REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Dietary Sodium Restriction: Take It with a Grain of Salt

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ABSTRACT

The American Heart Association recently strongly recommended a dietary sodium intake of <1500 mg/d for all Americans to achieve "Ideal Cardiovascular Health" by 2020. However, low sodium diets have not been shown to reduce cardiovascular events in normotensive individuals or in individuals with pre-hypertension or hypertension. Moreover, there is evidence that a low sodium diet may lead to a worse cardiovascular prognosis in patients with cardiometabolic risk and established cardiovascular disease. Low sodium diets may adversely affect insulin resistance, serum lipids, and neurohormonal pathways, leading to increases in the incidence of new cardiometabolic disease, the severity of existing cardiometabolic disease, and greater cardiovascular and all-cause mortality. Although a high sodium intake also may be deleterious, there is good reason to believe that sodium intake is regulated within such a tight physiologic range that there is little risk to leaving sodium intake to inherent biology as opposed to likely futile attempts at conscious control.
 • The American Journal of Medicine (2013) 126, 951-955

KEYWORDS: Cardiology; Cardiovascular health; Public health; Salt; Sodium

Guidelines by the Center for Nutrition Policy and Promotion recommend a daily sodium intake to be less than 2300 mg/d in the general population and 1500 mg/d among people at greater risk of cardiovascular diseases (ie, individuals aged >50 years, African Americans, and those who have hypertension, type 2 diabetes mellitus, or chronic kidney disease).[1] The American Heart Association has recently emphasized goals to achieve "Ideal Cardiovascular Health" by 2020, and one of the dietary metrics is daily sodium intake of less than 1500 mg/d.[2]

Evidence concerning a possible beneficial effect of dietary sodium restriction on cardiovascular events and cardiovascular and all-cause mortality is largely indirect. Most of the studies testing a "low sodium diet" use surrogate markers for detecting sodium intake, such as 24-hour dietary recall, food questionnaires, and urinary sodium excretion. Moreover, most trials testing a low sodium diet offer dietary advice to restrict sodium and do not randomize patients to the exact same diets, with the only difference being a reduction in the sodium intake.

On the outcomes side, most evidence for the effects of sodium on cardiovascular-related outcomes relates to blood pressure. Although there are reasonable data to support that sodium restriction lowers blood pressure, the effects may be transient and inconsistent, with some individuals even having paradoxical increases in blood pressure. The degree of blood pressure lowering on average might be clinically trivial, approximately 2 mm Hg in normotensive individuals and approximately 4 mm Hg in hypertensive individuals. Finally, sodium restriction also has the adverse effects of activating the renin-angiotensin-aldosterone system, increasing catecholamines, and adversely affecting insulin and lipids.[3] Whether a reduction in any of the surrogate markers will lead to a decrease in morbidity and mortality of the population needs to be established independently of these surrogates, and such evidence is scarce.[4]

Reaching a definitive position is further complicated because a large portion of evidence supporting low sodium

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2013.05.020

diets comes from observational studies and nonrandomized trials.[5] Among the randomized studies, many evaluated a large decrease in the sodium intake for a short period of time or a small decrease in the sodium intake for a long period of time. Both of these study designs represent situations that may not be directly applicable to real-life situations.

This review critically analyzes the data for low sodium diets, starting with surrogate markers such as blood pressure and other risk factors such as type 2 diabetes mellitus, and then moving to clinical outcomes such as cardiovascular morbidity and events, and cardiovascular and overall mortality.

CLINICAL SIGNIFICANCE

- Data are inconclusive regarding the cardiovascular benefits of dietary sodium restriction.
- Advising sodium restriction is unlikely to help most patients and may harm some.
- A low sodium diet may lead to adverse clinical outcomes in patients with diabetes or heart failure.

