Salt, Blood Pressure, and Human Health

Michael H. Alderman

Abstract—The positive relation of sodium intake and blood pressure, first recognized a century ago, has been well established in ecological, epidemiological, and experimental human studies. Equally well established is the association of increasing blood pressure and cardiovascular morbidity and mortality. Indeed, the pharmacological capacity to reduce blood pressure has produced one of the great public health accomplishments of the 20th century. These two facts—the positive relation of blood pressure to strokes and heart attacks and the positive association of sodium intake to blood pressure—underlie the hypothesis that a reduction in sodium intake, by virtue of its hypotensive effect, might prevent strokes and heart attacks. Moreover, even if the effect on blood pressure were in the range of a 1- to 2-mm Hg decline in blood pressure for every 75- to 100-mmol difference in sodium intake, the impact of such a change, applied to the whole population, would be enormous. The problem with this appealing possibility is that a reduction in salt consumption of this magnitude has other—and sometimes adverse—health consequences. The question, therefore, is whether the beneficial hypotensive effects of sodium restriction will outweigh its hazards. Unfortunately, few data link sodium intake to health outcomes, and that which is available is inconsistent. Without knowledge of the sum of the multiple effects of a reduced sodium diet, no single universal prescription for sodium intake can be scientifically justified. (Hypertension. 2000;36:890-893.)

Key Words: blood pressure ● hypertension, sodium dependent ● sodium, dietary ● renin-angiotensin system ● morbidity ● mortality

The first data indicating that differences in dietary sodium might be related to and perhaps produce changes in blood pressure came from cross-cultural studies. It was found that in nonindustrialized societies, blood pressures tended to be lower and did not appear to rise with age. This was in sharp contrast to the experience in most industrialized nations. Sodium intake, among many other factors, differed sharply between “developed” and “undeveloped” communities. In fact, where people were largely confined to an economy of hunting and gathering, there was little access to salt, and, as a result, daily intake of sodium often was limited to 20 to 40 mmol of sodium. By contrast, citizens of acculturated societies, given free access to salt, invariably consumed between 100 and 200 mmol of sodium. These profound differences in salt intake were associated with very different blood pressure patterns.

Because ecological studies identified an association of salt intake to blood pressure, it was naturally suspected that an alteration in sodium intake could alter pressure. To test that hypothesis, investigators first explored the effect of change in sodium diet produced by migration on blood pressure. Usually, migrants from an nonindustrialized environment to an urban setting manifested an increase in blood pressure compared with those left behind. Among the myriad of changes associated with migration, it was found that sodium intake generally increased to the higher level ingested by the host cosmopolitan population. Thus, studies of migrants tended to reinforce the view that an increase in sodium intake was responsible for the rise in blood pressure.

Recently, however, findings among the Kuna Indian, initially residents of the San Blas Islands off Panama, have cast doubt on the notion that salt is the factor responsible for the change in blood pressure associated with acculturation. Some 50 years ago, when all Kuna people were confined to an island with minimal access to sodium, both sodium intake and lifelong pressures were low. Since then, the same Kuna people have established trade relations with the mainland, and sodium availability increased to the level as consumed by mainland Panamanians. Remarkably, however, these island people, mostly maintaining their traditional cultural pattern, with the exception of increased dietary sodium, maintained the pattern of low blood pressures and revealed no tendency for it to rise with age.

Observational Studies of Sodium and Blood Pressure

With recognition of the inherent weakness of ecological studies, attempts have been made to relate sodium intake to blood pressure in epidemiological studies that identify characteristics of individuals. Perhaps the most ambitious of these has been Intersalt Study, a cross-sectional assessment of >10 000 subjects in 52 locations around the world. In that
study, it was again found that, given free access, the vast majority of people will invariably consume between 100 and 200 mmol of sodium. Overall, no association between sodium intake and blood pressure was identified by the Intersalt investigators in an analysis limited to the 48 centers consuming >100 mmol/24 hours. When the 4 centers consuming 0.2 to 50 mmol/24 hours were included, a significant association of sodium to blood pressure emerged. Moreover, after stratifying by age, in societies with greater sodium excretion, blood pressure increased more with age compared with those communities in which less sodium was consumed. Because Intersalt was not a prospective longitudinal study, the notion that pressure rises with age is an extrapolation from the cross-sectional data.

