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Dietary Sodium Intake: Scientific Basis for Public Policy

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Abstract
Background/Aims: National and international agencies recommend a reduction in dietary sodium intake. However, some have questioned the wisdom of these policies. The goal of this report was to assess the findings and quality of studies that have examined the relationship between dietary sodium and both blood pressure and cardiovascular disease. ***Methods:*** Literature review of the available observational studies and randomized controlled trials, including systematic reviews and meta-analyses. ***Results:*** A large body of evidence from observational studies and clinical trials documents a direct relationship between dietary sodium intake and the level of blood pressure, especially in persons with a higher level of blood pressure, African-Americans, and those who are older or have comorbidity, including chronic kidney disease. A majority of the available observational reports support the presence of a direct relationship between dietary sodium intake and cardiovascular disease but the quality of the evidence according to most studies is poor. The limited information available from clinical trials is consistent with a beneficial effect of reduced sodium intake on incidence of cardiovascular disease. ***Conclusions:*** The scientific underpinning for policies to reduce the usual intake of dietary sodium is strong. In the United States and many other countries, addition of sodium during food processing has led to a very high average intake of dietary sodium, with almost everyone exceeding the recommended goals. National programs utilizing voluntary and mandatory approaches have resulted in a successful reduction in sodium intake. Even a small reduction in sodium consumption is likely to yield sizable improvement in population health.
Video Journal Club 'Cappuccino with Claudio Ronco' at www.karger.com/?doi=368975.

Dietary Sodium Intake Guidelines

National health agencies in more than 40 countries and a variety of international organizations, including the World Health Organization (WHO), recommend a reduction in dietary sodium intake (Na) [1]. WHO recommends <2,000 mg/day Na for both adults and children [2]. In the United States, the federal government recommends <1,500 mg/day Na for adults who are African-American, >51 years, have hypertension (HT), chronic kidney disease or diabetes, and <2,300 mg/day Na for all others [3]. The American Heart Association recommends an intake of <1,500 mg/day Na for all Americans [4]. Every Institute of Medicine (IOM) committee that has reviewed the topic has recommended a reduction in Na. A 2005 IOM Dietary Reference Intakes panel recommended 1,500 mg/day as the adequate intake (AI) and 2,300 mg/day as the tolerable upper intake level (UL) for most adults [5]. A lower AI was

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recommended for adults ≥50 years and a lower UL was recommended for those likely to be more sensitive to the blood pressure (BP) effects of Na, including 'older persons; African-Americans; and individuals with hypertension, diabetes, or chronic kidney disease'. A 2013 IOM committee was charged to focus on studies linking Na to cardiovascular disease (CVD), stroke, and mortality [6]. Consistent with prior reports, the committee found the available reports to be 'highly variable in methodological quality' and determined that the 'variability in data collection methodologies limited the committee's ability to compare results across studies' [6]. The committee concluded that 'when considered collectively, it indicates a positive relationship between higher levels of sodium intake and risk of CVD. This evidence is consistent with existing evidence on blood pressure being a surrogate indicator of CVD risk' [6]. In the United Kingdom (UK), the National Institute for Health and Clinical Excellence (NICE) recommends a progressive reduction in dietary Na intake to 1,200 mg/day [7].

Scientific Basis for Guideline Recommendations

Na recommendations have generally been based on renal physiology, the need to meet requirements for other nutrients, and information that links Na to higher levels of BP, CVD, and other health outcomes (table 1). The human kidney has a remarkable capability to conserve Na. In the absence of kidney disease or drugs that interfere with Na transport, adults require a Na of <200 mg/day [5]. The primary reason for recommending a higher AI for Na is to facilitate consumption of a diet that meets the requirements for other nutrients [5]. The 2005 IOM UL and guideline recommendations for Na were based on a large body of data in animals and humans linking increased Na to adverse health outcomes, especially high BP and CVD. Subsequent research is consistent with the conclusions of the 2005 IOM panel [8, 9].

