Overview of Relation Between Sodium and Blood Pressure

Epidemiological studies conducted over the past 50 years have shown a clear curvilinear relation of higher adult blood pressure (BP) levels to higher rates of coronary heart disease (CHD), stroke, heart failure, and kidney failure. A continuous relation is apparent from below the 120/80 mm Hg level. Thus, a significant portion of CVD occurs in persons whose BP has not reached the arbitrary 140/90 mm Hg level defining hypertension. Studies show unequivocally that lowering high BP in hypertensive patients can reduce the likelihood of developing or dying from CVD, including CHD and stroke. Dietary factors in individuals and in the population at large have important effects on BP levels, which are generally assumed to translate to CVD risk.

For the nonhypertensive subset, a population-wide approach to lowering BP (an approach based on lifestyle modifications that have been shown to prevent or delay increases in BP) could affect the total CVD burden as much as or more than treating only those with established hypertension.

There is an abundance of scientific evidence demonstrating a direct relation between salt intake and BP. Studies in laboratory animals show that high BP can be induced by diet. Recent evidence comes from a randomized trial involving 26 chimpanzees that were given a low salt/high potassium diet (preintervention period). Subsequently, one half of these nonhuman primates continued this diet, and the remainder received increasing amounts of additional dietary salt (5 g/d for 19 weeks, 10 g/d for 3 weeks, and 15 g/d for 67 weeks). BP increased progressively to levels averaging 33/10 mm Hg higher in the group consuming additional salt. On cessation of the additional salt, the BPs fell quickly to preintervention levels.

A positive relation between dietary sodium and BP has been shown from observational studies in humans. The Yi People Study in China compared Yi farmers in remote areas with a group of Yi farmers who had migrated to an urban area and a group of Han residents of the same urban area. BP rose very little with age in the Yi farmers but increased with age in Yi migrants and Han residents. In a sample of 419 men, there was a positive relation between sodium intake and higher BP. Other factors, such as body mass index (BMI), were also involved.

Several large, long-term, randomized clinical trials have shown that a moderate reduction in sodium intake reduces BP levels. The Trials of Hypertension Prevention (TOHP), Phase II, evaluated the benefits of weight reduction and sodium reduction, alone and in combination, for individuals who were slightly to moderately overweight and had high normal BPs. Weight loss and sodium reduction reduced BP at 6 and at 36 months. BP effects declined from 2 to 4 mm Hg at 6 months to ≈1 mm Hg at 36 months, reflecting diminishing weight loss (4.5 to 2 kg) and sodium reduction (50 to 40 mmol) with longer follow-up. At 36 months, effects on systolic BP were statistically significant, and each of the interventions also lowered the incidence of hypertension by ≈20% over the 3- to 4-year duration of the trial.

The Trial of Nonpharmacologic Interventions in the Elderly (TONE) showed the effect of salt reduction and weight loss in individuals whose BPs were controlled with 1 antihypertensive medication. Compared with usual care, mean weight loss was ≈10 pounds, and the mean sodium reduction was estimated as 40 mmol/d. In the group that lost weight and reduced their salt intake, about half were able to stop and remain off medication versus about one third of those who received single interventions.

In summary, there is conclusive evidence that dietary salt is positively associated with BP and that BP can be lowered...
with reductions in sodium intake of 40 to 50 mmol in both hypertensive and nonhypertensive persons.

BP Responsiveness to Dietary Sodium and Other Nutrients

Typically, studies to determine individual differences in BP response to sodium intake have examined the effect, over several days, of a very low level (10 to 20 mEq sodium/d) followed by a very high level (>200 mEq sodium/d) of intake. Studies differ in the criteria used to designate salt sensitivity or salt resistance, ie, BP responsiveness to increase in or withdrawal of salt. Some individuals change classification from salt sensitive to salt resistant and vice versa. In a study of reproducibility, 18 of 28 responded consistently, 4 changed classification, and 6 were classified as indeterminate. Salt sensitivity also increases with age in both hypertensive and normotensive persons. The workshop discussion emphasized that the individual’s response is variable for any nutrient and that age, race, genetic background, medications, intake of other nutrients, and duration of the exposure can affect the response.

Population studies have often shown an inverse relation between potassium intake and BP and (less consistently) between calcium intake and BP. A recent meta-analysis of 33 randomized controlled trials (2609 participants) showed a 3/2 mm Hg decrease in BP for an ≈50 mmol higher median potassium excretion, with a greater decrease in trials with 80% African Americans. The effect of potassium was enhanced in those with a high intake of sodium.

