Salt and Hypertension: Is Salt Dietary Reduction Worth the Effort?

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ABSTRACT

In numerous epidemiologic, clinical, and experimental studies, dietary sodium intake has been linked to blood pressure, and a reduction in dietary salt intake has been documented to lower blood pressure. In young subjects, salt intake has a programming effect in that blood pressure remains elevated even after a high salt intake has been reduced. Elderly subjects, African Americans, and obese patients are more sensitive to the blood pressure-lowering effects of a decreased salt intake. Depending on the baseline blood pressure and degree of salt intake reduction, systolic blood pressure can be lowered by 4 to 8 mm Hg. A greater decrease in blood pressure is achieved when a reduced salt intake is combined with other lifestyle interventions, such as adherence to Dietary Approaches to Stop Hypertension. A high salt intake has been shown to increase not only blood pressure but also the risk of stroke, left ventricular hypertrophy, and proteinuria. Adverse effects associated with salt intake reduction, unless excessive, seem to be minimal. However, data linking a decreased salt intake to a decrease in morbidity and mortality in hypertensive patients are not unanimous. Dietary salt intake reduction can delay or prevent the incidence of antihypertensive therapy, can facilitate blood pressure reduction in hypertensive patients receiving medical therapy, and may represent a simple cost-saving mediator to reduce cardiovascular morbidity and mortality.

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Pharmacologic treatment for hypertension is effective in reducing both blood pressure and morbidity and mortality from cardiovascular and renal disease. However, long-term pharmacologic therapy can have adverse effects and requires continuing medical supervision. Lifestyle changes have been documented to effect real and significant blood pressure reductions.[1] The present review specifically addresses salt intake reduction, for which there is perhaps the most variety and strength of supporting evidence among the lifestyle interventions. We attempt to clarify for whom, and to what extent, salt intake reduction reduces blood pressure.

The current challenge is to disseminate and substantiate in the minds of physicians and patients that lifestyle interventions for blood pressure reduction are neither impractical nor ineffective, but rather simple, safe, and consequential mediators of blood pressure; and to design and implement public health initiatives that help sustain these non-drug interventions.

SALT

For most of our evolution, humans consumed less than 0.25 g of salt per day. Today, salt intake remains high because of its use in food seasoning, but especially because of highly salted processed foods. In 2005, only 9.6% of adults met recommended guidelines for sodium intake (<1.5 g/d for persons with hypertension, middle-aged and older adults, and blacks, and < 2.3 g/d for all other adults).[2]

MECHANISM OF ACTION: HOW SALT IS RELATED TO BLOOD PRESSURE

"Salt" and "sodium" are used synonymously. In fact, salt is only 40% sodium; 1 g of salt has 400 mg sodium. The

remaining 60% of salt—chloride—is an often forgotten but likely important part of the link between salt and blood pressure. Replacing sodium chloride with sodium citrate abolished the increase in plasma volume and blood pressure induced by sodium chloride.[3] Similar effects have been observed when sodium chloride was replaced by sodium phosphate or sodium bicarbonate. Therefore, with regard to blood pressure effects, it is useful to speak in terms of salt intake.

Although hypertension and age-related increases in blood pressure are virtually absent in populations in whom individual consumption of sodium is less than 50 mmol per day,[4] sodium intake in most populations throughout the world exceeds 100 mmol per day in the majority of people, yet many remain normotensive. Therefore, sodium intake that exceeds 50 to 100 mmol per day is necessary but not sufficient for the development of hypertension.

Total exchangeable sodium correlates positively with arterial pressure, a correlation that increases with age.[5] Of note, sodium does not increase blood pressure by increasing volume; despite an excess of sodium, extracellular fluid volume, plasma volume, and blood volume are not increased but rather decreased in essential hypertension.[6] In fact, there is an inverse relationship between plasma volume and total peripheral resistance.[7] High sodium and low potassium inhibit the sodium pump, increase intracellular sodium, and drive calcium into cells, which ultimately induces vascular smooth muscles contraction and increased peripheral vascular resistance.[4]

A new pathway of sodium storage in the human body has been identified.[8] Excess sodium stored in the subcutaneous lymphatic system (on proteoglycans in interstitial space), where it becomes osmotically inactive, can act as a fluid-buffering system to blunt the blood pressure increase during excessive salt intake. Such a finding is one of many that recast our thinking about how blood pressure regulation is a product of high salt intake interacting with genetic susceptibility.

