Dietary sodium and cardiovascular outcomes: A rational approach

S Brian Penner MD[1], Norm RC Campbell MD[2], Arun Chockalingam PhD[3], Kelly Zarnke MD[4], Bruce Van Vliet PhD[5]

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Hypertension, the leading risk factor for mortality in the world, affects nearly one in four Canadians. There is substantive evidence that high dietary sodium contributes to hypertension. Animal studies consistently demonstrate increased blood pressure and cardiovascular morbidity and mortality with high dietary sodium intake. Evidence of the adverse health effects in humans associated with increased sodium intake is accumulating rapidly. Previously, limitations on sodium consumption were recommended only for those identifiable groups of people shown to be at higher risk. With the lifetime risk of developing hypertension being more than 90% in an average lifespan, the need for a population-based approach to reducing hypertension is clear. The present paper reviews the evidence of sodium and cardiovascular disease, resulting in the 2007 Canadian Hypertension Education Program recommendation of daily intake of less than 100 mmol of sodium in both normotensive and hypertensive adults.

Key Words: *Diet; Education; Hypertension; Population health; Prevention of blood pressure elevation; Sodium*

Le sodium d'origine alimentaire et la santé cardiovasculaire : Approche rationnelle

L'hypertension artérielle (HTA), principal facteur de risque de mortalité dans le monde, touche presque une personne sur quatre au Canada. D'après des données solides, un apport élevé de sodium dans l'alimentation n'est pas étranger à l'apparition d'HTA. Des études expérimentales sur animal de différentes espèces montrent invariablement qu'une alimentation riche en sodium est associée à une augmentation de la pression artérielle ainsi que de la morbidité et de la mortalité d'origine cardiovasculaire. Le faisceau d'arguments sur les effets nocifs de la prise excessive de sodium chez l'homme augmente rapidement. Autrefois, les restrictions concernant la consommation de sodium se limitaient aux seuls groupes bien établis, connus pour être à risque élevé. Comme le risque d'être atteint d'hypertension au cours d'une vie normale est supérieur à 90 %, la nécessité d'élaborer une approche visant la population s'impose d'elle-même. Le présent article passe en revue les données probantes sur l'apport de sodium et les maladies cardiovasculaires, qui ont abouti aux recommandations 2007 du Programme d'éducation canadien sur l'hypertension, selon lesquelles la prise quotidienne de sodium devrait être inférieure à 100 mmol, et ce, tant chez les adultes normotendus que chez les adultes hypertendus.

Sodium, a nutrient found in various types of salt, is consumed throughout the world. Table salt (a common source of sodium) has been closely linked with humans historically, and recently, it has been found in increasing amounts in our food supply. In part, this is due to the increased consumption of processed foods containing significant quantities of sodium. Increased dietary sodium intake has been convincingly linked with hypertension in animal studies, human clinical studies and population-based observational studies. In the media and in information available to the public, however, this link is identified as controversial, and the health hazards of high dietary sodium intake are not clearly delineated. Health and scientific organizations around the world are promoting increasing levels of awareness and action throughout all levels of society. Critical assessment of the literature in Canada and elsewhere has demonstrated a correlation between blood pressure (BP) and high sodium intake in the normotensive and the previously linked hypertensive populations. This has resulted in revised guidelines from the Canadian Hypertension Education Program (CHEP) in 2007 (pages 529-538 of the current issue of the *Journal* [1]), which now recommend a goal sodium intake of less than 100 mmol of sodium per day to improve cardiovascular outcomes for Canadians.

Evidence from animals

The impact of excess dietary sodium on the cardiovascular system has been extensively studied in experimental animal models. The ability of increased sodium intake to raise BP has been demonstrated in a number of species (eg, baboons [2], chimpanzees [3], dogs [4], green monkeys [5], mice [6], pigs [7], rabbits [8] and rats [9]). By far, however, the most extensive investigations of the effects of sodium and the underlying mechanisms have been conducted in rats. In addition to the

[1]*Departments of Medicine, and Pharmacology and Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba;* [2]*Departments of Medicine, Community Health Sciences, and Pharmacology and Therapeutics, Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta;* [3]*Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia;* [4]*Departments of Medicine, Epidemiology and Biostatistics, University of Western Ontario, London, Ontario;* [5]*Basic Sciences Division, Faculty of Medicine, Memorial University of Newfoundland, St John's, Newfoundland and Labrador*

Correspondence: Dr S Brian Penner, Health Science Centre, GG 441, 820 Sherbrook Street, Winnipeg, Manitoba R3A 1R9. Telephone 204-787-3633, fax 204-787-4826, e-mail bpenner@cc.umanitoba.ca

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effect of sodium on BP, animal studies have also clearly documented the ability of excess sodium intake to cause hypertensive target organ damage, including hypertrophy and structural changes in the heart (10-14), kidney (4,9,10,12,14-18) and vasculature (9,16,19-22), and to promote hypertensive encephalopathy (23), stroke (22,24), heart failure (25) and premature death (9,10,16,23,25-27). Most important, many of the effects of excess sodium intake on target organ damage and mortality can be demonstrated to occur under conditions in which the effects of sodium on BP are absent or controlled for (12,13,19). Thus, the results of animal studies have strongly supported the concept of excess sodium intake contributing to cardiovascular disease (CVD) by both BP-dependent and BP-independent mechanisms (28).

