Dietary sodium: the dark horse amongst cardiovascular and renal risk factors

Albert Mimran and Guilhem du Cailar

Department of Internal Medicine, Hôpital Lapeyronie, Montpellier Cedex, France

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In American and European populations, the estimated median values of salt intake are 7 and 10 g/day in women and men, respectively. Whether these amounts of salt are innocuous or deleterious is a subject of large debate between pro [1–4] and con [5] recommendations of a large-scale reduction of sodium intake. In addition to the well-admitted effect of sodium on blood pressure, several clinical and experimental observations are in favour of non-pressure-related effects of salt that could contribute to its influence on cardiovascular outcome.

Dietary salt and blood pressure

In clinical research and practice, measurement of 24-h urinary sodium excretion is probably the most reliable estimate of sodium intake, with a variation coefficient of ∼20% [6]. Table salt accounts for ∼10%, whereas cooking and food salt represent 5 and 85% of total intake, respectively [7]. The use of the sodium-to-creatinine ratio on a single-spot urine sample, which is probably more convenient for population studies, may not be reliable, due to the strong influence of age and gender on urinary creatinine. In the Intersalt study [8] conducted in >10 000 male and female subjects aged 20–59 years, in 52 centres with mean values of 24-h natriuresis centre ranging from 0.5 mmol in Yanomamo Indians (Brazil) to 242 mmol/24 h in North China, a positive relationship between sodium intake and blood pressure or the prevalence of hypertension was found in 33/52 centres. Populations with a mean natriuresis and blood pressure or the prevalence of hypertension in North China, a positive relationship between sodium intake and blood pressure or the prevalence of hypertension was detected. The authors concluded that reduction of sodium intake by an average of 40 mmol/24 h was associated with a fall in blood pressure of 8/4.3 mmHg in untreated hypertensive populations, moderate reduction of sodium intake by an average of 40 mmol/24 h was associated with a fall in blood pressure of 8/4.3 mmHg in hypertensive subjects but no marked decrease in blood pressure was detected. The authors concluded that reducing sodium intake is associated with a rather negligible decrease in blood pressure.

Non-pressure mediated effects of dietary sodium

In essential hypertension, the presence of left ventricular hypertrophy (LVH) is a strong and independent predictor of increased cardiac and cerebrovascular [12] events and mortality; and in-treatment reduction in left ventricular mass (LVM) is associated with cardiovascular protection [13]. Recently, microalbuminuria (MA) (albuminuria between 30 and 300 mg/day) has emerged as a reliable predictor of cardiovascular risk in a large population [14], suggesting that sodium sensitivity may be more prevalent with older age [9]. Several studies of rather short duration have shown that reduction of salt intake is associated with a significant decrease in blood pressure. In the whole population of normotensive and hypertensive subjects maintained on their usual diet, the reduction of salt intake from 150 to 100 mmol/day (8.8–6 g/day sodium chloride), which is considered as acceptable, during a 4-week period was associated with a rather negligible decrease in blood pressure of 2.1/1.1 mmHg. Reducing sodium intake from 100 to 50 mmol/day (3 g/day sodium chloride) (considered as a drastic reduction in dietary sodium) resulted in an additional fall of blood pressure of 4.6/2.4 mmHg. In subjects constantly maintained on the DASH diet, the fall of blood pressure in response to the change from the high to the intermediate level of sodium intake was still negligible (−1.3/−0.6 mmHg). When the effect of the change from the high to intermediate sodium intake was considered, it was similar in normo and hypertensive people [10]. In a systematic review and meta-analysis of randomized controlled trials of various durations conducted in normotensive and untreated hypertensive populations, moderate reduction of sodium intake by an average of 40 mmol/24 h was associated with a fall in blood pressure of 8/4.3 mmHg in hypertensive subjects but no marked decrease in normal subjects (−2.3/−1.2 mmHg). No correlation between the degree of reduction of sodium intake and the change in blood pressure was detected. The authors concluded that reducing sodium intake is associated with a rather negligible decrease in blood pressure.

