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Pro/Con Debate

Dietary sodium and cardiovascular and renal disease risk factors: dark horse or phantom entry?

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Introduction

Identifying a nutritional cause of cardiovascular disease (CVD), a nutrient that could be manipulated to reverse CVD morbidity and mortality, would be finding the Holy Grail of nutrition and CV science. Cardiovascular researchers and public policy advocates have long labeled dietary sodium as this nutrient, what they consider the primary dietary factor in the pathogenesis of high blood pressure (BP) and subsequent CVD, despite the lack of valid scientific data to bear this out [1]. While Mimran *et al*. [2] promulgate this claim in their commentary in this issue, they fail to acknowledge the defects in their supporting evidence or the more carefully derived evidence demonstrating that dietary sodium holds no more than an ancillary, if any, role in the development of cardiovascular or renal disease in the general population. That assessment is not to suggest that the management of many patients with chronic kidney disease, congestive heart failure and liver disease among other specific medical conditions should not include sodium restriction. In these highly selected populations, though, the need for or, indeed, the benefits of reduced sodium intake are not universal either.

The short history of the race

For over a century, the medical sciences have explored the relationship between salt and BP [3]. In the 50 years that ensued investigators began to focus on sodium balance and volume regulation as a root cause. Clinical studies purporting to directly examine the salt/BP relationship emerged in the 1940s and continued over the next several decades. It was not until the 1980s, however, that such studies employed rigorous scientific standards, i.e. randomization of the interventions and longitudinal follow-up of larger populations with measures of sodium intake and health outcomes. Only in the last 10 years have intervention trials appropriately controlled for other factors that can influence the BP effects of sodium. Despite a century of research, the final and most important piece of scientific evidence has never been produced: indisputable data that lower sodium intake reduces all-cause mortality, the goal of all universal health policies.

The revisionist history of the race

My own interest in the BP effects of salt began with one hypertensive patient seen in 1976 [4]. Subsequent observational studies prompted by that patient's mineral metabolism disturbances catapulted my laboratory into the maelstrom surrounding sodium's purported effects on BP that existed even then [5]. Those efforts early on lead to our identification of another dietary pattern potentially more important: fruits, vegetables and dairy [6], which became the basis of the DASH diet and the US Food Guide Pyramid. Over the next 20 years our and others' work revealed critical weaknesses in the data used to support sodium restriction for the population-at-large. Evidence and reasoning defects identified then apply today to the commentary of Mimran *et al*. [2].

First, until the mid-1980s virtually all the animal studies of salt's BP effects and other cardiovascular outcomes employed levels of dietary sodium or metabolic perturbations (nephrectomy, steroid injection, inbreeding, etc.) that have no relevance to the human condition [7,8]. Subsequently, as our earlier observational studies in humans suggested [6,9], controlling animal studies for adequate mineral intake negated salt's effects in diverse animal models of hypertension [10,11] and cardiovascular sequelae. There is no debate that excessive amounts of sodium in laboratory animals, from rats [2] to chimpanzees [12], can impact CVD risk factors. However, applying those findings directly to the issue of human CVD risk and, most importantly, all-cause mortality and public health policy is more than a stretch.

Second, many of the early observational studies [7,13,14] and intervention trials [8,15] inadequately documented dietary sodium intake and that of other nutritional factors and minerals that are known to influence BP. For

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example, the randomized trials of MacGregor and colleagues that routinely demonstrated an effect of salt restriction or supplementation in humans were set up by simultaneously restricting dietary potassium as reflected by urinary potassium excretion measures [16,17]. This limitation of MacGregor's trials of sodium effects on BP is critical because the presence of adequate dietary potassium has been shown to blunt sodium sensitivity [18] and, of greater importance, reduce stroke risk [19]. Finally, in 1988, the Intersalt Study provided excellent measures of both 24-h urinary sodium and BP in over 10 000 subjects in 32 countries around the world [20]. Intersalt demonstrated that its two primary outcome measures were negative: there was no relationship between dietary sodium and mean BP or the prevalence of hypertension within a site or across all sites.

Third, the concept that sodium restriction would benefit the entire population was dealt a lasting blow by Luft *et al*. beginning in the late 1970s [21,22]. In a series of controlled interventions, they demonstrated that the BP response of both normal and hypertensive individuals to lower dietary sodium intake was heterogeneous, i.e. almost equal portions of the population experienced an increase or a decrease in BP. This finding of a heterogeneous response to sodium restriction has now been replicated numerous times [23]. Thus, the mantra for population-wide salt restriction, as exemplified by Mimran *et al*. [2], carries potential risk. Specifically, some portion of the 'non-salt sensitive' population, normotensive or hypertensive, will experience elevations in BP.