High BP and CVD are both important health outcomes. In the 2010 Global Burden of Disease Study, high BP was the leading risk factor, among 67 studied, for worldwide mortality (9.4 million, 95% CI 8.6, 10.1, deaths per year) and disability-adjusted life years (7.0%, 95% CI 6.2, 7.7%, of annual worldwide mortality) [10]. High BP was responsible for more deaths than the second (tobacco products) and third (acute respiratory infections) leading risk factors combined. This reflects the strong risk relationship between BP and CVD [11], and the high prevalence [12] and inadequate treatment of high BP (hypertension) in general populations [13]. CVD is the leading cause of death in the United States and worldwide. In 2010, ischemic heart disease (IHD) and stroke accounted for approximately 25% of deaths worldwide (12.9 million people and a 25% increase since 1990), with IHD and stroke ranked as the leading and third most important contributors to mortality and years of life lost [14].

Table 1. Main findings from research studies that have explored the relationship between the intake of dietary sodium (Na), blood pressure (BP) and cardiovascular disease (CVD)

Animal studies
Excess Na results in high BP, diminished effects of antihypertensive medications, ventricular hypertrophy, diastolic dysfunction, perivascular fibrosis of the coronary arteries, and progressive renal injury which also promotes sodium sensitivity.
Observational studies
Adequately powered studies have identified a direct relationship between Na and BP.
A majority of the evidence is consistent with conventional beliefs that Na is adversely related to CVD risk. All reports were based on secondary analysis of datasets from studies not designed to explore this relationship. Measurement error, residual confounding, and reverse causality complicate the interpretation of these reports. A recent studies of higher quality supports the presence of a direct Na-CVD relationship, down to Na of 1,500 mg/day.
Clinical trials
Meta-analyses have consistently indicated that Na reduction lowers BP, with greater effect in those with a higher BP, African-Americans, older persons, and more successful intervention.
Limited statistical power to identify the effect of Na reduction on CVD events but consistent beneficial trend in individual studies and statistically significant 20% reduction in meta-analyses.
Na in the general population
Na in the United States and worldwide well in excess of guideline recommendations.
No evidence of a decline over time in the United States but voluntary and mandated policy changes have led to important reductions in other countries.
Modeling studies indicate even a small reduction in Na should result in an important decrement in CVD morbidity and mortality.
Overall nutritional adequacy easy to achieve at Na much less than typical intake in the United States and can be attained at Na ≤1,500 mg/day when lower sodium content foods are chosen instead of higher sodium selections.

Na, BP, and CVD in Observational Studies

Animal studies and human observational migrant studies, ecologic studies, and cohort analyses have all identified a strong positive relationship between Na and

BP [8]. The INTERSALT Study employed a standardized protocol with careful attention to the measurement of BP and collection of 'gold standard' 24-hour urinary Na estimates in 10,079 adults from 32 countries, providing a wide range in Na (the exposure variable) [15]. A significant positive relationship was noted between dietary Na and BP for both within- and across-population analyses. For a 100 mmol higher level of 24-hour urinary Na in participants 20–39 and 40–59 years of age, respectively, within-population analyses identified a 1.8 and 4.6 mm Hg higher systolic BP, after adjustment for age, gender, urinary potassium excretion, alcohol intake and body mass index, and correction for regression dilution bias. The corresponding differences for across-population analyses were 1.9 and 7.0 mm Hg, respectively, and a 30 year 100 mmol difference in Na intake was associated with >10 mm Hg difference in systolic BP. A recently reported study with a larger sample size (n = 102,216) that employed a 'spot' morning urine specimen and had a less rigorous approach to quality control reported similar findings with a somewhat steeper slope for the relationship between Na and BP [16]. As in the INTERSALT Study, the relationship between Na and BP was greater in older compared to younger participants. Likewise, as expected, the slope of the relationship was steeper for those with a higher BP than those with a lower BP.

