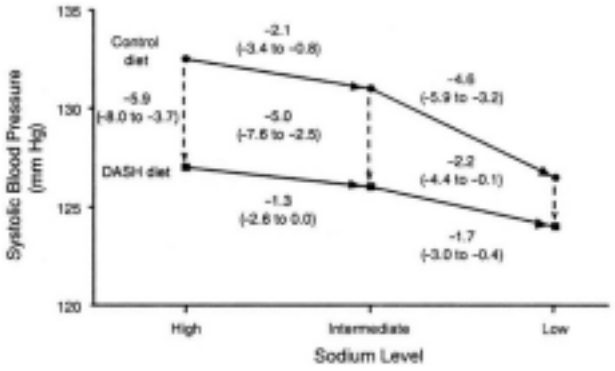

Fig. 1. *DASH-Sodium Trial: Effect of DASH diet and 3 different levels of sodium intake on systolic blood pressure [Re-drawn from Sacks FM, Svetkey LP, Vollmer WM, et al. For the DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001;344:3-10, with permission].*

lower BP 3.6/2.2 mmHg (systolic/diastolic) than the usual sodium group, despite no further intervention since infancy.

In most of cases, antihypertensive potential of low salt intake is uncertain because the extent of salt reduction was too short and too moderate. At least six weeks duration with 100 meq/day salt reduction will be needed in full observation of an effect.

5. Sodium intake and hypertension, Action Mechanism

1) Level of sodium intake

The development of hypertension seems to require a threshold level of salt intake. Therefore, essential hypertension is seen primarily in populations in which salt intake is above 100 meq/day (2.3 g sodium)[11]; in contrast, hypertension is a rare disorder in populations in which salt intake is less than 50 meq/day (1.2 g sodium).

2) Sodium sensitivity

The extent of BP change in response to abrupt differences in sodium intake varies considerably from person to person, as well as intra-personally. Sodium sensitivity increases with age and is more marked in African-Americans, obesity and patients with renal insufficiency.

3) Mechanism of sodium sensitivity

The mechanism of salt-sensitivity is not clear. One common abnormality is a defect in renal salt excretion that can cause initial volume expansion and then hypertension. Increase in renal perfusion pressure can, via the phenomenon of pressure natriuresis, directly enhance sodium excretion and restore normovolemia. Such an increase in BP is not required in normal subjects who can excrete a salt load by suppressing the release of renin and increasing that of atrial natriuretic peptide. By comparison, a lesser activation of the renin-aldosterone mechanism may explain the greater falls in BP with sodium reduction in the elderly, African-Americans, and patients with renal insufficiency.

(1) Sodium-hydrogen exchange

Another explanation for renal sodium retention in salt-sensitive hypertension is increased activity of the sodium-hydrogen exchanger that mediates sodium reabsorption in the proximal tubule.

(2) Adducin gene

One possible mechanism for sodium sensitivity is a defect in the gene for adducin, a cytoskeletal protein. One possibility is alterations in actin polymerization, leading to increased sodium reabsorption (in part via increased sodium-hydrogen exchange) throughout the kidney. One report evaluated both hypertension and normotensive individuals for polymorphisms in the alpha-adducin gene. The alpha-adducin polymorphism may help to identify salt-sensitive subjects.

(3) Other

Salt-sensitivity is associated with insulin resistance, dyslipidemia, and microalbuminuria, forming an atherogenic cluster that could also induce or aggravate hypertension.

(4) Other potential benefits of salt reduction

In addition to its direct effect, sodium restriction may enhance the efficacy of several different antihypertensive drugs. Restriction of sodium intake lower blood pressure and diminishes the degree of potassium depletion following treatment with a diuretics. It

can also interact synergistically with other nonpharmacologic modalities, such as weight loss.

Sodium restriction tends to activate the renin-angiotensin system, enhancing the response to a converting enzyme inhibitor.

A less responsive renin-angiotensin system may be one reason why blacks may be more sensitive to sodium restriction than whites.

A number of other consequences of a sodium reduction are independent of blood pressure

·Reduction in mortality from stroke

·Regression of left ventricular hypertrophy

·Lowering of urinary calcium excretion, which may protect against calcium stones and the osteoporotic change with aging process.

Potassium and Blood Pressure

Evidence from various investigations suggests that diet and physical inactivity play an important role in the genesis of age-related increases in blood pressure and occurrence of hypertension. Weight gain, alcohol consumption, excessive intake of sodium and insufficient dietary potassium are major possibilities as dietary causes of hypertension. Recent publications, including numerous cross-sectional studies in developed and developing countries, and clinical trial results have demonstrated the role of increasing potassium intake as a means to prevent and treat hypertension.

