Dietary Sodium, Surrogate Markers, and Human Health

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In classical Rome, the word for salt (salary), reflected the value ascribed to this essential dietary component. In this century, a more specific understanding of the relationship of sodium to human physiology has been established through ecological, epidemiological, and experimental studies. Because sodium intake was found to be linked to blood pressure, the potential health effect of dietary sodium has become a matter of both clinical and public health significance.

Heart attack and stroke, the principle morbid and mortal consequences of cardiovascular disease, are both, more likely to occur in persons with higher than lower blood pressure.

The first data indicating that differences in dietary sodium might be related to, and perhaps produce changes in blood pressure derived from cross cultural studies.[1] It was found that, in unacculturated 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 factors, differed sharply between "developed" and "undeveloped" communities. In fact, societies largely confined to an economy of hunting and gathering, had little access to salt, and therefore consumed 20 to 40 mmols of sodium per day. By contrast, citizens of acculturated societies, invariably, given free access to salt, consumed between 100 and 200 mmols of sodium. These profound differences in salt intake were associated with very different blood pressure patterns, but also very different expectations of life. Hunters and gatherers, with low sodium intake, and low blood pressure, had short lives. By contrast, those with markedly greater sodium intake had higher blood pressures, and much longer life expectancies. Indeed, the Japanese, enjoying the world's longest life, ingest more salt than most of the world's people.

Because salt intake could influence blood volume, and therefore, blood pressure, it was hypothesized that alteration in sodium intake could alter pressure. To test that hypothesis, investigators explored the effect of migration on both blood pressure and sodium intake. They found that, usually, migrants from an unacculturated environment to an urban setting experienced an increase in blood pressure compared to those left behind.[2] Among the myriad of changes associated with migration, it was found that sodium intake generally increased to the level enjoyed by the host population. Thus, studies of migrants tended to support the view that an increase in sodium intake was responsible for the rise in blood pressure.

Recently, however, findings among the Kuna Indians, initially island residents near the coast of Panama, have cast doubt upon the notion that salt is the factor responsible for the change in pressure associated with acculturation.[3] Some 50 years ago, when all Kuna people were confined to an island with minimal access to sodium, both sodium intake and pressures were low. Then 40 years later, two important changes came to the Kuna people. Part of the population moved to Panama where, as expected, both sodium intake and blood pressures were found to be much higher than those measured 40 years earlier. The surprising finding, however, related to those who had stayed behind. Having established trade relations with the mainland, sodium availability had increased, and intake rose to the same level as the mainland Panama. Remarkably,

however, these island people, mostly maintaining the cultural pattern of their ancestors, with the exception dietary sodium, still had low blood pressures and showed no tendency for it to rise with age. Clearly, factors other than sodium must have been responsible for the rise in pressure associated with migration.

Recognizing 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, involving the standardized assessment of more than 10,000 subjects in 52 locations around the world.[4] In that study, it was again found that, given free access, people will invariably consume between 100 and 200 mmols of sodium. Overall, no association between sodium intake and blood pressure was identified by the Intersalt investigators. However after stratifying by age groups, they found that in societies with greater sodium intake, blood pressure appeared to rise more with advancing age than in settings where less sodium was consumed. Because Intersalt was a cross sectional, and not a prospective longitudinal study, the notion that pressure rises with age is an extrapolation from the available data that would need confirmation in a prospective cohort study that actually measured sodium intake and blood pressure.

Because of the inability of observational studies to determine whether there was a causal relation of sodium intake and blood pressure, experimental studies were needed. Animal studies, including studies of a dozen apes, have generated a large body of data suggesting that a marked reduction in salt intake can produce a significant difference in arterial pressure.[5] In humans, the issue has been whether variation in sodium diet - generally aimed at producing a difference of 70 -100mmols of sodium or an amount equal to 50-75% of usual daily intake - would produce a measurable difference in blood pressure. Because of the difficulty in achieving and maintaining differences in sodium intake of this magnitude, many of the studies have resorted to sodium supplementation to create the gradient in short term studies. One uniform finding has been enormous variation between individuals of the effect of salt on pressure. This has given rise to the notion that the population includes salt "sensitive" and "insensitive" individuals. Attempts to distinguish such groups suggest that response to sodium variation is less likely to be dichotomous - responders vs. non-responders - but rather that the response to salt is distributed continuously and that any effort to separate two distinct groups is highly artificial.

Results of these many studies have been inconsistent. This has led to a sequence of meta-analyses designed to determine what effect of dietary salt is likely to mean for a population. Several rigorous meta-analysis are in general agreement. The most recent indicates that a 2-3 mmHg systolic, and about 1 mmHg Diastolic change in pressure is associated with a 75-100 mmol/24hour difference in sodium intake.[6] These studies reflect the experience in volunteers participating in well designed and managed study protocols. It would appear that the largest decline is achieved when small groups of subjects are studied for short periods of time. Whether blood pressure reductions of this magnitude would also be obtainable in the general, free living population remains to be determined.