In contrast to the consistency of the Na-BP findings in observational studies, the results from observational analyses of the relationship between Na and CVD have been more heterogeneous. All of the Na-CVD investigations have been based on secondary analysis in studies that were not originally designed to examine the relationship between Na and CVD. Many have had serious methodological shortcomings, including the use of imprecise and potentially biased estimates of Na, a high potential for reverse causality, and insufficient capacity to adjust for potential confounders of the relationship [8]. A recent systematic review of 31 Na-CVD investigations, conducted under the auspices of the American Heart Association, identified a direct positive association as the most common finding (42% of the explorations), but J-shaped curves (6%), null associations (26%), and inverse relationships (26%) were also frequent [17]. Using a prespecified standardized approach, an average of 3 to 4 methodological shortcomings per study were recognized. Issues with the potential to yield false negative results were noted in 88% of the studies. Issues with substantial potential to alter the direction of the association were noted in 96% of the analyses, with additional issues of lesser potential to alter the relationship being noted in 69% of the investigations. Only a minority of the studies (35%) based their estimates of Na on 'gold standard' 24-hour urinary sodium collections and all but two of these (8%) employed a single 24-hour urine collection. As a result, most lacked the ability to deal successfully with the known large day-to-day variability in Na [8]. A recently reported Na balance study identified an astonishing amount of day-to-day variation in Na [18]. Many of the cohorts used to study the Na-CVD relationship have included patients with hypertension, heart failure, chronic kidney disease, coronary heart disease, diabetes, and other illnesses in which a lower level of Na is quite likely to have been a consequence rather than a cause of their illness (reverse causality). Frequently, valid estimation of Na has further been compounded by the use of diuretics and other drugs that can distort the evaluation. Having a large study sample size [19] and pooling of results from different studies [20] will provide more precise estimates but will do nothing to correct bias resulting from inaccurate estimation of Na or reverse causality [21]. However, these types of reports may inadvertently be interpreted as providing more compelling results than those from smaller studies of higher quality. Review panels have repeatedly expressed serious concerns regarding the quality of the observational data in studies of the Na-CVD relationship [6, 8, 17, 22]. For example, the 2012 WHO Na Guideline report concluded that a significant direct relationship existed between Na and CVD but the use of GRADE methodology classified the quality of the evidence from the available observational studies as 'very low' [22]. The 2013 IOM Committee identified observational studies of the Na-CVD relationship as 'highly variable in methodological quality, particularly in assessing sodium intake' and further stated 'It was the consensus of the committee that the lack of consistency among studies in the methods used for defining sodium intakes at both high and low ends of the range of typical intakes among various population groups precluded deriving a numerical definition for high and low intakes in its findings and conclusions' [6].

Two recent studies that were not yet published when the AHA, WHO, and IOM systematic reviews were conducted are of much higher quality than any of the previous analyses [23, 24]. Cook et al studied the Na-CVD relationship in 2,275 Trials of Hypertension Prevention (TOHP) participants who were not enrolled in the Na reduction component of the trial [23]. Special strengths of this analysis included the fact that (1) the participants were young, healthy, and not on BP-lowering medication-making reverse causality improbable, (2) an average of 3–7 carefully collected 24-hour urine samples was available to estimate Na, diminishing the likelihood of

systematic and random error in Na estimation, (3) the distribution of Na was similar to that noted in the US general population, (4) the categorization of Na used was based on recommendations in the public domain, (5) follow-up was conducted over >10–15 years, (6) CVD outcomes were assessed by a committee that was blinded to participant Na and employed a standardized diagnostic protocol. There was an apparent linear trend in the Na-CVD relationship, extending to those with Na of 1,500 mg/day, with a 1,000 mg/day higher Na being associated with a 17% increase in risk of CVD.