It is of note that studies using extremely low salt or salt-deficient diets can be harmful. Ivanovski et al (29) fed seven-week-old apolipoprotein E-deficient (genetically atherosclerotic-prone) mice a very low sodium diet containing only slightly greater than 5% of a normal sodium diet. In these genetically modified mice, atherosclerotic changes were accelerated (29). Although these results are contrary to the general literature, it is a clear reminder that if one subjects almost any model to an extreme of normal, adverse consequences are likely. This emphasizes the need for using dietary interventions in animal studies that can be extrapolated to humans.

Animal studies have also provided information regarding ways in which the effects of excess sodium intake may manifest in humans. In particular, the results of animal studies demonstrate that it is important to distinguish between acute and long-term BP responses to sodium, because these two extremes are associated with distinct characteristics and may be mediated by different mechanisms (30). At one extreme, changes in sodium intake have frequently been observed to cause changes in BP within several days to several weeks (6,30-34), a time scale that has most often been used in investigations of salt sensitivity in humans (35-38). Because sodium-induced changes in BP on this time scale are rapidly reversible (30), they may be assessed using short periods of either sodium loading or restriction. At the other extreme, a much slower progression of salt-induced hypertension has also been described. In chimpanzees (3) fed a high-sodium diet for 20 months, BP and pulse pressure rose slowly and progressively in a susceptible fraction of the population. A similar effect on BP has been documented in the baboon (2) and in outbred rats (9,39) during a one-year exposure to elevated dietary sodium. When outbred rats were selectively bred for this trait (eg, the Dahl [16,26,30,40] and Sabra [41,42] strains), all individuals exhibited a form of salt sensitivity consisting of a severe and accelerated form of progressive salt-induced hypertension. In humans, a corresponding slow and progressive effect of sodium on BP is evident as a salt dependency of age-associated BP changes (43-45).

Animal studies have also demonstrated several characteristics of the epidemiology of salt-induced hypertension that would be difficult to investigate directly in humans. They include the following observations.

- The dose-response relationship of the effect of dietary sodium on BP is continuous over a wide range of salt levels (9,26,39,46); there is no obvious ceiling above which dietary sodium begins to exert its influence on BP. Even modest increases in sodium intake can lead to increased BP and mortality if sustained long enough (9,10,39).

- Although it is common to classify individuals as either salt-sensitive or salt-resistant, an individual's BP response to salt may increase with the duration and level of salt exposure (9,26,39,46). Within a population of outbred (Sprague-Dawley) rats, all individuals exhibited unequivocal signs of salt sensitivity when exposed to sodium for one year (approximately 40% of their lifespan) (9). Thus, classifications based on short-term increases in sodium intake have the potential to underestimate the proportion of individuals who will eventually be (or may have already been) affected by salt. As discussed above, the acute and long-term responses to increased sodium intake appear to represent distinct phenomena mediated by different mechanisms (30). While the two have been shown to be related in Dahl salt-sensitive rats (30), the ability of short-term testing to predict susceptibility to progressive salt-induced hypertension has not been well established.

- The effects of long-term sodium exposure on BP often may not be rapidly reversible, if at all (3,27,30), and the ability of short-term sodium restriction to predict susceptibility to progressive salt-induced hypertension caused by long-term sodium exposure has not been well established. Thus, investigations of short-term BP responses to sodium restriction have the potential to underestimate the long-term effects and complete impact of excess sodium intake on BP.

Thus, animal studies strongly support the principle that excess sodium intake can promote hypertension, target organ damage and premature death. These results are uniquely instructive because they have been collected under highly controlled experimental conditions over a wide range of sodium intakes and, in some cases, durations of sodium exposure ranging up to significant fractions of an animal's lifespan. Such conditions are highly relevant to the effects of sodium in humans, but would be difficult to achieve in clinical studies. In addition to confirming the adverse consequences of excess sodium intake, the results of such investigations also provide insight into the fundamental characteristics of salt sensitivity in animals, which may have bearing on the study of salt sensitivity in humans.

