Flawed Evidence Should Not Derail Sound Policy: The Case Remains Strong for Population-Wide Sodium Reduction

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A recent report from Institute of Medicine (IOM)[1] along with misinterpretation of its findings by the press[2] has generated considerable confusion among the general public, scientists, and policy makers about the health effects of sodium reduction. A subsequent communication by members of the IOM committee summarized the report's findings in an attempt to clarify their position.[3] The purpose of this editorial is to comment on the evidence used by the IOM committee to reach its conclusions and to provide our opinion about the use of this IOM report to guide policy on sodium reduction.

The rationale for population-wide sodium reduction is compelling (See Table 1). Worldwide, the burden of cardiovascular disease (CVD) related to elevated blood pressure (BP) is enormous. A recent report from the Global Burden of Disease Study identified elevated BP as the leading modifiable cause of death and disability adjusted life-years worldwide.[4] The burden of elevated BP reflects the high prevalence of elevated BP,[5] concomitant with the well-documented, direct risk relationship of BP to CVD in the general population.[6] As advocated by numerous professional organizations and policy-making organizations, this pandemic of BP-related CVD warrants a comprehensive approach, including both a traditional high-risk approach in which persons with established hypertension receive pharmacologic therapy and a population-wide approach that addresses the underlying causes of elevated BP.[7,8] A diverse body of evidence has strongly implicated excess sodium intake as a major etiologic determinant of elevated BP.[9] Under a variety of scenarios, the projected benefits of modest sodium reduction on CVD morbidity and mortality are substantial.[10]

The context for the IOM report is important. During the past few years, several studies have reported paradoxical findings (e.g., a higher risk of CVD in persons with an apparently low intake of sodium,[11,12] in the range recommended by national and professional societies). Given the results of these studies, the Centers for Disease Control and Prevention asked the IOM to convene a committee with the goal of reviewing studies, published after the last IOM report on sodium in 2003,[13] that have attempted to link sodium intake with direct health outcomes other than BP. As part of their charge, the IOM committee was asked to focus on the health effects of sodium intake in the range of 1,500–2,300 mg/d; 2,300 mg/d corresponds to 2010 US Dietary Guidelines for Americans upper limit for the general adult population, whereas 1,500 mg/d corresponds to the goal for individuals at high risk for BP-related CVD and is the goal set for all Americans by the American Heart Association.[8,14] It is important to point out that the focus of the IOM report was narrow in scope. It neither reviewed nor based its recommendations on the compelling body of evidence, accumulated over decades, that links excess sodium intake with elevated BP.

The IOM committee evaluated evidence on the relationship of sodium with health outcomes and noted that for CVD events the evidence was predominantly from observational studies. In addition, they considered a few randomized trials from a center in Italy that tested sodium reduction in patients with heart failure.[15,16] The heart failure trials are irrelevant to recommendations for sodium intake in the general population and likely irrelevant to the treatment of patients with heart failure, given the unconventional management approach of investigators.[17] In the observational studies, the relationship of estimated sodium intake with CVD was extremely inconsistent: direct, inverse, j-shaped, and often null. Although some have posited that the j-shaped or inverse relationships reflects a causal relationship (i.e., a very low sodium intake increased CVD risk),[18] a more plausible explanation is that such findings resulted from methodological limitations of the studies—most important, inaccurate measurement of sodium intake in free-living persons and the potential for reverse causality.

Measurement of sodium intake in free-living populations is fraught with error. The gold standard for estimating dietary sodium intake is measuring sodium excretion from 24-hour urine collections. In healthy individuals, dietary sodium is nearly completely absorbed, and little is excreted in stool or sweat; hence, in a steady state, urinary excretion of sodium should accurately reflect dietary intake. Given large intra-individual variation in daily sodium intake, multiple urinary collections are needed to characterize an individual's intake.[19,20]

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Table 1. Key take home points

Worldwide, elevated blood pressure is extraordinarily common and is the leading cause of preventable death and disability.
The massive scope of the blood pressure epidemic requires both a population-wide approach that targets the underlying causes of elevated blood pressure and pharmacologic treatment of persons with established hypertension.
A large and diverse body of evidence has implicated dietary factors, particularly excess sodium intake, as etiologically related to elevated blood pressure.
Well-designed trials, often feeding studies, have documented that the relationship of sodium intake to blood pressure is direct and progressive without a threshold.
There is a consistent trend for less cardiovascular disease events and/or mortality in randomized controlled trials of sodium reduction conducted in the general population.
Observational studies that relate estimated dietary sodium intake with cardiovascular disease outcomes have methodological challenges and the potential for paradoxical results (i.e., inverse or j-shaped relationship).
Recent observational studies that have associated low estimated sodium intake with an increased risk of cardiovascular disease are replete with these types of methodological problems and should not be used to guide policy.
Evidence that relates excess sodium intake to elevated blood pressure, along with the results of the available trials of sodium reduction with clinical cardiovascular disease outcomes in the general population, provide a compelling rationale to recommend population-wide sodium reduction.