1. Epidemiology

The most precise estimates come from the International Study of Salt and Blood Pressure (INTERSALT), a cross-sectional investigation conducted in 10,079 men and women aged 20 to 59 years from 52 populations around the world. In this study, a 50 mmol/day higher level of urinary potassium excreton was associated with a 3.4 [95% confidence interval (CI), 1.5 to 5.2] mmHg lower level of systolic and 1.9 (95% CI, 0.7 to 3.0)mmHg lower level of diastolic BP after adjustment for the potentially confounding influences of age, sex, body mass index, alcohol consumption, and urinary sodium excretion.

Epidemiologic studies are also consistent with the suggestion that potassium deficiency may play a special role in the high incidence and prevalence of hypertension in blacks and the elderly.

Migration studies have identified a relationship between progressive diminution in potassium intake and hypertension. Typically, these changes have been noted in a setting in which there is a concurrent increase in sodium, calorie, and alcohol consumption and a decrease in physical activity. It has been hard to separate the independent contribution of each of these changes to the concurrent change in BP.

2. Clinical Trials

Whelton et al. identified 33 randomized, controlled trials (2,563 participants) in which the effects of an increased intake of potassium on BP were evaluated. Of these, 21 trials (2,565 participants) were conducted in hypertensive and 12 in normotensive (1,005 participants) persons, In all except 2 trials, the dose of potassium prescribed in the active intervention was >60 mmol per day. The weighted mean net change in urinary potassium excretion for the intervention vesus control group was 53 mmol per 24 hours in

Table 2. Urinary Excretion of Potassium and sodium/Potassium Ration in 7 Low Blood Pressure Populations

Population	Urinary Potassoim mmoL/24 hr	Urinary sodium/ Potassium Ratio
Yanomamo Indians, Brazil	152	0.01
Kung bushmen, Botswana	70-103	0.28-0.44
Xigu Indians, Brazil	78-96	0.19-0.20
Asaro Valley, Papua New Guinea	62-79	0.53-0.70
Luo tribesmen, Kenya	32-35	1.9

Data from He J, Whelton PK, Potassium, blood pressure, and cardiovascular disease : an epidemiologic perspective. Cardiol Rev 5:255-260, 1997

the 31 trials in which such information was available. Overall, increased potassium intake was associated with a significant reduction in mean (95% CI) systolic and diastolic BP of 4.4 (2.5-6.4) and 2.5 (0.7-4.2) mmHg, respectively (Table 3) Subgroup analysis suggested that the treatment effect was enhanced in hypertensives, blacks, and those consuming a high intake of sodium. In trials in which the participants were consuming a diet high in sodium content, there was a significant ($p<0.001$) dose-dependent relationship between 24-hour urinary potassium excretion and treatment effect size.

In a trial performed in China, potassium supplementation resulted in a 5.0 mmHg reduction in systolic BP, Krishna et al. have demonstrated that short-term potassium depletion produces an increases in BP in hypertensives and normotensives.

Two randomized controlled trials have showed the effects of increased potassium intake in reducing the need for antihypertensive drug modification trial, and increased intake of potassium significantly reduced the need for antihypertensive drug therapy.

Clinical trials have shown that consumption of a diet that is rich in fruits, vegetables, and low-fat dairy foods and with a reduced saturated and total fat content [Dietary Approaches to Stop Hypertension (DASH) diet] results in a substantial lowering of BP in hypertensives and normotensives. The high intake of dietary potassium in the DASH diet may have good effect in lowering BP .

Various mechanisms have been proposed to explain the influence of potassium in BP (Table 4). Many studies have demonstrated short-term changes in sodium excretion, but it is not clear whether any long-term effects on BP can be ascribed to a decrease in intravascular volume resulting from this initial and transient natriuresis.

3. Effects on Stroke and Heart Disease

In addition to its hypotensive potentials, increased potassium intake may have vascular-protective properties independently. In animal models, including spontaneously hypertensive and Dahl salt-sensitive

Table 4. Reduction of Blood Pressue from Potassium, Mechanism of action

Direct natriuretic effect
Suppression of the renin-angiotensin and sympathetic nervous systems
Effect on kallikreins and eicosanoids
Improvement of baroreceptor function
Antagonism of the effects of natriuretic hormone
Direct arterial vasodilatation

Table 3. Pooled Estimates of Change in Blood Pressure (BP) after Potassium Supplementation in 33 Randomized Controlled Clinical Trals