**Experimental Studies of Sodium and Blood Pressure**

Recent efforts to sort out the salt-to-blood pressure relation have focused on experimental study. Animal studies have shown that sodium reduction can lower pressure, and, conversely, that sodium addition, as was the case in a study involving a dozen chimpanzees, can produce a significant difference in arterial pressure. In humans, the issue has been whether variation in sodium diet—generally aimed at producing a difference of 70 to 100 mmol of sodium or an amount equal to 50% to 75% of usual daily intake—would produce a measurable difference in blood pressure. However, there has been enormous variation between individuals regarding the effect of salt on pressure. This has given rise to the notion that the population includes “salt-sensitive” and “salt-insensitive” individuals.

Results of these clinical trials have been inconsistent. This has led to a sequence of meta-analyses designed to determine the most likely overall effect of dietary salt for a population. All meta-analyses are limited by the character of the studies included. Unfortunately, the well-designed and well-conducted studies involved considerable variation in sodium consumption, and many were of short duration; nevertheless, the most rigorous meta-analyses are in general agreement. The most recent indicates that among hypertensive and older subjects, a 3- to 5-mm Hg systolic and 1-mm Hg diastolic change in pressure is associated with a 75 to 100 mmol/24 hour difference in sodium intake. The effect on younger and normotensive subjects is less: 2 to 3 mm Hg for systolic and <1 mm Hg for diastolic. It would appear that the largest decline is achieved when small groups of subjects are studied for short periods of time. It has been difficult to sustain, over periods beyond a year, either the blood pressure or the sodium restriction in free-living subjects. It should be noted, however, that a sustained decrease of even a few millimeters of mercury could, assuming that the method of its achievement produced no harm, produce more reduction in morbidity and mortality rates than is currently achieved by treatment of high blood pressure. This possibility encourages advocates of sodium restriction.

Thus, a large reduction in sodium intake will produce a detectable decline in blood pressure. However, individual responses to the sodium reduction has varied widely in these studies.

**Other Effects of Sodium Restriction**

The next question is, of course, “what price is paid for this modest change in blood pressure?” Data from randomized controlled studies define several potentially important non-blood pressure effects of sodium restriction. Notably, increases in plasma renin activity (PRA), sympathetic nerve activity, insulin resistance, and fasting glucose have been documented. These may be adversely associated with the occurrence of cardiovascular disease (CVD) events. There are, of course, likely to be other effects as yet unrecognized that might positively or negatively influence cardiovascular health.

To determine the net effect of any medical intervention, all of its multiple effects must be considered. Exclusive attention to any one—blood pressure, for example—may result in having another unwanted effect overlooked. It is impossible to predict what effects might have been produced by changing daily diets with the sole objective of accommodating a halving of sodium intake, from 10 to 5 g.

Thus, medical interventions must be tested for their effects on human health, in addition to determining whether the intervention will be able to produce the targeted effect. For example, in an analogous situation, pregnant women were once advised to limit weight gain during pregnancy to <20 pounds to reduce the risk of rising blood pressure and eclampsia. In fact, this did produce those two desired outcomes. Unfortunately, and unexpectedly, limiting weight gain in pregnancy increased fetal morbidity and mortality rates. Women are no longer advised to limit weight gain in pregnancy.

