Dietary Sodium: A Perspective on Recent Sodium Evidence—Its Interpretation and Controversies

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The World Health Organization (WHO) aided by investigators from the Cochrane Collaboration published an updated review of randomized trials and prospective cohort studies on dietary sodium conducted in healthy populations.[1,2] Their quantitative analyses indicated that sodium intake <2000 mg/d was associated with reductions in blood pressure. In cohort studies, higher sodium intake was associated with a 24% higher risk of stroke, a 63% higher risk of stroke death, and a 32% higher risk of coronary heart disease death. There was inadequate statistical power to address other endpoints in the analysis. There was no adverse effect on lipids, catecholamines, or renal function in adults with less sodium intake. High dietary sodium intake caused higher blood pressure in children.* These findings resulted in a renewed WHO recommendation for dietary sodium to be <2000 mg/d in adults and to even less in children based on their relatively lower caloric requirements. The American Heart Association also recently updated its comprehensive review of the literature reiterating its recommendation for dietary sodium to be less than 1500 mg/d.[3]

Biomedical, evolutionary, and aspects of epidemiologic and clinical research were not included in the WHO review but also strongly support harmful effects of "higher than physiological levels" of dietary sodium.[2–12] A wide variety of animal species exposed to higher than physiological levels of dietary sodium develop hypertension, vascular, cardiac, and renal adverse outcomes.[4,13] To our knowledge, barring settings of acute sodium depletion, there is no animal species in which higher than physiological sodium intake improves health, and, in all settings, sodium-induced hypertension is harmful. Increased dietary sodium is a procarcinogen in animal studies (gastric cancer) and is associated with gastric cancer in human studies,[14,15] particularly in association with *Helicobacter pylori* infection. Adult human physiological sodium needs are <1000 mg based on analyses in "hunter gather" populations or analyses of "primitive" diets.[16,17] Societies where sodium intakes remain <1000 mg have no increase in blood pressure with age and hypertension is uncommon.[4] If people from the hunter-gather societies who consume physiological levels of dietary sodium migrate to communities where there is high sodium intake or if sodium is introduced into their society's food supply, blood pressure increases and vascular diseases develop.[4,18] Reducing dietary sodium in communities or populations has been associated with reduced blood pressure and vascular events.[4] In clinical trials, lowering dietary sodium reduces blood pressure,[4] and there is no evidence for less of an impact of reduced dietary sodium on blood pressure at the lowest levels of sodium intake tested (1200 mg sodium). It is estimated that there are up to 3.1 million sodium-related deaths per year and that reducing dietary sodium is one of the most effective (and cost-effective) interventions to improve health.[19]

CONTROVERSY

Two reviews have recently generated controversy. A review by Yusuf and colleagues proclaims that "there is no convincing evidence that moderate intake of sodium (3–5 g/d**) is associated with increased risk of cardiovascular disease compared with lower levels of sodium consumption."[20] However, there are several issues regarding the conclusions reported. The methodology employed in the Yusuf review is similar to many of the previous critiques of attempts to reduce dietary sodium towards physiological levels in (1) not being a systematic review (there is not even a pretense of being comprehensive), (2) selectively highlighting inconsistent studies rather than totality of evidence, (3) dismissing or ignoring substantive science that indicates harm from increased dietary sodium, (4) citing research findings that find sodium reduction harmful as facts while not disclosing the study's major design and methodological flaws as likely explanations, and (5) not clearly indicating how divergent their opinion is but rather implying they are clarifying scientific understanding.[21] Thus, this review may be affected by bias in selection and only

*The terms 'high' and 'low' dietary sodium are relative terms without accepted definition. The World Health Organization recommends diets contain less than 2000 mg of sodium while diets comprised of foods without added salt are likely to contain less than 1000 mg of sodium.

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**sodium = 3000 to 5000 mg sodium or 7.5 to 12.5 g salt per day, sodium is used throughout this commentary.

focuses on selected studies rather than the full body of evidence.