Many individual genes influence the body's handling of sodium to varying degrees. It is hypothesized that in most cases essential hypertension is a genetic disorder,[9] which becomes expressed when intake of salt becomes excessive. In the Framingham Offspring cohort, heterozygote carriers of rare gene variants (Bartter and Gitelman syndromes), identified in 1.2% of the study cohort, had a systolic blood pressure 6 to 9 mm Hg greater than that of noncarriers.[10]

CLINICAL SIGNIFICANCE

- Salt intake reduction can delay or prevent hypertension in non-hypertensive subjects and contribute to blood pressure reduction in hypertensive subjects receiving medical therapy.

- A growing body of evidence suggests that salt intake reduction confers a risk reduction effect on cardiovascular disease end points.

- Salt intake reduction at the population level seems safe and cost-effective but will require public policy implementation because most salt intake comes from processed foods.

Individuals vary intrinsically in the extent to which their blood pressure is "salt-sensitive."[5] A lesser activation of the renin-angiotensin-aldosterone system may explain the greater decreases in blood pressure with reduced sodium intake seen in the elderly, among African Americans, the obese,[11] and patients with chronic kidney disease or metabolic syndrome.

AGE: SALT INTAKE REDUCTION ON BLOOD PRESSURE IN THE YOUNG VERSUS OLD(ER)

Salt intake first increases at 6 to 9 months of age when solid foods are introduced. Almost all 12- to 24-month-old toddlers have salt intake exceeding "adequate levels."[12] Salt intake in children and adolescents remains high because of increasing consumption of processed foods.

In children aged 8 to 16 years, sodium intake reduction of 42% yielded a reduction in blood pressure of 1.17/1.29 mm Hg. In infants, salt intake reduction of 54% yielded a systolic blood pressure reduction of 2.47 mm Hg. In the young, the decrease in blood pressure associated with modest salt intake reduction occurs relatively quickly and, of perhaps greater importance, may be long-lasting.

It has been shown that blood pressure in children follows a tracking pattern that continues into the third and fourth decades of life.[13] These results fit in well with multiple animal experiments, suggesting salt intake in early life has a programming effect on blood pressure; reduction early in life has a blood pressure effect beyond the termination of diminished salt intake. Newborns on a low-sodium diet for 6 months, achieving systolic blood pressure 2.1 mm Hg lower than in the control group, went on also to have systolic blood pressure 3.6 mm Hg lower than the original control group at 15-year follow-up.[14]

Hypertension is an extremely common problem in the elderly, more so than in the young.[15] Further, the elderly, a more salt-sensitive subset of the population, can benefit greatly from salt intake reduction.

Sodium reduction to a level of 1500 mg/d lowers blood pressure more in older adults than younger adults.[16] Systolic blood pressure decreased by 8.1 mm Hg in those aged 55 to 76 years, compared with 4.8 mm Hg for adults aged 23 to 41 years. In persons without hypertension, blood pressure decreased by 7.0 mm Hg in those aged more than 45 years compared with 3.7 mm Hg in those aged less than 45 years. For individuals aged 60 to 80 years, salt intake reduction corresponded with blood

pressure reduction of 10/4 mm Hg for 100 mmol/d reduction in urinary sodium excretion.[17]

Salt intake reduction in the young has immediate and sustained effects on blood pressure. In the more salt-sensitive elderly, who to a greater degree experience the effects of hypertension and the adverse effects of antihypertensive medications, salt intake reduction is a particularly valuable modality for blood pressure management, but no longer portends a "programming" effect.