**Overall Health Effects of Sodium Restriction**

The only way to assess the effect of sodium on health is to assess morbidity and mortality in human beings. Unfortunately, very few data currently exist linking salt intake to the duration or quality of life. Ecological data, linking sodium intake to life expectancy, are a rather weak and difficult-to-interpret source of guidance regarding individual experience. However, it may be of note that nonindustrialized societies with minimal sodium intake have short life spans. By contrast, in developed societies with rather uniform sodium intake (between 100 and 200 mmol/24 hours), life expectancy is nearly twice as long. Thus, ecological data provide no suggestion that a reduced sodium intake will extend life nor that a high sodium intake is inconsistent with a prolonged life expectancy.

Epidemiological data, in which individual sodium intake and health outcomes are linked, would be the next level of evidence to support the notion that dietary sodium might influence the length or quality of life. Unfortunately, despite intense interest in this issue, regrettably few solid data are available. The Scottish Heart Study, a population-based longitudinal study of 10,000 persons designed to assess the association of a variety of individual characteristics measured at baseline to subsequent morbidity and mortality, did include a questionnaire-derived measure of sodium intake. In this study, no association between sodium intake and cardiovascular or all-cause mortality was found.

In a subsequent study of 3000 treated hypertensive patients in whom pretreatment 24-hour sodium intake measured after advice to refrain from excess salt intake for 5 days and baseline PRA were measured, there was a stepwise, significant, and independent relation between level of sodium measured in 24-hour urine and...
subsequent strokes and heart attacks. Although this relation held for the group as a whole, after stratification it was only significant for men, who accounted for 75% of events. Among men, this relation persisted after stratification by age, ventricular mass, and race (Figure). Not unexpectedly, in view of the inverse association of sodium intake and PRA, a good deal of the association of sodium to events was accounted for by level of PRA. Nevertheless, even after accounting for PRA, sodium intake retained an independent association with CVD events.

Our group also analyzed the National Heath and Nutrition Examination Survey (NHANES) I epidemiological follow-up data to further explore the relation of sodium intake to CVD and all-cause mortality. In this study of 14,000 adults selected randomly to represent the entire US population, sodium intake was estimated on the basis of a 24-hour dietary recall. Again, sodium intake proved to be inversely related to CVD mortality. Those in the lowest quartile of sodium intake were 20% more likely to die of a cardiovascular cause than were those in the highest quartile of sodium consumers.

He and colleagues reanalyzed the same NHANES I epidemiological follow-up data. Presumably, although not stated, their analysis of the entire data set did not differ from that already published. Perhaps to explore the suggestion we had previously made that no single sodium intake was likely to be optimal for all people and that heterogeneity as the result of environment, genetics, and behavior is likely to characterize the association of sodium intake to health outcomes, these investigators dissected the data for subgroup assessment. By eliminating participants with prior evidence of CVD and removing a large fraction of cardiovascular end points from consideration, they found that the 28% of subjects in the remaining subgroup, who were obese, expressed a direct relation of sodium to morbid and mortal outcomes. For the 72% of this subset who were not obese, no association of sodium intake to the restricted definition of CVD morbidity and mortality was found (Table). These data are consistent with the expectation that there would be heterogeneity in the relation of sodium intake to health outcomes.

Finally, an analysis of the available Multiple Risk Factor Intervention Trial data, available only in abstract, found no relation between sodium intake, estimated by an overnight urine collection, and subsequent CVD events or mortality, although the data appear to suggest a tendency for those consuming the least sodium to have the highest event rates.

Each of these epidemiological studies share the weakness associated with nonexperimental techniques. Unrecognized confounders that influence both the exposure variable and the outcome may have distorted the results. All studies attempt to control for recognized confounders. No matter how diligent, however, this may be imperfect. Moreover, all these studies are based on a single determination of sodium intake. The inevitable intraindividual variation in such measures would tend to diminish any association between an exposure and outcomes. The fact that in 3 of the 5 available studies a significant independent association between salt intake and outcome was found suggests that the available data may underestimate the true strength of the association of sodium intake to morbidity and mortality. In sum, the available data suggest that the association of sodium intake to health outcomes reflected in morbidity and mortality rates is modest and inconsistent. Therefore, on the basis of the existing evidence, it seems highly unlikely that any single dietary sodium intake will be appropriate or desirable for each member of an entire population.