Evidence in humans

Dietary sodium intake is only one of multiple determinants of BP and BP is only one of multiple risk factors for atherosclerotic disease. With atherosclerotic disease being only one of multiple causes of death and major morbidities, the assessment of evidence for a casual relationship among sodium, atherosclerotic disease and mortality is complex. Assessment of this multistepped relationship is undoubtedly vulnerable to potential confounding effects of many possible covariates. Furthermore, many potential covariates exhibit variability in themselves and thus introduce issues related to reliable measurement. An appropriate and meaningful way to attempt to support or refute this complex causal hypothesis in

noninterventional (observational) research is through comprehensive multivariable analyses.

Not surprisingly, in recent years, several observational studies (47-50), in particular, three from one group and one other, have suggested that low salt levels may in fact be harmful, or that higher sodium intake does not alter BP or result in adverse outcomes. It is important to note that all of the following four observational studies face many of the same issues. First, not all potential confounders are known, and those that are not known cannot obviously be measured. This is particularly relevant to analyses of existing databases constructed for other research questions. Second, of the potential confounders that are known, not all have been measured, and if they are not measured, they cannot be included in adjusted analyses. This, too, is relevant in retrospective analyses of previously collected data for reasons other than the question at hand. Third, of those potential confounders that are known and measured, not all are measured well. Casual variable measurement may be vulnerable to both systematic (biased) and random errors. Adjustments based on the former may lead to spurious, erroneous results, while the latter may lead to failing to detect relationships that truly exist. Furthermore, with complex confounders such as lipid fractions or socioeconomic status, the decision regarding which of several component(s) to include is not always clear. Thus, for variables not measured comprehensively, attempts at adjustment will be incomplete. Fourth, of those covariates known and measured well, the most appropriate handling of adjustments in the context of assessing causation is not always clear. Many statistical issues arise, such as the handling of assumptions implicit in stepwise models, assumptions regarding linearity of relationships and testing for interactions and colinearity among many variables.

Using an appraisal method of assessing multivariable models developed by Concato et al (51), we found that of nine applicable criteria, the following four papers met four to six of these, suggesting that each had three to five criteria deficiencies; a few of these deficiencies that are noteworthy for each paper are summarized below.

Alderman et al (47) in 1995 used National Health and Nutrition Examination Survey (NHANES) I data to imply that increased cardiac events were associated with low sodium intake. However, it appears that some important potential confounders were not measured or included in the analyses of this study, including the presence of diabetes, lipid fractions and smoking history. In some of the analyses, important confounders have been eliminated. These considerations increase the likelihood that residual confounding effects may exist. Concerns also arise because of the multiplicity of analyses without appropriate adjustments for the number of comparisons made, and because of the focus on myocardial infarction as the primary outcome when more extensive data on all vascular outcomes are available.

Subsequently, two further papers (48,49) came out with another analysis of this data set, the second using NHANES II data (49). It is probable that bias in the assessment of sodium intake occurred; adjustment of both measured and well-recognized confounders of mortality outcomes is incomplete, and the likelihood of the confounding of exposure by indication is not fully addressed. These important methodological shortfalls limit conclusions that may be drawn from these analyses of NHANES I data. The most recent article by some of the same investigators (49) used an adjusted analysis in this observational study that was quite robust. However, the truncation of more than 20% of the study population may have excluded those who were likely the most susceptible to the adverse effects of excess dietary sodium. In addition, given the inequality of measured confounders between the low and high sodium intake strata, the potential for residual but unanalyzable confounding effects on account of unmeasured but identifiable variables exists. Last, the Scottish heart study (50) markedly and incompletely adjusted analyses and the possible ceiling/threshold effects limit due to low event rates in a younger study population, concluding that sodium intake has no adverse relationship with cardiovascular or mortal outcomes in this study population, even though a high sodium intake was present.

In summary, of the four main studies refuting the concept of high dietary sodium intake presenting health hazards, only one had a robust analysis with the possibility of a serious population bias, while the others had significant methodological shortcomings. In contrast, several prominent analyses have emerged recently that support the hazards of high dietary sodium intake.