CORRELATION OF SALT INTAKE TO BLOOD PRESSURE

The relationship of salt intake and blood pressure is direct and progressive. There is a consistent dose-response relation between salt intake and blood pressure within the range of 3 to 12 g of salt per day.[18] A reduction of only 3 g/d predicts a decrease in blood pressure of 3.6 to 5.6/1.9 to 3.2 mm Hg in hypertensive subjects and 1.8 to 3.5/0.8 to 1.8 mm Hg in normotensive subjects. A modest reduction of 6 g in salt intake for 4 or more weeks predicted a decrease in blood pressure of 7.11/3.88 mm Hg in hypertensive individuals and 3.57/1.66 mm Hg in normotensive individuals.

This relationship holds across the range of daily salt intakes and human blood pressures. Among normotensive individuals, a modest 2 g salt intake reduction over 18 months led to a 35% decreased incidence of hypertension at 7-year follow-up. Meanwhile, for individuals already with elevated blood pressure, a reduction by 4.6 g/d of salt yielded a mean reduction in blood pressure of 5.06/2.70 mm Hg.[19] Data are more striking for patients with resistant hypertension; among patients who remain hypertensive despite multiple drug treatment for hypertension, reducing sodium intake by 4.6 g/d decreased systolic/diastolic blood pressure by 22.7/9.1 mm Hg.[20]

Of note, the studies that have cast doubt on the relationship between sodium intake and blood pressure were often of short duration and entailed severe salt restriction. Salt intake reduction, when precipitous and short-lived, does not produce the antihypertensive effect that long-term, even if modest, salt intake reduction does.

NON-BLOOD PRESSURE-RELATED EFFECTS OF DIETARY SALT

Increasing evidence suggests that a high salt intake may *directly* (ie, beyond the effect of salt intake on blood pressure) increase the risk of stroke, left ventricular hypertrophy, and proteinuric renal disease; is related to renal stones and osteoporosis and to the severity of asthma; and is probably a major cause of stomach cancer (**Table**).

Stroke
In a study of Japanese men and women, sodium intake was significantly and positively associated with death from intracerebral hemorrhage and ischemic stroke in men.[21] A possible mechanism is salt-mediated vascular oxidative stress leading to vascular damage and eventually stroke. The relationship between 24-hour urinary sodium and stroke mortality seems to be stronger than the relationship between urinary sodium and blood pressure.[22]

Left Ventricular Hypertrophy
Left ventricular hypertrophy is known to confer an independent risk for cardiovascular disease outcomes and mortality. Salt intake is a significant and independent predictor of left ventricular mass.[23] Salt intake exerts hypertrophic effects on the left (and potentially also on the right) ventricle even after correcting for 24-hour blood pressure in hypertensive but not normotensive individuals. A similar close relationship also was observed in children.[24] Various authors hypothesize that dietary salt may sensitize the heart to the hypertrophic stimulus of pressure load (**Figure 1**).

Proteinuric Kidney Disease
There is a direct association between salt intake and urinary albumin excretion that is independent of blood pressure.[25] This association is modified by body mass index; for the same sodium intake, overweight and obese individuals have a higher urinary albumin excretion than lean subjects. Of note, increased salt intake offsets the antiproteinuric effect

	RCTs	Cohort Studies	Ecological Studies	Experimental Studies
Table Type of Evidence of the Recognized Effects of Lower Dietary Salt Intake				
Lower rate of increase in BP with age			x	x
BP reduction in HTN and normotension	x			x
Decreased risk of cardiovascular events		x		x
Decreased risk of stroke		x	x	x
Reduction in left ventricular hypertrophy	x			x
Reduced rate of albuminuria	x			x
Improved arterial elasticity	x			
Lower risk of calcium nephrolithiasis	x	x		
Lower risk of gastric cancer		x	x	