Fourth, until recently, most experts assumed that lowering BP equated with lowering CVD risk, which would be reflected in reduced all-cause mortality. Still prevalent today [24] and advanced by champions of population-wide sodium restriction, that assumption is no longer defensible as other experts have indicated [25]. We learned from the NIH-sponsored ALLHAT Trial that how BP is lowered matters in terms of reducing CVD and all-cause mortality. In ALLHAT, one of the antihypertensive medications that effectively lowered BP was actually associated with increased risk of CVD and death [26]. In a landmark study, Alderman *et al*. [27] published data from an NIH-funded trial where high-risk participants were provided standard nutritional advice including dietary recommendations thought to improve favorable health outcomes. This study indicated that lower sodium intakes were associated with an increase in myocardial infarction and CVD-related deaths. This finding, suggesting a risk, has now been observed in a variety of databases [28–30], including large federally supported databases with longitudinal data reflecting the general population. Several have found no relationship in either direction, thus no benefit or harm [30]. A few have identified an all-cause mortality benefit of lower dietary sodium in subgroups [31], but not across the general population [32].

Have the bookies skewed the odds?

After 100 years of research and still no credible evidence that reduced salt intake imparts a net balance of cardiovascular benefits such that all-cause mortality is lowered, why are some investigators continuing their mission to codify population-wide sodium restriction into public health policy? The simple answer is that zealous advocates of reduced sodium have consistently overstated and misrepresented the case [2,33,34]. They have played with the odds in an attempt to turn a phantom entry into a dark horse in their race for the Holy Grail, the nutritional cause of CVD. Playing with the data, or in this case the 'odds', has its roots in a series of often-cited publications. The advocates, or here the 'bookies', have stacked the odds by repeatedly citing compromised reports, stacked one upon another, to build their argument that salt is the odds-on favorite.

We must recognize that the wealth of animal studies are interesting in exploring mechanisms, but are immaterial to the only piece of evidence that should matter at this stage: Do humans live longer when they consume less sodium? The meta-analyses of human trials typically cited to support the push for universal restriction are helpful, but their accuracy is in question. As noted above, if the randomized trials that showed the biggest effect were not properly designed or the data were not fully reported, they would compromise the validity of any meta-analysis in which they are included. Remove those studies from the meta-analyses and any dietary sodium effect would be markedly different [35,36] and likely of no significance.

The overestimated effect is important because numerous salt restriction proponents, i.e. bookies, have published quantitative estimates of lives that would be saved if sodium intake were reduced [37]. But when manipulating the data or odds is taken into consideration, the value of these estimates is zero. If the calculations begin with an incorrect number, then there is no accurate basis from which to assess the public health impact.

A better estimate can be made from the DASH-Sodium trial [38], as it controlled for nutritional and demographic variables that might influence sodium's effects on BP. Yet, here again the bookies have skewed the odds, greatly inflating and selectively reporting the salt reduction effects [39]. It is this interpretation that Mimran *et al*. [2] and Dickinson *et al*. [34] use to bolster their case for universal dietary sodium restriction, and, more importantly, that is the basis of the argument that sodium restriction will lower BP in normotensive persons.

Why is it inflated? How did the bookies stack the odds? Simply put, the DASH-Sodium cohort was heavily weighted toward typically salt-sensitive subjects (e.g. African American, hypertensive, overweight). The subjects were 'stacked' to amplify any potential impact of sodium restriction. Normally that would be acceptable, provided that the appropriate multivariate analysis was employed to factor out known confounding characteristics; however, despite numerous [39,40] and public requests for this analysis, it has never been published. Thus, the results of even the best designed intervention trial have been overstated and then incorporated into estimates of the odds by these bookies.

The home stretch

No matter how much data Mimran *et al*. [2] or others [34] expound on sodium's effects on BP or what they term

non-pressure effects of dietary sodium (LVH, albuminuria, etc.), a substantive body of data proving that lower salt intake will reduce all-cause mortality, that humans will live longer, healthier lives, does not exist. We have at least a dozen observational studies [30,41,42] that shed some light on that question, and while none can provide the definitive answer, collectively they raise the distinct possibility we would cause more harm than good. In the end, public health policy must rest on health outcomes. Do humans live longer? Those are the odds we should primarily be concerned with, not surrogate end-points.