The 2013 report from the Institute of Medicine (IOM) also claimed that the evidence supporting dietary sodium intake <2300 mg was "inconclusive,"[22] but the IOM did not dispute the evidence for reducing sodium to this level. The IOM review was conducted largely by epidemiologists and several aspects of their review are flawed. The perspective that adding sodium to food has the potential to harm the public does not seem to have been the prime consideration. The main consideration was to assess whether interventions to reduce dietary sodium directly reduce cardiovascular disease. The review focused on recent controlled trials and cohort studies on sodium intake <2300 mg/d and on sodium reduction in the settings of disease. Although (1) hypertension is the most expensive cardiovascular disease category in the United States, (2) impacts 30% of the adult population, (3) there is a causal relationship between blood pressure and cardiovascular disease to the extent hypertension is the leading global risk for death and disability, and (4) 30% of hypertension is caused by increased dietary sodium, the IOM committee did not consider sodium-induced hypertension to be an outcome on which to base recommendations.[23,24] Furthermore many of the invited experts presenting at the public program of the IOM had in the past made public statements against lowering dietary sodium and or disclosed financial interests.[22]

The IOM committee examined cohort studies qualitatively and noted many had substantive methodological flaws. For example, nearly all the studies that did not find a benefit of sodium intake <2300 mg/d controlled for blood pressure and hence were not designed to assess sodium outcomes related to blood pressure. The controversial publication by Stolarz-Skrzypek and colleagues represents an example of where it was concluded that high salt intake did not cause cardiovascular disease, even though blood pressure was controlled.[25] Some of the studies that did not find benefits of lower sodium intake used estimates of sodium intake that were frail and one even retrospectively assessed random spot urine sodium in trials where about 30% of participants were prescribed diuretic therapy. A series of 4 studies, representing a significant proportion of the research, were conducted by a single research group, all finding that high dietary sodium was associated with reduced disease. In addition, the senior investigator on that research team was a consultant with the Salt Institute. Two of the same databases were examined by other investigators and the repeat analyses found harm from increased sodium intake (albeit only in obese patients in one analysis).[26–30] The refuted studies were still considered by the IOM (as were the refuting studies) without comment. The meta-analysis of cohort studies in healthy populations conducted by WHO does not seem to have been considered, or the updated Cochrane analysis.[31,32]

Many of the cohort studies considered by the IOM were conducted in patients with substantive disease where people ingesting lower sodium were likely to be much sicker and sick people do not eat leading to a reduced sodium intake, ie, reverse causality. Perhaps most notable were a series of unusual but large randomized controlled trials conducted in patients with heart failure. Those with heart failure were treated with large, fixed doses of furosemide 500 to 1000 mg/d as well as spironolactone and drugs designed to block the renin-angiotensin system. Even though they had features of salt and water depletion, they were then randomized to lower dietary sodium and water intake and found to have worse outcomes. That it is possible to harm patients with heart failure who are sodium and volume depleted by very high doses of furosemide (or any other mechanism) and then restricting sodium and water is not surprising. It is surprising that such trial evidence is considered when clinical recommendations are to individualize use of diuretics and to use diuretics only to reduce clinical evidence of excess fluid.[33] However, a meta-analysis of these studies has now been withdrawn due to obvious discrepancies in some of the results and therefore these heart failure trial results can no longer be considered until reanalysis of original data by an independent committee is published.

LIKELY MECHANISMS CONTRIBUTING TO CONTROVERSY

Low-Quality Science

Low-quality and poorly designed research on dietary sodium has become common and is a major source of controversy. Such studies are those (1) in patients with diseases with a high probability of reverse causality (in cohort studies, patients with more severe disease are likely to have worse outcomes but also likely to eat less sodium), (2) with flimsy assessment of sodium intake in settings where multiple days of carefully performed 24-hour urine sodium assessments (or in some specific circumstances dietary assessment) are needed to reliably define an individual's sodium intake, (3) that control for blood pressure (the major mechanism for sodium causing harm), (4) that do not adequately control for other substantive confounding factors, and (5) that disregard confounding pharmacologic agents (diuretics and antihypertensive drugs). Another potential marker of a low-quality study is when the author's discussion cites only evidence that supports the manuscript's findings without the context of the overall literature and its interpretation.