BP = blood pressure; HTN = hypertension; RCT = randomized controlled trial.
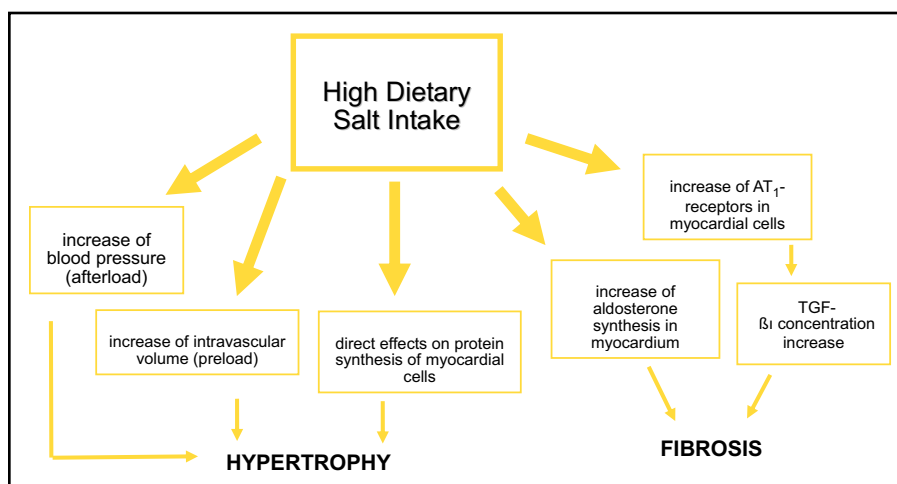
Figure 1 Hypothetical link among salt intake, blood pressure, and changes in left ventricular structure. TGF = transforming growth factor; AT = angiotensin.

of angiotensin-converting enzyme inhibitors and calcium antagonists in proteinuric hypertensive patients.[26] A low salt intake has been shown to reduce blood pressure and proteinuria in nondiabetic nephropathy better than addition of angiotensin receptor blockade to angiotensin-converting enzyme inhibitor.[27]

SALT AND HEART FAILURE

Any physician who cares for patients with heart failure knows how salt intake can tip the balance between compensated and decompensated heart failure; the increase in cardiogenic pulmonary edema admissions after holiday seasons among patients with heart failure is empirically ascribed to excessive salt intake and treated (with good effect) accordingly. However, there is a paucity of evidence clearly delineating the relationship between salt intake and heart failure incidence or progression, or delineating just how far salt intake should be reduced in heart failure. The relative risk of congestive heart failure among overweight participants was 1.43 (95% confidence interval, 1.07-1.91) for those with sodium intake > 113.6 mmol/d compared with those with sodium intake < 50.2 mmol/d.[28] Administration of drugs that promote sodium and fluid retention, such as nonsteroidal anti-inflammatory drugs or thiazolidinediones, has been shown to increase the risk of congestive heart failure. Salt reduction in combination with other lifestyle changes reduced left ventricular mass.[29] Diastolic dysfunction is related to blood pressure and salt intake.[30] Although no specific guidelines exist, taken together, the data favor sodium restriction in those with heart failure to prevent fluid retention and symptomatic deterioration.

ARE THERE ADVERSE EFFECTS OF SALT REDUCTION?

There is still insufficient power to exclude clinically important effects of reduced dietary salt intake on mortality or

cardiovascular morbidity.[31] Nonetheless, for modest salt reduction, there was no detectable change in plasma renin activity or in total cholesterol, triglycerides, and low- or high-density lipoprotein cholesterol.[18] Reduced sodium intake was not associated with adverse effects but rather with fewer instances of angina and significantly fewer reports of headache.[17]

The argument that restriction of salt intake has major effects on procreation, gestation, and lactation was made on the basis of findings in arthropods, rodents, and mammals.[32] In humans, the group with worsened sexual function compared with placebo was the group assigned to chlorthalidone treatment; the low sodium diet was not itself associated with greater rates of sexual dysfunction.[33]