SURROGATE MARKERS

Salt and Blood Pressure

Much of the support for the idea that a low sodium diet leads to a lower blood pressure comes from the Dietary Approaches to Stop Hypertension (DASH) study.[6] This study enrolled 412 participants and randomly assigned them to receive the control diet or the DASH diet. In both groups, the participants were assigned randomly to a high sodium diet (150 mmol/d), normal sodium diet (100 mmol/d), or low sodium diet (50 mmol/d) for 30 consecutive days and were then crossed over within their assigned groups. When the participants were shifted from a high sodium diet to a normal sodium diet, the systolic blood pressure decreased by 2.1 mm Hg ($P < .001$) in the control group and by 1.3 mm Hg ($P = .03$) in the DASH group. When they were shifted from a normal sodium diet to a low sodium diet, there was a further reduction in systolic blood pressure of 4.6 mm Hg in the control group ($P < .001$) and 1.7 mm Hg in the DASH group ($P < .01$). When compared with the controls, the DASH diet led to a lower systolic blood pressure of 7.1 mm Hg in participants without hypertension and 11.5 mm Hg in participants with hypertension. However, the DASH diet was significantly different from the control diet in terms of more fruits, vegetables, low-fat dairy foods, whole grains, poultry, fish, nuts, potassium, calcium, magnesium, dietary fiber, and protein, and less red meat, sweets, sugar-containing beverages, total and saturated fat, and cholesterol. Although the group on the DASH diet had a lower urinary sodium excretion, this does not necessarily imply that the benefit was being solely delivered by a dietary sodium reduction. In addition, this study did not evaluate the long-term effects of the intervention and the clinically relevant variables, such as mortality or morbidity.

Salt and Type 2 Diabetes Mellitus

In patients with type 2 diabetes mellitus, a low sodium diet has been associated with increased cardiovascular and all-cause mortality.[7] Even moderate salt reduction may lead to increased activation of the sympathetic nervous system and renin-angiotensin-aldosterone system, and insulin resistance.

A cohort study[7] enrolled 638 diabetic persons who were consistently followed for a period of 9.9 years. Their baseline urinary sodium excretion levels were 184 ± 73 mmol/24 hours, which remained constant throughout the study duration. Urinary sodium levels were inversely related to the all-cause mortality rate ($P < .001$) and cardiovascular mortality rate (sub-hazard ratio [HR], 0.65; confidence interval [CI], 0.44-0.95; $P = .03$). Each 100 mmol increase in the urinary sodium excretion led to a decrease in all-cause mortality of 28% (95% CI, 6-45; $P = .02$). This study implies a potential contraindication to a low sodium diet not only in those with type 2 diabetes mellitus but also by extension in the general population because of the widespread prevalence of type 2 diabetes mellitus. This leads to the question, are the current dietary guideline recommendations for a low sodium diet in the general population (including type 2 diabetes mellitus) appropriate? The limitation index of these data is that the results are based on a cohort study examining urinary sodium excretion levels versus a randomized controlled trial of patients receiving identical diets, with the only variation being the amount of sodium intake.

PATIENT-ORIENTED OUTCOMES: MORBIDITY AND MORTALITY

Congestive heart failure is characterized by various processes that lead to reduced renal perfusion and activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system.[8] This leads to preferential retention of water compared with sodium and can cause hyponatremia. Restricted dietary sodium intake may further exacerbate these processes, therefore precipitating hyponatremia.

A study[9] enrolled 410 patients with congestive heart failure and followed them for 6 months to compare the dietary sodium intake levels with doses of diuretics in these patients. These patients were divided into 8 groups: group A received 1000 mL/d of fluid intake, 120 mmol/d, and 250 mg furosemide twice daily; group B received 1000 mL/d of fluid intake, 120 mmol/d, and 125 mg furosemide twice daily; group C received 1000 mL/d fluid intake, 80 mmol/d, and 250 mg furosemide twice daily; group D received 1000 mL/d fluid intake, 80 mmol/d, and 125 mg furosemide twice daily; group E received 2000 mL/d fluid intake, 120 mmol/d, and 250 mg furosemide twice daily; group F received 2000 mL/d fluid intake, 120 mmol/d, and 125 mg furosemide twice daily; group G received 2000 mL/d fluid