Trials in Analysis	Systolic BP		Diastolic BP	
	Mean Change	95% Confidence Interval	Mean Change	95% Confidence Interval
All trials (N=33)	-4.4	-2.53, -6.36	-2.5	-0.74, -4.16
Obel trial excluded (N=32)	-3.1	-1.91, -4.31	-2.0	-0.52, -3.42
Hypertensive trialsa (N=20)	-4.4	-2.2, -6.6	-2.5	-0.1, -4.9
Normotensive trials (N=12)	-1.8	-0.6, -2.9	-1.0	0.0, -2.1
Trials in blacks* (N=6)	-5.6	-2.4, -8.7	-3.0	-0.7, -5.3
Trials in whites (N=25)	-2.0	-0.9, -3.0	-1.1	-0.1, -2.1
Urinary Na, mmol/d†				
<140 (N=10)	-1.2	0.0, -2.4	0.1	1.1, -1.0
140-164 (N=10)	-2.1	-0.3, -4.0	-1.4	0.0, -2.8
≥165 (N=10)	-7.3	-4.6, -10.1	-4.7	-1.1, -8.3

*Excludes outlier trial by Obel AO.
†Urinary sodium excretion during follow-up.
Adapted from Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressue: meta-analysis of randomized controlled clinical trials. JAMA. 1997;277:1624-1632.

Table 5. Stroke Associated with a Low Dietary Intake of Potassium during 19 Years of Follow-Up of 9,805 Male and Female Participants in the National Health and Examination Survey 1 Epidemilogic Follow-up Study

Adjustment Model	Hazard Ration (95% Confidence Interval)	*p* value
Age-, energy-adjusted	1.37 (1.20-1.54)	<.0001
Age-, race-, sex, energy-adjusted	1.26 (1.11-1.45)	.0007
Multivariatea	1.28 (1.11-1.47)	.0001

*Additionally adjusted for systolic blood pressure, serum cholesterol, body mass index, history of diabetes, physical activity, education level, regular alcohol consumption, current cigarettes smoking, vitamin supplement use, saturated fat intake, cholesterol intake, sodium intake, calcium intake, dietary fiber, vitamin C intake, and vitamin A intake (N=9,244).
Adapted from Bazzano LA, He J, Ogden LG, et al. Dietary potassium intake and risk of stroke in US men and women. National Health and Nutrition Examination Survery Epidemiologic Follow-Up Study. Stroke. 2001;32: 1473-1480

rats, Tobian reported that the addition of potassium chloride or potassium citrate markedly reduced the probability of death from a stroke.

Bazzano et al. studied 9,805 U.S. men and women who had participated in the First National Health and Nutrition Examination Survery (NHANES I) who were followed for more than an average of 19 years, yielding 927 stroke and 1,847 coronary heart disease events (Table 5). After adjustment for a broad array of potential cardiovascular disease risk factors, those who had consumed a low potassium diet at baseline (first quartile, <34.6 mmol/day) experienced a 28% higher (95% CI, 11% to 47%) risk of stroke compared to the remainder of the cohort. Most of epidemiologic studies suggests that stroke mortality is inversely related to intake of vegetables and fruits. A vascular-protective effect from increased potassium intake may reduce mortalities from cardiovascular and strokes risks.

Summary

The evidence for both safety and efficacy of moderate sodium restriction is overwhelming. It will usually lower high blood pressure and may prevent the occurence of hypertension. Thus, the 2003 7th Joint National Committee report and the World Health Organization-International Society of Hypertensive guidelines recommend moderate sodium restriction as part of the nonpharmacologic therapy of hypertension.

The recommendation is to reduce dietary intake from the usual 150 to 200 meq/day down to 100 meq/day (approximately 2.3 g of sodium or 6 g of salt [one gram of sodium = 44 meq; one gram of sodium chloride contains 17 meq of sodium]).

The American Heart Association recommends that dietary salt consumption be less than 108 meq/day (6 g salt/day) in the general population and a lower level in subjects who are hypertensive. Since 80 percent of dietary sodium is derived from the sodium added in food and drink processing population-wide reduction is by lowering the amount of sodium added by food processors. This can be accomplished in a gradual manner with no loss in taste.

Increased potassium intake reduces systolic and diastolic blood pressure; this effect is more pronounced in hypertensives compared to normotensives, and in populations consuming a high intake of sodium.

Increased potassium intake in combination with sodium restriction may provide the optimal means for prevention and treatment of hypertension.

Increased potassium intake may have vasculoprotective potential and reduce the risk of stroke independent of its effects on blood pressure.