The relation between calcium intake and BP has also been examined in meta-analyses. One meta-analysis pooled data from 22 clinical trials (1231 persons) involving calcium supplements of 400 to 2160 mg/d. It showed a decrease in systolic BP of 0.5 mm Hg for trials involving normotensive persons and 1.7 mm Hg for trials involving hypertensive persons. A second meta-analysis of 33 trials involving calcium supplements of 1000 to 2000 mg/d showed a reduction in systolic BP of 1.3 mm Hg in normotensive participants. These data indicate that calcium supplementation has a small effect on systolic BP level in hypertensive persons and an uncertain effect in normotensive individuals.

There are inconsistent findings associating magnesium with BP level. A recent review of 29 observational studies concluded that the evidence suggested an inverse association between magnesium intake and BP level. However, recent controlled clinical studies showed no significant effect of magnesium on BP.

The Dietary Approaches to Stop Hypertension (DASH) trial showed that in addition to calorie balance and intake of sodium chloride and alcohol, multiple nutrients influence BP. In this 8-week feeding study, a “combination” diet that was high in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts and low in fats, red meat, and sweets produced relatively large decreases in BP. The BP reduction averaged 11/6 mm Hg among those with hypertension and 4/2 mm Hg among those without hypertension, with the greatest reduction in black hypertensive persons. The BP results almost certainly are not attributable to the influence of a single nutrient. Compared with the control diet, the DASH diet had an increase in calcium content, a lower than average sodium content (3000 mg/d), 173% higher magnesium, 150% higher potassium, 240% higher fiber, and 30% higher protein. Other nontargeted nutrients were also higher: vitamins A, B, C, and E, folate, riboflavin, phosphorus, and zinc.

Sodium and BP in the Young

Some but not all studies in children and adolescents have found sodium to be positively associated with BP. In certain groups of adolescents, a relation between sodium intake and BP appears to be linked with family history of hypertension, obesity, and African American ethnicity. In 1980, a randomized trial was initiated among 476 Dutch newborns to study the BP effect of a diet reduced in sodium by approximately two thirds during the first 6 months of life. At the end of the trial, systolic BP in the low sodium group was 2.1 mm Hg lower than in the control group. After 15 years, BP in 167 of the 476 children from the original cohort was 3.6/2.2 mm Hg lower in adolescents who as infants had been in the low sodium group compared with the control group. These authors have suggested that sodium intake in infancy may relate to BP later in life.

Clinical Trials and Clinical Studies

Meta-Analyses of Effect of Dietary Sodium on BP

Three recent meta-analyses of randomized clinical trials are available for estimating the effect of dietary sodium on BP. In the most recent examination, data pooled from 58 studies of 3000 hypertensive participants with a median age of 49 years showed that an average reduction of urinary sodium excretion of 129 mmol/24 h was associated with a mean BP decrease of 4.5/2.3 mm Hg. In the 56 studies of >2000 normotensive participants with a median age of 27 years, mean BP decreased by 1.6/0.4 mm Hg, per 165 mmol/24 h of urinary sodium excretion. The workshop discussion emphasized the consistent finding from the meta-analyses: sodium reduction has a small but significant effect on BP. Issues were raised regarding the heterogeneity of the trials and the data on dietary adherence and on the collection and measurement of urine. Also discussed was the possibility of publication bias and problems in interpretation of some of the data.

Sodium and BP in Subsets of the Population

Hypertension develops earlier in life and average BPs are higher in African Americans than in whites. The Treatment of Mild Hypertension Study (TOMHS) showed that education and income levels were inversely correlated with sodium excretion and with systolic BP in African Americans. The TOMHS participants with less education had a higher sodium intake, but they also experienced the largest decrease in sodium excretion with intervention. TOHP, Phase I, found a 40% reduction in estimated sodium excretion after 18 months of a “sodium-light lifestyle.” There were no significant differences in the effect on BP in blacks versus whites. However, women had a greater decrease in systolic BP.
The prevalence of salt sensitivity was investigated in 1 study of 200 healthy white and African American nonobese postmenopausal women, half of whom were hypertensive. When a 200 mEq sodium intake preceded or followed a low sodium intake, the prevalence of salt sensitivity was similar in white versus African American women. However, preliminary data suggest that the mechanism of salt sensitivity may differ between African Americans and whites.\textsuperscript{30}

Quality of Life
Several clinical trials have studied the effect of interventions on the quality of life, ie, the ability to function well in daily living, maintain psychological and physical well-being, pursue social and leisure activity, and obtain reasonable satisfaction with life. These studies found that a majority of participants gave high ratings to food with a lower content of sodium\textsuperscript{31} and that moderate sodium reduction was not associated with physical complaints or with impairment of the quality of life.\textsuperscript{32,33}