intake, 80 mmol/d, and 250 mg furosemide twice daily; and group H received 2000 mL/d fluid intake, 80 mmol/d, and 125 mg furosemide twice daily for 30 days or more after discharge and for 180 days afterward. Group A showed the greatest statistically significant reduction in readmissions, brain natriuretic peptide, aldosterone, and plasma renin activity compared with the other groups ($P < .001$). Therefore, a normal sodium diet (2.8 g/d) and a higher dose of a diuretic (250 mg twice daily) yielded the best results as opposed to a low sodium diet (1.8 g/d) and a lower diuretic dose (125 mg twice daily).

The low sodium diet caused increased mortality and heart failure hospitalizations versus a normal sodium diet in patients with systolic heart failure. These results have been verified across multiple randomized controlled trials in patients with systolic heart failure.[10-13] These findings can be explained partially on the basis of studies conducted in mice.[14] It has been shown that the renin-angiotensin-aldosterone system has a central role in atherogenesis and that dietary salt intake plays a significant role in controlling this system. A study in rats has shown a 4-fold increase in plaque formation with a low sodium diet compared with a normal sodium diet, and this effect can be blocked by the use of angiotensin-converting enzyme inhibition, which suggests that it is mediated by the renin-angiotensin-aldosterone system. Effects observed with a high sodium diet include reduced vascular inflammation and atherogenesis and a modest increase in systolic blood pressure (5 ± 1 mm Hg). These data, although generated from mice, may explain the inverse relationship between dietary sodium intake and mortality rate.

The majority of data relating dietary sodium to cardiovascular health are based on its effects on blood pressure. Data from the 3 epidemiologic studies National Health And Nutrition Examination Survey (NHANES) I to III have been analyzed to assess the relationship between dietary sodium intake and cardiovascular mortality rates.[15-17] NHANES I acquired information from 20,729 participants via interview and examination, and followed them using interview, tracking, and vital events registry. An inverse association was seen between dietary salt intake and all-cause mortality (lowest to highest salt intake quartile 23.18 to 19.01, $P < .0001$) and cardiovascular mortality (sodium 11.80 to 9.60, $P < .0019$; calories 12.80 to 8.94, $P < .0002$; sodium/calorie ratio 9.73 to 11.35, $P = .017$).[15] Moreover, sodium intake was inversely associated with all-cause ($P = .0069$) and cardiovascular mortality ($P = .086$). NHANES II followed a similar population of 7154 participants for 13.7 years and yielded similar results. The sodium adjusted for calories and sodium/calorie ratio were both independently and inversely associated with cardiovascular mortality ($P = .03$ and $P = .008$, respectively; adjusted HR of cardiovascular mortality for sodium <2300 mg, 1.37; CI, 1.03-1.81; $P = .033$) and all-cause mortality (HR, 1.28; CI, 1.10-1.50; $P = .003$).[16] However, these results did not hold true for participants aged more than 55 years, obese participants, and non-white participants. NHANES III was a cohort study based on 8699 participants who were followed using national vital entries registries for the outcomes of all-cause and cardiovascular mortality.[17] An inverse association between dietary sodium intake and cardiovascular mortality was shown (HR, 1.80; CI, 1.05-3.08; $P = .03$). Moreover, an inverse association of continuous sodium (per 1000 mg) intake with cardiovascular and all-cause mortality was observed with a 99% CI of 0.73 to 1.06 ($P = .07$) and 0.86 to 1.04 ($P = .11$), respectively. These findings question any potential survival advantage with a low sodium diet and indicate caution for population-wide sodium restriction.