Unfortunately, 24-hour urine collections that are routinely obtained in clinic settings and in research settings where 24-hour urine collections are not a primary variable of interest are often of poor quality. Furthermore, the accuracy of 24-hour urinary sodium excretion as an estimate of dietary intake in individuals with chronic illness (e.g., heart failure, ischemic heart disease, chronic kidney disease, and diabetes) is uncertain. These illnesses, their treatment (e.g., diuretics),[21] and concomitant conditions (e.g., benign prostatic hypertrophy) may influence the accuracy of 24-hour urine collections. To minimize participant burden, investigators commonly use overnight, spot, or timed collections, which are suboptimal as a means to estimate usual intake of sodium.[19,22,23] Finally, dietary recalls and food frequency questionnaires can be used but are prone to error because individuals underreport dietary intake, the methods do not adequately capture sodium added at the table or in cooking, and because the accuracy of food composition tables are highly variable with respect to the sodium content of reported foods.

The second major methodological issue is reverse causality (i.e., in sick individuals, illness might be responsible for the apparently low sodium intake either because of medical advice or an illness-related reduction in food consumption).[24] A major determinant of sodium intake is total calorie intake. The correlation of sodium with calorie intake is extremely high (r = 0.81).[25] As individuals age and develop chronic disease, calorie intake falls. Hence, there is great potential for a low sodium intake to be confounded by numerous factors, which could lead to misinterpretation that low levels of dietary sodium intake result in subsequent disease, when is it is likely that the chronic illness itself is responsible for the low level of sodium intake.[24]

Clinical trials have the potential to overcome these methodological challenges. Numerous trials, including well-controlled feeding studies, have documented that the relationship of sodium intake to BP is direct and progressive without a threshold. None have been explicitly designed and powered to test the effects of sodium reduction on health outcomes, such as CVD in the general population. Although some have argued that a trial with hard outcomes should be initiated, a behavioral intervention trial of sodium reduction in the general population would be virtually impossible to conduct in the United States and most other countries because of major feasibility concerns. In particular, a contrast in sodium intake is likely not achievable, given that sodium consumption is largely determined by the sodium content of the food supply rather than individual choice.

Several trials that tested the long-term effects of sodium reduction on incident hypertension and/or BP control also reported the effects of sodium reduction on clinical outcomes.[26–30] Some of the reports included an extended follow-up period after active intervention ended.[26,27,30] In each of these reports, there is a consistent trend for less CVD events and/or mortality in those originally assigned to a reduced sodium intervention. In a meta-analysis of these studies, assignment to a reduced sodium intervention significantly lowered the risk of CVD by 20%.[31]

Further, there is no credible evidence of harm from sodium reduction. As previously discussed, cohort studies that reported adverse effects from sodium reduction are replete with methodological limitations that can lead to spurious results. The trials of sodium reduction in heart failure patients had major design flaws. Finally, sodium reduction has no significant impact on blood lipids, catecholamine levels, and renal function.[32] Sodium reduction does increase plasma renin activity, a counter-regulatory hormone that rises in response to a wide variety of BP reduction therapies that lower CVD risk.

A key issue, not directly addressed by the IOM report, is whether BP is an adequate surrogate outcome on which to base policy. In general, the evidence base to support use of most surrogate outcomes for policy making is weak.[33] However, BP is viewed as one of the few surrogate outcomes with a sufficiently robust evidence base to guide policy.[33] At the US Food and Drug Administration, evidence that diverse BP-reducing agents lower CVD risk, together with substantial data linking elevated BP with CVD events, provides the basis for their use of BP as a surrogate outcome. Interestingly, at the 2013 Annual Meeting of the American Society of Hypertension, nearly 2 weeks after the IOM report was released, Thomas Fleming, who is

an expert in surrogate outcomes,[34] congratulated the society's membership for developing the research database that supported use of BP as a valid surrogate outcome for policy making.

In summary, although we concur with the IOM committee on the need for additional research on the health effects of sodium, we firmly believe that evidence supporting population-wide reduction in sodium intake is compelling. In this context, we urge policy makers to expand their efforts to lower population intake levels of sodium. Flawed evidence should not derail sound policy.

DISCLOSURE

The authors declared no conflict of interest.

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