Na, BP, and CVD in Randomized Controlled Trials

Randomized controlled trials (RCT) provide the most valid opportunity to assess the relationship between Na, BP, and CVD. Meta-analyses have repeatedly and consistently documented a BP-lowering effect of reduced Na, with greater than average reductions in African-Americans, participants with a higher baseline level of BP, and older individuals [9]. In meta-analyses of RCT restricted to adults with (1) hypertension but no other illnesses, (2) duration ≥4 weeks, (3) no concomitant interventions, (4) documented intervention effect (Na reduced ≥40 mmol/day), the overall reduction in systolic BP was approximately 4 mm Hg with no evidence of an adverse effect in lipid or catecholamine levels [25]. The only RCT explicitly designed to test the efficacy of reduced Na in preventing CVD reported a CVD mortality hazard ratio of 0.59 (95% CI, 0.37–0.95) for the group assigned to lower compared to usual Na [26]. In addition, the authors reported a reduction in inpatient health care costs and an improvement in life expectancy. However, the analysis did not account for the use of a cluster design and the intervention was based on the use of a salt substitute in which approximately 50% of sodium was replaced by potassium. None of the BP-lowering Na reduction RCT were powered to recognize an effect on CVD. However, Trial of Nonpharmacologic Intervention in the Elderly (TONE) participants randomized to Na reduction experienced a nonsignificant 23% lower rate of CVD events compared to usual care during a median follow-up of 29 months [27]. Phases I and II of the TOHP tested a Na reduction intervention over 18 months and 3–4 years of follow-up, respectively (TOHP I, TOHP II). During a 10–15 year period of extended post-trial follow-up, a significant 30% reduction in CVD events and a nonsignificant 20% reduction in CVD mortality was noted in those originally randomized to Na reduction compared to usual care [28]. A meta-analysis of clinical events experience from BP-lowering RCT identified a significant 20% reduction (95% CI, 0.64–0.99) in CVD events in those assigned to Na reduction compared to the control group [29]. Supplementing our current knowledge with the experience from more definitive RCT powered to recognize the effect of Na reduction on CVD morbidity and mortality would be ideal, but practical and financial barriers make this an unlikely prospect. Clinical events RCT are well suited to testing the value of treatments in high-risk settings but are not practical for the evaluation of prevention strategies such as Na reduction, cholesterol reduction, weight loss, physical activity, and other non-pharmacologic interventions that are typically implemented in the lower risk settings. It has been estimated that a traditional 2-arm RCT designed to test the efficacy of Na reduction for the prevention of clinical events would require five years of experience in a sample size of approximately 30,000 adults [8].

Population Estimates of Na Intake

Estimates based on dietary recall and 24-hour urine collections identify high average Na in the United States and worldwide [8, 30]. The estimated mean value (25–75th percentile) for Na in the 2003–2008 NHANES was 4,008 (3,326–4,787) mg/day in men and 2,826 (2,357–3,382) mg/day in women [31]. These values were based on 24-hour dietary recalls and likely under-estimate true Na by about 25% [8]. Even so, 95.2% of those for whom the *2010 Dietary Guidelines for Americans* recommended a Na of <2,300 mg/day and 98.8% of those with a recommendation for <1,500 mg/day exceeded their goal. Modeling studies suggest that Na >2,000 mg/day may account for 1.65 million deaths from CVD, worldwide, each year [32]. Even a small reduction in Na would likely lead to major health benefits [33]. In the United States and other countries, the vast majority of Na comes from the addition of sodium during food processing [8]. This 'unplanned experiment' is deeply rooted in food processing practices. Surveys in the United States and Canada provide little or no evidence of a reduction in Na from food products and restaurant meals in recent decades [9]. However, both voluntary and policy-based mandated changes in manufacturing can yield meaningful reductions in Na [9]. Overall nutritional adequacy is easy to achieve at Na much less than the typical intake in the United States and can be attained at Na ≤1,500 mg/day when lower sodium content foods chosen instead of higher sodium selections [8].

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