A low sodium diet is associated with stimulation of the renin-angiotensin system and the sympathetic nervous system, which offsets the blood pressure reduction (though less so for the elderly, those of African origin, and hypertensive individuals).[34] Sodium loading significantly decreases the total glycemic response (area under the curve) in the oral glucose tolerance test in salt-sensitive hypertensive patients.[35] Thus, an abundant sodium intake may actually improve glucose tolerance and insulin resistance in some patients. Conversely, insulin resistance can be ameliorated by salt restriction in young salt-sensitive subjects.[36]

SALT INTAKE AND CARDIOVASCULAR PROGNOSIS

It has been estimated that reducing salt intake by 9 g/d (eg, from 12 to 3 g/d) would reduce strokes by approximately one third and ischemic heart disease by one quarter, and this would prevent 20,500 stroke deaths and 31,400 ischemic heart disease deaths per year in the United Kingdom.[37] Salt intake reduction of 5 g was related to a 23% reduction in stroke and a 17% reduction in the rate of cardiovascular disease.[38] Among overweight individuals, a higher salt in-

take was associated with a higher risk of developing heart failure over a 19-year follow-up period.[28] However, low salt intake (<2.4 g/d) may be associated with an increased risk of cardiovascular death.[39] In countries with high salt intake, there was a significant association of high salt intake with increased cardiovascular mortality,[40] whereas no or only a modest overall association has been observed in countries with moderate salt intake.[41] In patients at high cardiovascular risk, an increased sodium excretion was a strong determinant of all-cause death, myocardial infarction, stroke, and hospitalization for congestive heart failure, but low sodium intake also was related to an increased risk of cardiovascular death, suggesting a J- or U-shaped relationship between sodium intake and cardiovascular morbidity and mortality.

Salt restriction seems to decrease cardiovascular morbid events as long as the salt intake does not decrease to < 2.4 g/d. Given our current salt intake of 10 to 12 g/d on average, it is exceedingly unlikely that we will get close to these levels in the near future. However, one recent study shows rather different findings; although systolic (but not diastolic) blood pressure increased in line with increases in urinary sodium excretion, this association did not translate into a higher risk of hypertension or cardiovascular complications.[42] The authors found the opposite: a consistent and inverse, albeit weak, association between cardiovascular mortality and 24-hour urinary sodium excretion at baseline. At this time, it is not easy to reconcile this one study's results with the contradictory results of others that have preceded it; perhaps this study questions the indices used to measure salt intake as much as the actual association between salt intake and blood pressure. There has been a well-publicized response to the findings of the above study.[43]

IS ACCOMPLISHING POPULATION-WIDE SALT INTAKE REDUCTION REALISTIC?

It is difficult to reduce salt intake at the community level.[44] The challenge must be approached at the level of the consumers and the producers; a strategy to change the salt contents of foods will require the cooperation of the food industry. More than 80% of excess salt intake, especially in developed countries, comes from salt added to processed foods (eg, sandwiches, pizza, soups) by producers and not from salt added by the consumer during cooking.[45] A strategy of 10% to 20% yearly or biyearly reductions in salt intake would likely not be detectable by human salt taste receptors and would reach goal levels (5-6 g/d; most diets today include 10 g salt intake daily) in approximately 5 years.

In Norway, salt-reduction interventions are estimated to save $270 million over 25 years; in Canada, reducing salt intake by half is estimated to save the healthcare system $430 million per year in hypertension treatment costs alone.[46] In the United States, a regulatory intervention designed to achieve a reduction in salt intake of 3 g per day was projected to save 194,000 to 392,000 quality-adjusted life-years and $10 billion to $24 billion in health care costs annually.[47]

Is this public health initiative worth the effort? Could a thiazide diuretic, for example, impart the same population-wide blood pressure-reducing effect more easily? With chronic thiazide use, there may be excessive volume depletion and as a result, orthostatic hypotension, tachycardia, or postural symptoms, along with hypokalemia, hyponatremia, and metabolic alkalosis. Thiazides also may increase the concentration of low-density lipoprotein cholesterol by 5% to 15%, total cholesterol by 12%, and triglycerides by 10%. They may exacerbate metabolic syndrome, increase abdominal fat accumulation, and even increase cardiovascular risk.[48] Erectile dysfunction may be observed with the use of thiazide diuretics. Risk of many of these adverse effects is lower with low-dose diuretics, which in turn are not effective antihypertensives. Thus, adverse effects of the most used antihypertensives are significant compared with the relative safety associated with salt intake reduction.