There is a need for developing and setting standards for clinical research on dietary sodium. Such standards could be used by researchers in designing studies, funding bodies in assessing proposals, journal reviewers, and editorial bodies in selecting articles to publish. Setting standards have been successfully utilized in the past to improve designs for conducting clinical trials and systematic reviews but have not been disease-specific. WHO or major international scientific organizations could develop such standards. Notably, the Pan Amer-

ican Health Organization (of WHO) Technical Advisory Group on dietary salt reduction has proposed to develop such standards.

Context of the Review

Humans evolved on <1000 mg of sodium per day. There is an estimated 3.1 million deaths per year attributed to the widespread addition of sodium to food (making sodium additives to food one of the most lethal and disabling interventions of industrialization) and little evidence to select a safe threshold of adding sodium to food. Requiring incontrovertible proof of benefit to reduce dietary sodium to a given level is a food industry commercial perspective on a major public health issue. Establishing a safe level (if there is one) for the addition of sodium to food is the public health question at issue. Indeed, if incontrovertible proof for other aspects of nutrition is required, no public health policy on nutrition would be advocated, eg, no action on obesity, fruit and vegetable consumption, trans fats, saturated fat, and sugar consumption.

The IOM, even with their limited scope, should have estimated the numbers of Americans with hypertension related to sodium intake >2300 mg/d vs <2300 mg/d and the direct costs. Given the public health context and causing hypertension in a large number of people, the IOM would likely have concluded (as have all other scientific review bodies, including the 2013 WHO report) that reducing dietary salt to <2300 mg/d is one of the more important health interventions to improve health.

Selective Review of Sodium Evidence and Use of Experts With Select Expertise

Another factor likely generating controversy is the examination of select research without the context that is known about dietary sodium or the context of public health research on food (where sodium has been more extensively and thoroughly studied than other nutrients). Performing limited reviews of the evidence, by those with great expertise in narrow areas of research with select perspectives on what constitutes acceptable evidence, does not seem to be a reasonable mechanism to address a major societal public health issue. The IOM review focused on limited evidence (cohort studies and randomized controlled trials published after 2003 with limited outcomes [mostly cardiovascular]). Given the importance, with the millions of lives and billions of dollars at stake, only comprehensive reviews of all the evidence by committees with broad expertise, conducted under the auspices of highly regarded institutions, should be considered relevant.

CONFLICTS OF INTERESTS

Another major factor that has likely generated controversy is financial conflicts of interest. The food and salt industry has been active in promoting commercial interpretations of the evidence. Salt Institute consultants and staff regularly provide commentary and assist with media releases that support a commercially beneficial perspective sometimes without disclosure. Quite worrying are instances where academics have received funding or been consultants with the food industry but not disclosed, or even in some settings denied, these associations.

The food/salt sector has (1) sponsored reviews of the sodium evidence, which counter those of the health and scientific community, and were published in an academic journal without disclosure of commercial interests and continue to be disseminated free of charge[34] (International Life Sciences Institute Web site accessed June 19, 2013), (2) continued to invite dissident scientists to present at sponsored symposia, (3) developed educational material on the health benefits of sodium for schools, and (4) even promoted that sodium intake is associated with greater intelligence and longevity (http://www.bmj.com/content/344/bmj.e2769/rr/582338). Newspapers and even scientific journals require readerships to be commercially viable and seem to promote controversy around dietary sodium. The commercial sector and those with commercial interest should have a very limited and defined role in conducting and interpreting pivotal health research and an even lesser role in the policy development stage. Further, governments could and should hold and allow the public to hold industry and their consultants accountable for health costs, death, and disability.

CONCLUSIONS

The more comprehensive and systematic the review, the more credible the review institution and reviewers, the less commercial influence in the review, and the better the science the less controversial the efforts to normalize sodium ingestion are. Much controversy is generated by limited or low-quality reviews, science, are commercial interests. Efforts to address these issues are needed to guide efforts to improve the health and well-being of our populations. Reducing dietary sodium by 30% is one of the agreed targets approved by the United Nations and the World Health Assembly, and reducing dietary salt to <2000 mg/d is one of a few recommended best buys to reduce noncommunicable diseases by WHO. There is an urgent need for coordinated actions by governments, industry, academia, and civil society to reduce dietary salt to maintain health and well-being.