Conversely, some studies have suggested a lower and higher mortality rate with a high sodium diet depending on the New York Heart Association (NYHA) functional class status. An observational study[18] in 302 patients showed that patients with a daily urinary sodium excretion level >3 g had a reduced risk for a cardiovascular events (HR, 0.44; CI, 0.20-0.97) for NYHA functional class I/II congestive heart failure, but an increased risk (HR, 2.54; CI, 1.10-5.84) for NYHA III/IV congestive heart failure compared with a urinary sodium excretion level <3 g. This study was an observational study, in contrast to the randomized controlled trials indicating benefits of a normal sodium diet, and used urinary sodium levels as a measure of dietary sodium intake, which may be a reasonable surrogate marker for normal individuals but not for patients with congestive heart failure, who have severe renal excretory disturbances.

A large observational analysis of 2 cohorts,[19] including 28,880 patients (from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial [ONTARGET] and Telmisartan Randomized Assessment Study in ACE-intolerant Subjects With Cardiovascular Disease [TRANSCEND] trials), was conducted to investigate the effects of sodium and potassium intakes on the incidence of cardiovascular disease. The primary composite outcome measure was death related to cardiovascular causes, myocardial infarction, stroke, and hospitalization for congestive heart failure. The mean estimated baseline 24-hour urinary sodium excretion and standard deviation were 4.77 g (1.61) and 4 to 5.99 g, respectively, in the reference group. The patients were followed for an average of 56 months, during which the primary outcome was observed in 4729 patients (16.4%), with 2057 cardiovascular deaths, 1412 patients with myocardial infarction, 1282 patients with stroke, and 1213 patients hospitalized for congestive heart failure. In the control group, there was an incidence of 6.3% cardiovascular death, 4.6% myocardial infarction, 4.2% stroke, and 3.8% hospitalizations with congestive heart failure. In the cohort, a higher and lower urinary sodium excretion was associated with increased cardiovascular mortality. A higher baseline urinary sodium excretion had a statistically significant association with cardiovascular death (9.7% for 7-8 g/d; HR, 1.53; 95% CI, 1.26-1.86; and 11.2% for >8 g/d; HR, 1.66; 95% CI, 1.31-2.10), myocardial infarction (6.8%; HR, 1.48; 95% CI, 1.11-1.98 for >8 g/d), stroke (6.6%; HR, 1.48; 95% CI, 1.09-2.01 for >8 g/d), and hospitalization for congestive heart failure

(6.5%; HR, 1.51; 1.12-2.05 for >8 g/d). Likewise, a lower urinary sodium excretion also had a statistically significant correlation with an increased risk of cardiovascular death (8.6%; HR, 1.19; 95% CI, 1.02-1.39 for 2-2.99 g/d; 10.6%; HR, 1.37; 95% CI, 1.09-1.73 for <2 g/d) and hospitalization for congestive heart failure (5.2%; HR, 1.23; 95% CI, 1.01-1.49 for 2-2.99 g/d). This cohort study suggests a J-shaped relationship between dietary sodium intake and cardiovascular risk factor; therefore, a higher and lower dietary sodium intake may be related to adverse cardiovascular outcomes. Moreover, the lowest cardiovascular event rates occurred in the moderate sodium excretion (4-5.99 g/d) and high potassium excretion (>3 g/d) groups. Thus, it seems that a normal sodium diet (4-6 g/d) in addition to a high potassium intake may be best for the general population.