Observational Studies in Populations
INTERSALT
The International Study of Salt and Blood Pressure (INTER-SALT Study),\textsuperscript{34–36} a cross-sectional study, involved >10 000 individuals, aged 20 to 59 years, in 52 population samples from 32 countries. Across the 52 populations, 24-hour sodium excretion was significantly related to BP level, age, and prevalence of hypertension. In both normotensive and hypertensive subgroups, there was a lower systolic BP of 3 to 6 mm Hg per 100 mmol/d lower level of sodium excretion. Across populations, when individuals aged 25 years were compared with those aged 55 years, there was a 10 mm Hg lesser rise in systolic BP per 100 mmol/d lower sodium excretion with age. Other factors, such as a higher alcohol intake, higher BMI, and lower potassium intake, were also related to higher BP. Persons with less education tended to eat more sodium, drink more alcohol, consume less potassium, and have higher BMI and BP.\textsuperscript{37}

The discussion relative to INTERSALT emphasized that the strengths of the study included its large sample size and sophisticated statistical analyses. Concerns raised about the study related to the method of adjustment for BMI and prior specification of hypotheses. The study investigators stated that the set of a priori cross-population hypotheses included examination of increased BP with age. It was suggested that the relation between sodium consumption and BP in individuals was underestimated because of incomplete urine collections and the use of antihypertensive medications by some of the participants. During the subsequent extensive discussion, it was noted that complex statistical issues underlie the interpretation of these data.

A Worksite Cohort, the Scottish Heart Health Study, and NHANES I
The Worksite Cohort Study,\textsuperscript{38} The Scottish Heart Health Study,\textsuperscript{39} and the National Health and Nutrition Examination Survey (NHANES I) Follow-up Study\textsuperscript{40} have examined the direct relation between sodium intake and subsequent CVD. Some individuals have suggested that the results of these studies call into question the current recommendations for reducing salt intake in the general population. In the Worksite Cohort,\textsuperscript{38} after 3.8 years of follow-up among hypertensive patients, estimated sodium excretion, based on one 24-hour urine sample, was inversely associated with cardiovascular events, particularly myocardial infarction, in men but not women. Several concerns that had been raised previously\textsuperscript{41} were noted in the workshop discussion. Among these was the fact that sodium excretion in the lowest quartile was unusually low and that patients had been counseled to limit their sodium intake for 4 to 5 days before baseline urine collection. The results also could have been biased by the fact that those with the highest risk may have reduced their sodium intake more extensively.\textsuperscript{42}

In the Scottish Heart Health Study,\textsuperscript{39} baseline urinary sodium excretion and incidence of myocardial infarction after 7.6 years of follow-up were associated in women only.

In the 20-year follow-up of NHANES I,\textsuperscript{40} an inverse association was identified between sodium intake at baseline (based on a single 24-hour recall) and all-cause and CVD mortality. However, when corrected for caloric intake, there was a positive association of mortality with sodium.\textsuperscript{40} The discussion reflected concerns about the analysis and conclusions: undermeasurement of calorie intake and sodium (calculated from one 24-hour dietary recall with no measure of discretionary salt or urinary sodium excretion), calorie and weight discrepancies, and collinearity between sodium and calories. Without such information, it was considered difficult to attribute mortality to the level of sodium intake. Also, follow-up data from NHANES II failed to show a relation between baseline sodium intake and mortality.

MRFIT Follow-Up
A recent analysis from the Multiple Risk Factor Intervention Trial (MRFIT) follow-up\textsuperscript{43} tested the hypothesis that sodium intake influences mortality risk. A total of 11 697 men, aged 42 to 64 years at the sixth annual visit, had three to five 24-hour dietary recalls during the trial. The average levels of sodium intake in the lowest and highest quintiles of averaged sodium intake were \( \approx 1600 \) and 4300 mg, respectively, for both the intervention and usual care groups. Urinary sodium excretion was not measured. Multiple regression analyses of posttrial follow-up (1982 to 1996) data adjusted for CHD risk factors and other confounders showed no significant differences across the quintiles of sodium intake for all cause mortality, acute myocardial infarction, CHD, and CVD. The findings were similar in the subgroup of 6193 hypertensive men. This analysis from MRFIT does not support the hypothesis that differences in sodium intake influence mortality risk.\textsuperscript{43} Potential confounding factors that were discussed included the possibility that the men at greatest risk of CVD might have made the greatest reduction in sodium intake over time because they were aware of such increased risk.

Genetic Research
Findings from basic research and genetic studies in the United States and other populations have linked the development of hypertension and increased BP with particular genotypes. Persons with a genetic predisposition to develop
hypertension may have differential responses to environmental changes, such as sodium reduction or weight loss. Data from TOHP participants indicate that persons with weight loss and sodium reduction may be particularly effective for persons with angiotensin phenotype AA. Further research is needed to determine the mechanisms relating sodium reduction and weight loss in different phenotypes.