Even in this area, the bookies have skewed the odds, impeding efforts to determine the magnitude of the risk. In their report of long-term CVD outcomes in TOHP I and II participants, Cook *et al*. [42] portray the data as showing that instruction in a lower sodium diet 10–15 years previous was associated with a reduction in all-cause mortality. Careful reading, however, reveals that their conclusion was based on multiple comparisons that did not demonstrate a significant reduction in all-cause mortality. They carry this misconstruction into the discussion, claiming these non-significant results 'reinforce' the need to lower sodium in the general population. This is simply untrue—TOHP I and II did not study a normal population; improvements in CVD outcomes, while possibly significant, did not translate into a significant reduction in mortality. This critical limitation is acknowledged where the authors state, 'The magnitude of risk reduction in this full intention to treat analysis... there was a 20% lower mortality among those in the sodium reduction group (0.80, 0.51 to 1.26, $P = 0.34$)'—not a *significant* finding. Equally important, nothing is known about the actual diets of these participants in these poststudy years. Their classification of sodium intake was simply based on the initial randomization more than 10 years earlier.

Contrasting the TOHP I and II results is the recent report from the Rotterdam Study [43], which provided longitudinal health outcomes data based on the most accurate measure of dietary sodium, urinary excretion of the electrolyte. That case-cohort study from the original population of almost 8000 adults >55 years did not find an association between sodium intake and either CVD or all-cause mortality, although there was a suggestion of risk from a *lower* sodium diet. Table 3 of that report indicates that the risk was not in the subjects 'free of CVD'. Follow-up communiqués (personal communication) with one of the authors did confirm that subjects with a prior CVD history had a *significant* 27% greater risk of CVD mortality and a borderline significant 17% increase in all-cause mortality on lower sodium intakes.

In fact, the TOHP I and II data based on the appropriate adjusted 'intention to treat' analysis and the Rotterdam findings are consistent with the comprehensive analysis of published papers addressing the mortality issue with sodium restriction. Alderman provided this assessment in his 2007 Presidential Address to the International Society of Hypertension [44]. He noted that there were 10 publications in populations with sodium intake within the normal range (the TOHP and Rotterdam data had not been published at the time of his writing). These reports all provided health outcomes data and estimates of sodium intake, and none showed any consistent evidence of lower mortality with lower sodium. Quite the contrary, they strongly suggest harm, i.e. increased deaths with lower sodium. Table 2 of that paper notes that the 10 studies comprise over 131 000 subjects, 1.2 million years of patient observations and almost 7800 outcome events—hardly small numbers, making the odds remote that they are misleading. The addition of TOHP and Rotterdam data simply strengthens those odds.

And the winner is. . .

I believe science is the winner. Our patients and the entire population deserve public health policies based on reproducible scientific data that assure safety and efficacy. Medical science, particularly the science of public health, has not always adhered to that standard. For example, millions of women worldwide were exposed to significant CVD and cancer risks for decades because of the broad endorsement of hormone replacement therapy, and hundreds of millions of individuals have been exposed to the cardiovascular risk of trans-fats in the diet. These public health fiascos could have been prevented by feasible trials at the outset to document the safety of the policies that perpetrated these outcomes.

The same is true for universal dietary sodium reduction. We need to do the study. The pilot has been done, TOHP II. We simply need to replicate that basic study design with good measures of sodium intake as we learned how to do in the Intersalt Study. Finally, we need to assess both CVD and all-cause mortality. We know how to do that. It is time, well past time, to answer the 'lower sodium/higher life expectancy' question. I cannot imagine any responsible scientist betting against the importance of answering this question. Some bookies might though because it will likely show that their dark horse is merely a phantom entry.

Today's better bet

A better bet to lower CVD risk and improve all-cause mortality in persons at risk of hypertensive heart disease would be to rely on the proven lifestyle workhorses: weight control, moderate alcohol intake, smoking cessation and improved diet quality. The benefits of the latter were recently reinforced by data from over 88 000 women in the Nurses' Health Study [45]. In that large cohort followed for 24 years, improved diet quality, defined primarily by greater intake of fruits, vegetables and low-fat dairy foods (DASH diet), was associated with a 27% reduction in total CHD and a 34% reduction in fatal CHD. Total stroke incidence was reduced 17%. All these improvements in health outcomes were highly significant. Not surprising to this betting investigator, sodium intake did not vary statistically across the quintiles of the DASH profile. Of even greater significance, the impact of the DASH diet was most pronounced in those women at greatest CVD risk: smokers, overweight, hypertensive and the sedentary.

As scientists and the bookmakers, who set the odds for our patients' benefits, we need to focus on these 'thoroughbreds' of lifestyle factors. Betting on phantom entries, such as sodium restriction, risks more than health-care currency; it may also reduce the quality and the length of life.

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(See related article by S. Shaldon and J. Vienken. The long forgotten salt factor and the benefits of using a 5-g-salt-restricted diet in all ESRD patients. *Nephrol Dial Transplant* 2008; 23: 2118–2120.)

(See related article by B. M. Moinier and T. B. Drüeke. Aphrodite, sex and salt—from butterfly to man. *Nephrol Dial Transplant* 2008; 23: 2154–2161.)

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