Trials of Hypertension Prevention (TOHP) phases I and II were 2 large randomized controlled trials enrolling 2182 and 2382 patients, respectively. In TOHP I,[20] the patients were randomized to 3 interventions, one of which was a low sodium diet; however, the low sodium diet and control groups were not given the exact same diets. Although a lowered dietary sodium intake, as measured by a urinary sodium excretion of 44 mmol/24 hours, was able to reduce the diastolic blood pressure by 0.9 mm Hg ($P < .05$) and systolic blood pressure by 1.7 mm Hg ($P < .01$), it may have been due to the diet that lowers urinary sodium and not necessarily the lower sodium content. In TOHP II,[21] counseling was used to reduce the dietary sodium intake in the test group. During the study period, the urinary sodium excretion decreased 50 and 40 mmol/d at 6 and 36 months, respectively. This decrease in urinary sodium excretion was associated with a 2.9/1.6 mm Hg decrease in the intervention group (all groups, $P < .001$). However, this study treated the intervention group differently from the control group. The groups were not given the same diets, and the intervention group was counseled to reduce sodium in their diet. Moreover, the intervention group also was counseled to increase spices, which alone may have cardiovascular benefits. Thus, a lower urinary sodium does not necessarily indicate that the results are due to a lowered sodium intake.

OTHER UNINTENDED CONSEQUENCES RELEVANT TO CARDIOVASCULAR HEALTH

A Cochrane review based on 167 studies showed that a low sodium diet in normotensive whites leads to a small reduction in systolic blood pressure (−1.27 mm Hg; CI, −1.88 to −0.66; $P = .0001$), without significantly reducing diastolic blood pressure (−0.05 mm Hg; CI, −0.51 to 0.42; $P = .85$).[22] However, a low sodium diet caused an increase in renin ($P < .00001$), aldosterone ($P < .00001$), noradrenaline ($P < .00001$), adrenaline ($P < .0002$), cholesterol ($P < .001$), and triglycerides ($P < .0008$). This meta-analysis included studies that were only 2 weeks long and did not use good screening measures for quality. Inclusion of trials with an acute reduction in dietary sodium intake may not fully elucidate its long-term effects. Despite this fact, the potential harmful effects of sodium reduction may outweigh its benefits, especially in those individuals who generally did not have a significant reduction in blood pressure (normotensive whites and Asians).

With a lack of consistent efficacy of a low sodium diet, and potential harm, the cost-effectiveness of such a worldwide approach to a low sodium diet is questionable. A major source of dietary iodine is through salt. Therefore, a low sodium diet could lead to worsening of thyroid diseases. Salt also gives palatability to food and possesses numerous antimicrobial effects. It is possible, at least theoretically, that food-borne infections could increase if we were to decrease the amount of salt in foods.

A low sodium diet may even be counterproductive from a public health perspective. In addition to possibly exacerbating, it may distract efforts from other, more worthwhile programs that have a stronger foundation in evidence.[23] Here again, the possibility that a low sodium diet may lead to worsened cardiovascular survival rates is a concern. The potential population-level effects of such an extreme intervention, with the American Heart Association recommending a sodium intake of <1.5 g/d for all Americans,[2] can be expected to lead to potentially negative results on morbidity and mortality.

Even if a low sodium diet was advisable, is it physiologically possible? Although a low sodium diet may have benefit, there is still evidence that states it is not possible to modify human sodium intake levels because of complex neurohumoral homeostatic mechanisms.[24] This makes public health programs focusing on salt reduction in the general population potentially counterproductive. Whether or not dietary salt intake is physiologically determined is still not known.[25] If it is physiologically determined, with an optimal dietary range, then any modification to the dietary intake may be risky.

CONCLUSIONS

There is no conclusive evidence that a low sodium diet reduces cardiovascular events in normotensive and pre-hypertensive or hypertensive individuals. On the contrary, there is sound evidence that a low sodium diet leads to a worse cardiovascular prognosis in patients with systolic congestive heart failure or type 2 diabetes mellitus. Worldwide sodium restriction, through its adverse effects on insulin resistance, may lead to an increase in the rates of type 2 diabetes mellitus. By potentially moving the food industry to produce lower-sodium products could lead to greater consumption of processed foods and greater incidence of metabolic syndrome. Other adverse effects also are possible with attempted sodium restrictions, whereas low sodium diets themselves may not be possible because of inherent physiologic regulation. Advising low sodium diets seems misguided and potentially dangerous and illustrates the problem of guidelines based on flawed studies using surrogate measures.

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