He and MacGregor (52) completed a meta-analysis published through the Cochrane library on the effects of salt on BP. This analysis showed a BP reduction of 5.1/2.7 mmHg for a 78 mmol/day reduction in dietary sodium intake and a BP reduction of 7.2/3.8 mmHg for a 100 mmol/day reduction in dietary sodium intake in hypertensive patients. Of particular note was a BP reduction of 2/1 mmHg associated with a 74 mmol/day decrease in dietary sodium intake, with a further BP reduction of 3.6/1.7 mmHg if the dietary sodium intake was reduced by 100 mmol/day in normotensive individuals. A subsequent meta-analysis (53) by the National Institute for Clinical Evaluation published in 2006 showed similar reductions in BP in hypertensive patients, but the prevention of hypertension was not considered. Chang et al (54) completed a prospective study that examined the effects of reduced-sodium and potassium-enriched diets on cardiovascular mortality in elderly men. Five kitchens in a veteran retirement home were randomly assigned to either a control, or normal salt, group or a potassium-enriched, low-salt group. A total of 1981 veterans were included in the analysis and followed for approximately 31 months. CVD mortality in the control group was 20.5 per 1000 (66 deaths in 3218 person-years) and in the experimental group it was 13.1 per 1000 (27 deaths in 2057 person-years). A significant reduction in CVD mortality with an age-adjusted hazard ratio of 0.59 (95% CI 37 to 0.95) was observed. Veterans in the experimental group lived longer and spent less time in inpatient care for CVD. There was an increase in potassium and a moderate reduction in sodium intake. Although there are potential methodology problems, such as the measurement of salt balance using only sodium to creatinine ratios and potassium to creatinine ratios, this is still consistent with all the other data indicating a benefit to lowering sodium intake. This is also the first long-term controlled study to look at this issue.

There are isolated populations with low sodium intake that do not have the same progressive rise in BP as observed in the general population. One of the most famous indigenous populations is the Yanomamo Indians living between Venezuela and Brazil, with a mean salt intake of less than 0.5 g/day and a mean BP in 50-year-old men of 100/64 mmHg

(55). The converse has also been well described, particularly in northern Japan, where the inhabitants had a daily salt intake in excess of 27 g/day (56,57). Associated with this was the highest incidence of cerebral hemorrhage observed in any population.

Perhaps the most heartening evidence comes from a practical implementation of a population-based dietary sodium reduction in Finland. Due to very high levels of cardiovascular-related mortality in the late 1970s, the Finnish government undertook mandatory sodium reduction in the food supply as a mechanism for controlling cardiovascular mortality. The effects were profound, with a significant drop in cardiovascular mortality seen in Finland since 1979, and dramatic reductions in 24 h urinary sodium secretion (58,59).

In summary, there is strong observational evidence and some clinical evidence that reducing dietary sodium intake has substantial health benefits, particularly in the areas of CVD and relating to a primary cardiovascular risk factor, namely, hypertension.

Implications for Canada

After an extensive review of the literature, a number of scientific organizations have recommended the limitation of dietary salt to less than 100 mmol/day, or 2300 mg/day of sodium. The organizations include the CHEP (1), the World Health Organization (60), the US Department of Health and Human Services, and the United States Department of Agriculture (61), as well as the American Heart Association (62). In the United Kingdom, substantial sodium reductions have been recommended and are being implemented (63).

A recent survey found that adult Canadians consume, on average, 3100 mg/day of sodium, excluding the salt added in cooking (64). Within this population, there are other confounding variables that complicate the picture, such as smoking, obesity, genetic variability and the variable salt intake in any given individual's diet. It is estimated that more than 70% of dietary sodium intake in Canada comes from sodium additives to food (65). The recommended daily intake of sodium accepted by the Canadian government is 1300 mg to 2300 mg daily (64). Approximately one in four Canadians has hypertension, and the lifetime risk for developing hypertension in an average lifespan is more than 90% (66,67). As discussed, evidence from animal and human studies strongly supports the prevention of hypertension and other cardiovascular risk factors by reducing dietary sodium intake. A recent analysis by Joffres et al (68) used Canadian Heart Health Surveys data to calculate data specific to Canada. Reducing dietary sodium additives by 80 mmol/day would result in the average sodium consumption being consistent with Canadian recommendations for best health. This reduction is estimated to decrease prevalence of hypertension by 30%, resulting in one million fewer hypertensive people, and almost double the treatment and control rate. The direct cost savings from fewer physician visits and laboratory tests, and less medication use are estimated to be $430 to $538 million per year. Much more substantive cost savings would occur due to reduced CVD and indirect costs. Clearly, reducing dietary sodium would have major health care benefits and result in cost savings for Canada.

Based on the scientific evidence, the CHEP has recommended a sodium intake goal of less than 100 mmol/day to both prevent and manage hypertension.

CONCLUSIONS

Increased sodium intake is associated with adverse outcomes in animal models across a broad range of species both with short-term and long-term exposure, and with BP-dependent and BP-independent responses. In humans, the extremes of intake are most definitive in demonstrating either benefit with lower sodium intake or adverse cardiovascular events with high sodium consumption. Review of the extensive literature available, including a few outlying observational studies, has demonstrated that a decreased sodium intake across populations of both hypertensive and normotensive adults results in significant decreases in BP, with resulting decreases in CVD-related mortality and costs. A review of global evidence and global policies to date indicates that there is growing support for population reductions of dietary sodium intake. Limiting the total daily sodium intake to less than 100 mmol/day, as recommended by the CHEP, is well supported by extensive literature and can prevent substantial numbers of Canadians from becoming hypertensive and suffering from the associated complications.

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