References

1) Chobanian AV, Hill M : National Heart, Lung, and Blood Institute Workshop on sodium and blood pressure, Acritical review of current scientific evidence. *Hypertension* **35:**858-863, 2000
2) Denton D, Weisinger R, Mundy NI : The effect of increased salt intake on blood pressure in chim-

panzees. *Nat Med* **1:**1009-1016, 1995
3) Elliott P : The INTERSALT study: an addition of the evidence on salt and blood pressure, and some implications. *J Hum Hypertens* **3:**289-298, 1989
4) Elliott P : Observational studies of salt and blood pressure. *Hypertension* **17:**I-3-I8, 1991
5) INTERSALT Cooperative Group : INTERSALT: an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium excretion. *BMJ* **297:**319-328, 1988
6) MacGregor GA, Markandu ND, Sagnella GA : Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. *Lancet* **2:**1244-1247, 1989
7) National Research CouncilCommittee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences. *Diet and Health: implications for reducing chronic disease. Washington, DC* : National Academy Press 413-430, 1989
8) Sacks FM, Svetkey LP, Vollmer W : for DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* **344:**3-10, 2001
9) Stamler J, The INTERSALT Study : background, methods, findings, and implications. *Am J Clin Nutr* 65:626S-642S, 1997
10) Tuomilehto J, Jousilahti P, Rastenyte D : Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* **357:**848-851, 2001
11) Appel LA, Moore TJ, Obarzanek E : for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* **336:**1117-1124, 1997
12) Bazzano LA, He J, Ogden LG : Dietary potassium intake and risk of stroke in US men and women. National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Stroke* **32:**1473-1480, 2001
13) Gu D, He J, Wu X : Effect of potassium supplementation on blood pressure in Chinese : a randomized, placebo-controlled trial. *J Hypertens* **19:**1325-1331, 2001
14) Johnstion SC. Potassium, stroke, and the bounds of epidemiological studies. *Stroke* **32:**1479-1480, 2001
15) Joshipura KJ, Ascherio A, Manson MJ : Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA* **282:**1233-1239, 1999
16) Klag MJ, He J, Coresh J : The contribution of urinary cations to the blood pressure differences associated with migration. *Am J Epidemiol* **142:**295-303, 1995
17) National High Blood Pressure Education Program Working Group : Report on primary prevention of hypertension. *Arch Intern Med* **153:**186-208, 1993
18) The sixth report of the Joing National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 157:2413-2446, 1997
19) Whelton PK, He J, Cutler JA : Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA* **277:**1624-1632, 1997
20) Weinberger MH : Salt sensitivity of blood pressure in humans. Hypertension 27:481, 1996
21) Obarzanek E, Proschan MA, Vollmer WM, Moore TJ : Individual blood pressure responses to changes in salt intake: results from the DASH-Sodium trial. *Hypertension* **42:**459, 2003
22) Campese V : Salt sensitivity in hypertension. Renal and cardiovascular implications. *Hypertension* **23:**531, 1994
23) Paassen PV, Zeeuw DD, Jong PE, Navis G : Renin inhibition improves pressure natriuresis in essential hypertension. *J Am Soc Nephrol* **11:**1813, 2000
24) Aviv A, Hollenberg NK, Weder AB : Kidney Int **65:**361, 2004
25) Siffert W, Dusing R : Sodium-proton exchange and primary hypertension. An update. *Hypertension* **26:**649, 1995
26) Kuro-o, M, Hanaoka, K, Hiroi, Y : Salt-sensitive hypertension in transgenic mice overexpressing Na^+-proton exchanger. *Circ Res* 76:148, 1995
27) Tripodi, G, Valtorta, F, Torielli, L : Hypertension associated point mutations in the adducin alpha and beta subunits affect actin cytoskeleton and ion transport. *J Clin Invest* 97:2815, 1996
28) Cusi D, Barlassina C, Azzani T : Polymorphisms of alpha-adducin and salt sensitivity in patients with essential hypertension. *Lancet* **349:**1353, 1997
29) Bigazzi R, Bianchi S, Baldari G, Campese VM : Clustering of cardiovascular risk factors in salt-sensitive patients with essential hypertension: Role of insulin. *Am J Hypertens* **9:**24, 1995
30) Campese, VM, Romoff, MS, Levitan, D : Abnormal relationship between sodium intake and sympathetic nervous system activity in salt-sensitive patients with essential hypertension. *Kidney Int* **21:**371, 1982
31) Morris, RC Jr, Sebastian, A, Forman, A : Normotensive salt sensitivity. Effects of race and dietary potassium. *Hypertension* **33:**18, 1999
32) Ram CV, Garrett BN, Kaplan NM : Moderate sodium restriction and various diuretics in the treatment of hypertension. Effects on potassium wastage and blood pressure control. Arch Intern Med **141:**1015, 1981
33) MacGregor GA, Markandu ND, Singer DR : Moderate sodium restriction with angiotensin converting enzyme inhibitors in essential hypertension:

A double blind study. *Br Med J* **294:**531, 1987
34) He FJ, Markandu ND, Sagenella G, MacGregor GA. Importance of the renin system in determining blood pressure fall with salt restriction in black and white hypertensives. *Hypertension* **32:**820, 1998
35) Jula AM, Karanko HM : Effects on left ventricular hypertrophy of long-term nonpharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation* **89:**1023, 1994