Sodium Intake and Other CVD and Non-CVD Conditions

Several studies have shown direct associations between sodium intake and other conditions, including urinary stones, osteoporosis, indicators of asthma, and left ventricular mass (LVM). The first 2 of these conditions have been recently investigated. A study of 3625 Italian adults reported that dietary calcium and urinary sodium excretion were positively associated with urinary stones. Sodium intake estimated from food frequency questionnaires was positively associated with 12-year risk of urinary stones in 91,731 nurses. In a 2-year longitudinal study of 124 postmenopausal women, increased urinary sodium excretion was associated with bone loss at the hip, independent of calcium intake, physical activity, and weight. A study of 59 postmenopausal women found that a reduction of salt intake lowered urinary hydroxyproline, an indicator of bone reabsorption.

The evidence to support an association between dietary sodium and asthma is mixed. A randomized trial found that a high sodium intake increased asthma symptoms, timed forced expiratory volume, and the use of medications. However, another randomized crossover study found no effect of sodium intake on expiratory flow in mild asthma.

A high salt intake may stimulate LVM, and in rats with renovascular hypertension, it influenced the magnitude of LVM independently and more consistently than BP. In the TOMHS, LVM reduction was seen with weight loss and sodium reduction.

Association of Very Low Sodium Intake With Plasma Lipids and Insulin

Studies on the effect of sodium intake on plasma lipids and lipid levels generally have been of short duration and have included small numbers of individuals. A 1997 review found that very low sodium intakes (≤20 mmol/d) were associated with higher total and LDL cholesterol and plasma insulin levels. However, the MRFFIT study showed that moderate reductions in salt intake had no significant association with serum cholesterol, serum uric acid, and plasma glucose. In the discussion period, it was emphasized that short-term and long-term physiological responses to very low dietary sodium probably differ. The immediate and dramatic metabolic and hormonal responses that occur soon after marked salt depletion are not sustained, and few individuals are able to maintain such low levels of sodium intake for any appreciable period of time. Therefore, the effects of extremely low levels of sodium intake probably have limited relevance to dietary guidance policy for moderate sodium intakes in populations.

Research Needs

Many research opportunities were discussed, including the need to continue studies involving the role of salt in normal and pathophysiological functions, the identification of genes that determine the influence of salt on BP and other conditions, the characterization of individuals who carry these genetic mutations, and the study of the mechanisms involved in salt-related hypertension. Clinical and population studies were recommended in the following areas: improved measurements to assess trends in dietary intake and BP level, continued study of the effects of a moderate salt intake on both non-CVD and CVD outcomes, continued assessment of knowledge and attitudes regarding salt and health, and development of new strategies to reduce salt intake. There should be consideration of further analysis and follow-up of existing cohort data to look at sodium intake and health outcomes.

There was no support for a randomized clinical trial to determine whether dietary sodium reduces CVD morbidity/mortality for the general population. The cost would be prohibitive, and it would be difficult to isolate the effect of sodium reduction from other factors, including other dietary changes, exercise habits, and weight changes. Also, evidence shows that a moderate sodium intake, being one component of an overall strategy to reduce all CVD risk factors of the population, can have a salutary effect on health outcomes.

There was one suggestion for a randomized clinical trial to determine the effect of a reduced sodium intake on total mortality in older hypertensive individuals. However, ethical concerns in not offering pharmaceutical treatment for individuals with hypertension were raised.

Public Policy Considerations

A review of the history of dietary guidance policy regarding sodium intake showed consistent recommendation for a moderate sodium intake (1800 to 2400 mg) from the first US policy statement (the 1970 Senate Goals) to the most recent (the 1995 Dietary Guidelines for Americans). Several guiding principles have been useful in developing these dietary guidance policies: scientific evidence is central, with policy based on the totality of the evidence, not the outliers; individual people matter, and thus, distinctions between groups should be recognized; numbers are useful (eg, quantitative indicators can help guide consumers in the marketplace and guide the food industry to offer more food product choices that are consistent with the recommendations); food products count, and foods (not just nutrients) should be discussed; cultural factors and diverse dietary habits need to be considered; consistency in recommendations should be maintained whenever possible, both over time and among expert groups; and no harm to people should come from the recommendations. It was also suggested that in addition to salt and sodium intake, associated factors such as iodine intake should continue to be monitored.

The discussion emphasized the importance of the principles that for 3 decades have guided the development of dietary guidance public policy. It was agreed that information on diet and its relation to health influences consumer demand
and in turn changes the types of foods available in the marketplace.

Conclusion

The workshop reviewed evidence from the last decade about the relation between sodium intake and BP. The evidence continues to demonstrate that higher sodium intake is associated with higher BP levels and other cardiovascular conditions. Americans consume more sodium than they physiologically need. A population-wide strategy to reduce salt in the food supply is an important public health strategy that can lower BP among populations. The workshop speakers also recommended that research and surveillance must be ongoing to develop new information concerning diet, BP, and CVD.

[Information regarding the agenda, presenters, and discussants and an unabridged summary of the workshop may be found online at www.nhlbi.nih.gov.]

References


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