What Further Data Are Needed
The gold standard for assessing the value of any medical or health intervention is the randomized clinical trial. In this
Multivariate Relative Risk (95% Confidence Interval) of CVD and Total Mortality Associated With 100-mmol Increase in Dietary Sodium Intake Among Nonoverweight and Overweight Participants

<table>
<thead>
<tr>
<th>Sodium-to-energy ratio, 100 mmol/7452 kJ</th>
<th>Nonoverweight (n=6797)</th>
<th>Overweight (n=2688)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke incidence</td>
<td>0.98 (0.83–1.16)</td>
<td>1.32 (1.07–1.64)</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>0.90 (0.63–1.28)</td>
<td>1.89 (1.31–2.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHD incidence</td>
<td>0.95 (0.83–1.10)</td>
<td>1.06 (0.88–1.29)</td>
<td>0.39</td>
</tr>
<tr>
<td>CHD mortality</td>
<td>1.07 (0.87–1.31)</td>
<td>1.44 (1.14–1.81)</td>
<td>0.07</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>1.02 (0.85–1.22)</td>
<td>1.61 (1.32–1.96)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mortality from all causes</td>
<td>1.00 (0.90–1.11)</td>
<td>1.39 (1.23–1.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dietary sodium intake, 100 mmol/d</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>0.99 (0.81–1.21)</td>
<td>1.39 (1.09–1.77)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>0.82 (0.55–1.22)</td>
<td>1.98 (1.25–3.14)</td>
<td>0.003</td>
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<tr>
<td>CHD incidence</td>
<td>0.96 (0.86–1.08)</td>
<td>0.94 (0.76–1.17)</td>
<td>0.87</td>
</tr>
<tr>
<td>CHD mortality</td>
<td>1.07 (0.89–1.28)</td>
<td>1.29 (1.01–1.64)</td>
<td>0.22</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>1.00 (0.84–1.19)</td>
<td>1.45 (1.20–1.75)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mortality from all causes</td>
<td>0.98 (0.88–1.09)</td>
<td>1.32 (1.16–1.50)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are stratified by birth cohort and adjusted for age, sex, race, systolic blood pressure, serum cholesterol level, body mass index, history of diabetes, diuretic use, physical activity, level of education, regular alcohol consumption, current cigarette smoking, and total energy intake. Reprinted with permission of the American Medical Association (JAMA 1999;282:2027–2034). Copyrighted 1999, American Medical Association.

*P value for interaction between sodium intake and body weight (nonoverweight vs overweight).

Methods, participants are randomly allocated to the experimental and control arms of the study. The goal is to have similar subjects, selected without bias, exposed to regimens that differ only in terms of the intervention in question. No such study has been designed to assess the effect of sodium intake on cardiovascular morbidity and mortality. However, several randomized studies have reported some health outcomes. Whelton and others have reported no difference in headaches, hospitalizations, and so forth, between the low sodium/weight loss groups and the control population among mildly hypertensive subjects. Although 8 deaths occurred in this study, the distribution of those deaths was not reported.

Conclusions

In summary, little controversy surrounds much of what is known about the effects of dietary sodium. Substantial variation in intake (75 to 100 mmol/24 hours) can produce measurable but modest changes in blood pressure. However, that effect is variable, and subjects can be arbitrarily classified as salt sensitive and salt resistant. The effect appears to be more substantial in older subjects and in those with higher pressures. However, the decision to adopt a low sodium diet should be made with awareness that there is no evidence that this approach to blood pressure reduction is either safe, in terms of ultimate health impact, or that it is as effective in producing cardioprotection as has been proven for some drug therapies.

I believe that a dietary salt recommendation should reflect knowledge of the sum of its multiple consequences in terms of the quality and duration of human life. Without such knowledge, no single universal dietary recommendation can be scientifically justified.

References

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