COMPARING AND COMBINING MODALITIES

The optimal effect on blood pressure is achieved with correction not just of salt intake but of multiple contributors to hypertension. It seems that the blood pressure effects of weight loss and sodium intake reduction, for example, are partly additive in that patients who lost weight and reduced sodium intake delayed onset of hypertension more than those who only lost weight or reduced sodium intake.[49] Combining low salt intake with the Dietary Approaches to Stop Hypertension is another example of added blood pressure benefit in combination lifestyle interventions (**Figure 2**). Comparing a Dietary Approaches to Stop Hypertension diet plus lowest salt intake with a control diet plus high salt intake showed a −8.9/−4.5 mm Hg difference in blood pressure (among hypertensive subjects, the systolic blood pressure decrease was 11.5 mm Hg).

Finally, low salt intake increases the efficacy of blockers of the renin-angiotensin system in terms of their blood pressure-lowering (on par with the effect of adding a thiazide to a renin-angiotensin system blocking drug),[50] renal hemodynamic, and antiproteinuric effects.

CONCLUSIONS

Physicians influence patients through simple assessments and basic advice. However, because most dietary salt comes from processed food, an effective public health strategy must complement this patient/physician-based approach. Salt intake reduction can delay or prevent incidence of or treatment for hypertension in non-hypertensive subjects and contribute to blood pressure reduction in hypertensive subjects already receiving medical therapy. There is a growing body of evidence that salt intake reduction has a cardiovas-
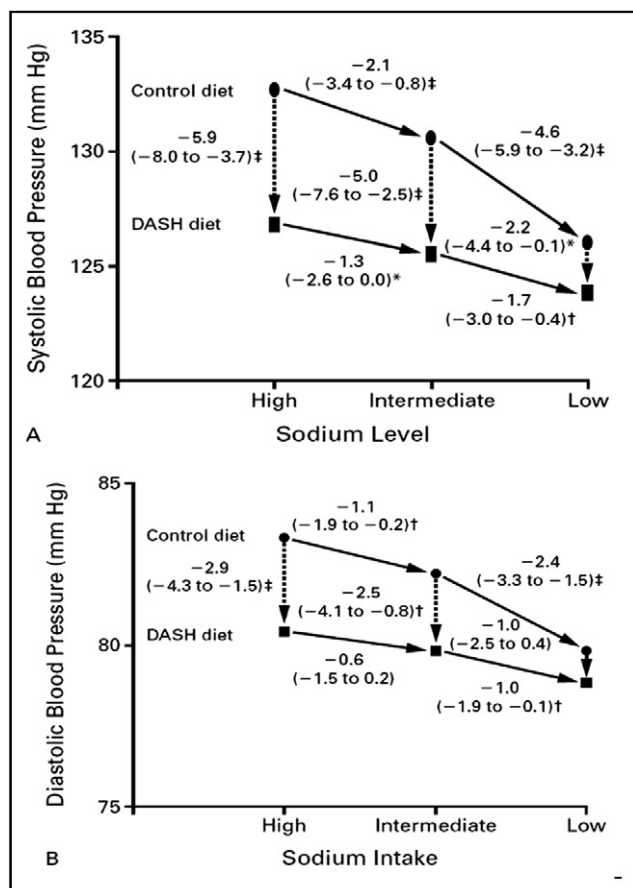
Figure 2 Combining modalities for reducing blood pressure can have additive effects: Dietary Approaches to Stop Hypertension plus salt restriction reduced blood pressure differentially for each level of salt intake. Reprinted with permission from Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344: 3-10.

cular disease risk reduction effect, at least partially mediated by decreased blood pressure.

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