Reference

1. Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ*. 2013;346:f1326.
2. World Health Organization. WHO guideline: sodium intake for adults and children. Report. Geneva, Switzerland: WHO Press; 2012: i–46.
3. Whelton PK, Appel LJ, Sacco RL, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation*. 2012;126:2880–2889.
4. He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens*. 2009;23:363–384.
5. Legetic B, Campbell N. Reducing salt intake in the Americas: Pan American health organization actions. *J Health Commun*. 2011;16 (suppl 2):37–48.

6. Cappuccio FP, Capewell S, Lincoln P, McPherson K. Policy options to reduce population salt intake. *BMJ*. 2011;343:d4995.
7. Webster JL, Dunford EK, Hawkes C, Neal BC. Salt reduction initiatives around the world. *J Hypertens*. 2011;29:1043–1050.
8. Appel LJ, Frohlich ED, Hall JE, et al. The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. *Circulation*. 2011;123:1138–1143.
9. Panel on Dietary Reference Intakes for Electrolytes and Water, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for water, potassium, sodium, chloride and sulfate. Scientific Evaluation of Dietary Reference 2004;1–640.
10. Scientific Advisory Committee on Nutrition. *Salt and Health*. Scientific Advisory Committee on Nutrition 2003. Norwich, UK: The Stationery Office; 2003:1–134.
11. He FJ, Campbell NRC, MacGregor GA. Reducing salt intake to prevent hypertension and cardiovascular disease. Special Report. *Rev Panam Salud Publica*. 2012;32:265–300.
12. Lackland DT, Egan BM. Dietary salt restriction and blood pressure in clinical trials. *Curr Hypertens Rep*. 2007;9:314–319.
13. VanVliet BN, Montani JP. The time course of salt-induced hypertension, and why it matters. *Int J Obes (Lond)*. 2008;32(Suppl 6):S35–S47.
14. D'Elia L, Rossi G, Ippolito R, et al. Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clin Nutr*. 2012;31:489–498.
15. Wang XQ, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol*. 2009;15:2204–2213.
16. Elliott P, Stamler J, Nichols R, et al. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. *BMJ*. 1996;312:1249–1253.
17. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med*. 1985;312:283–289.
18. Freis ED. Salt, volume and the prevention of hypertension. *Circulation*. 1976;53:589–595.
19. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2013;380:2224–2260.
20. O'Donnell MJ, Mente A, Smyth A, Yusuf S. Salt intake and cardiovascular disease: why are the data inconsistent? *Eur Heart J*. 2013;34:1034–1040.
21. Alderman MH. Presidential address: 21st scientific meeting of the international society of hypertension: dietary sodium and cardiovascular disease: the 'J'-shaped relation. *J Hypertens*. 2007;25:903–907.
22. Institute of Medicine of the National Academies. *Sodium Intake in Populations: Assessment of Evidence*. Strom BL, Yaktine AL, Oria M, eds. Report, V-F-44. Washington, DC: The Academies Press; 2013.
23. Institute of Medicine of the National Academies. A population-based policy and systems change approach to prevent and control hypertension-brief report. Report. Washington, DC: National Academy Press; 2010:1–4.
24. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944.
25. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011;305:1777–1785.
26. Cohen HW, Hailpern SM, Fang J, Alderman MH. Sodium Intake and Mortality in the NHANES II Follow-Up Study. *Am J Med*. 2006;119:275.
27. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Survey (NHANES I). *Lancet*. 1998;351:781–785.
28. Yang Q, Liu T, Kuklina EV, et al. Sodium and potassium intake and mortality among US adults: prospective data from the third national health and nutrition examination survey. *Arch Intern Med*. 2011;171:1183–1191.
29. He J, Ogden LG, Vupputuri S, et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA*. 1999;282:2027–2034.
30. Cohen HW, Hailpern SM, Alderman MH. Sodium intake and mortality follow-up in the Third National Health and Nutrition Examination Survey (NHANES III). *J Gen Intern Med*. 2008;23:1297–1302.
31. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet*. 2011;378:380–382.
32. He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ*. 2013;346:f1325.
33. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;123:123–124.
34. Logan AG. Dietary sodium intake and its relation to human health: a summary of the evidence. *J Am Coll Nutr*. 2006;25:4F–169F.