Thus, good evidence supports the view that a large reduction, or at least a large difference in sodium intake, will produce, in aggregate, a detectable decline in blood pressure. Individual responses to the sodium reduction has varied widely in these studies.

The next question is, of course, "what price is paid for this modest change in blood pressure?" Understandably, when diet is modified to such a marked extent, it is not surprising that other physiological effects will occur. Although most of the salt deprivation research emanates from centers concerned primarily with the blood pressure consequences of dietary sodium manipulation, some data, again from randomized controlled studies, defines 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.[6] These are all adversely associated with the occurrence of cardiovascular disease events. For example, it has been shown that, in hypertensive subjects, increase in plasma renin activity, reflecting activation of the Renin-angiotensin-aldosterone System, bears a

robust, significant, independent, and step-wise relationship to cardiovascular events.[7] Similar data links these other non-blood pressure effects to adverse stroke and heart attack experience.

The value of any medical intervention is the result of the sum of all of its multiple effects. Exclusive attention to any one effect - blood pressure for example - may result in having another unwanted effect overlooked. It is impossible to predict what the sum total of effects might be of an intervention as pervasive as dietary change. Thus, medical interventions need to be tested for their effects on human health, in addition to determining whether the intervention will be able to produce the targeted effect. Indeed, there are several examples of medical therapies which achieve their designed goal, but had sufficiently important adverse effects to render its use unacceptable. Most relevant to the sodium story, however, is the consequence of recommendations to contain weight gain during pregnancy to less than 20 pounds. It made perfectly good sense to restrict weight gain to reduce the risk of rising blood pressure and eclampsia. In fact, this strategy did produce those two desired outcomes. Unfortunately, however, limiting weight gain in pregnancy increased fetal morbidity and mortality. As a result, obstetricians no longer advise women to limit weight gain in pregnancy.

The only means to assess effect on health is to study the effect of sodium on morbidity and mortality in human beings. Unfortunately, very little data currently exists linking salt intake to the duration or quality of life. Animal data, which may or may not be relevant to human experience, suggests that animals deprived of sodium fail to thrive and have rather shortened life expectancy. Ecological data, linking sodium intake to life expectancy, is a rather weak source of guidance regarding individual experience. However, it may be of note that non-acculturated societies with minimal sodium intake, have short life spans. By contrast, in developed societies, with rather uniform sodium intake (between 100 - 200 mmols/24hours), life expectancy is nearly twice as long. Moreover, the Japanese, whose sodium intake is quite high (perhaps 12 -15 grams/day) are world leaders in life expectancy. Thus, ecological data provides 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 little solid data is 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.[8] In this study, no association between sodium intake and cardiovascular or all cause mortality was found. A subsequent study of 3000 treated hypertensive patients, in whom pretreatment 24 hour sodium intake, and baseline plasma renin activity were measured, there was a stepwise, significant, and independent relationship between level of sodium measured in a 24 hour urine, and subsequent strokes and heart attacks.[9] Not unexpectedly, in view of the inverse relation 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 NHANES 1 Epidemiological Follow-up data to further explore the relationship of sodium intake to CVD and all cause mortality.[10] In this study of 14,00 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. Finally, an analysis of the available MRFIT data, available only in abstract, found no relationship between sodium intake, estimated by an overnight urine collection, and subsequent CVD events or mortality, although the data appears to suggest a tendency for those consuming the least sodium to have the highest event rates.[11]

All of these epidemiological studies share the weakness associated with non-experimental 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 upon a single determination of sodium intake. The inevitable intraindividual variation in such measures would tend to diminish any association between an exposure an outcomes. The fact that in 2 of the 4 studies, an association was indeed found, suggests that the available data may underestimate the true strength of the inverse association of sodium intake and morbidity and mortality. Thus, while the weight of the available evidence suggests that more rather than less sodium may be better, it is surely not a sufficient basis upon which to make a general recommendation.

The gold standard for assessing the value of any medical or health intervention is the randomized clinical trial. In this method, 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 morbidity and mortality. Several randomized studies have, however, reported some health outcomes. Whelton and others have reported no difference in headaches, hospitalizations, etc, between the low sodium/weight loss groups and the control population among mildly hypertensive subjects.[12] Although 8 deaths occurred in this study, the distribution of those deaths was not reported. A randomized study of sodium restriction as a supplement to antihypertensive therapy suggested that, in combination with diuretic therapy, a low sodium diet may contribute to sexual dysfunction in men.[13]

In summary, little controversy surrounds much of what is known about the effects of dietary sodium. A minimal amount is necessary to sustain life. Substantial variation in intake (75 - 100 mmols/24 hours) can produce measurable, but modest changes in blood pressure in groups. However, that effect is variable, and subjects have been arbitrarily described as salt sensitive and resistant. Changes of sodium intake also influence insulin resistance, the renin-angiotensin-aldosterone axis, and sympathetic nerve activity. The global impact reflecting the sum of these multiple consequences of variation in dietary sodium on the quality and duration of human life is unknown. Absent knowledge of whether a particular sodium intake would produce health benefit or harm suggests that universal dietary guidelines are unwarranted at this time.

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