Correspondence and offprint requests to: Albert Mimran, Department of Internal Medicine, Hôpital Lapeyronie, 34295 Montpellier Cedex 5, France. Tel: +33-4-67-33-84-43; Fax +33-4-67-33-84-53; E-mail: amimran@wanadoo.fr
normotensive subjects [15] and essential hypertension [16], with a significant increase in risk >7 mg/day [17]. In addition, even for values well below the usually accepted threshold of 30 mg/day, albuminuria (UAE) predicted the subsequent development of hypertension in normotensive individuals [18].

The level of systemic pressure is the most powerful determinant of UAE and LVM, and several factors including overweight and C-reactive protein were shown to potentiate the relationship between arterial pressure and UAE [19].

Almost 20 years ago, Schmieder et al. [20] found a positive correlation between LVM index and sodium intake, estimated by 24-h natriuresis. The existence of this relationship, independent of blood pressure, was confirmed by us [21] and others [22]. In a totally ignored but interesting study conducted in 717 patients with essential hypertension and published in 1972, Swaye et al. [23] reported that, only in male subjects, the prevalence of electrocardiographic LVH was significantly higher in patients who added salt to food before tasting as compared to subjects who did not (39 versus 22%, P < 0.01). Natriuresis, which was measured in 47 individuals, averaged 151 mmol/day in salt-adders and 111 mmol/day in non-salt-adders. Of interest, the severity of hypertension was not influenced by salt intake in hypertensive men.

In a cohort of 336 normotensive (arterial pressure <140/90) subjects and 503 patients with never-treated essential hypertension, sodium intake was higher than 172 and 131 mmol/day (corresponding to 10 and 7.7 g sodium chloride) in 40% of men and women, respectively. A progressive increase in LVM index and UAE with increasing quintile of sodium intake was observed in the whole population, and the slope of the linear relationship between systolic arterial pressure and LVM index or UAE was progressively steeper from the lowest to the highest quintile of natriuresis [24]. In the normotensive cohort, multivariate analysis showed that echographic LVM index was positively correlated with natriuresis, independent of gender, age and mean arterial pressure, thus confirming our previous findings [21]. As shown in Figure 1, in 450 patients with never-treated hypertension, the prevalence of left ventricular hypertrophy (LVH), MA or both clearly increased from the lowest to the highest quintile of natriuresis, despite similar mean values of age and blood pressure in all quintiles of urinary sodium [24]. In contrast, in the cross-sectional study of the Framingham Offspring Study cohort conducted in 2660 individuals including 36% of participants with hypertension, no influence of sodium intake (estimated as the sodium-to-creatinine ratio on a single-morning-spot urine sample) on LVM was detected [25]. Nevertheless in the same population, a positive correlation between the sodium-to-creatinine ratio and albuminuria was recently reported [26]. Such a discrepancy may be related to the inaccuracy of the sodium-to-creatinine ratio, especially in elderly subjects, and the heterogeneity of the population.

In our cohort, analysis of pulse pressure (PP), a marker of elastic artery stiffness and a predictor of cardiovascular events [27], showed that in subjects >40 years (>40 years of age PP is positively correlated with age, whereas it is negatively correlated with age <40 years), PP increased with increasing sodium intake [28]. The deleterious influence of sodium on the stiffness of large arteries, assessed by pulse wave velocity (PWV), was documented in a study showing a lower PWV in normotensive urban (Beijing area, mean natriuresis of 230 mmol/day) as compared to rural (Guangzhou area, natriuresis of 130 mmol/day) Chinese people [29]. In urban Australian volunteers, the same group demonstrated that a rather severe reduction of dietary salt to ∼44 mmol/day and for a period of ∼2 years resulted in a significant reduction in aortic PWV, independent of changes in blood pressure in normotensive individuals. Nevertheless, results should be taken with caution due to the notoriously poor reliability of dietary recall as well as the sodium-to-potassium ratio without determination of urinary creatinine as indexes of sodium intake [30].

### Does the effect of dietary sodium on the cardiovascular system translate into an influence on cardiovascular risk in observational studies?

In 1998, analysis of the NHANES I (First National Health and Nutrition Examination Survey Epidemiologic Follow-up study) database concluded that sodium intake, as estimated by a single dietary recall, was inversely associated with cardiovascular and all-cause mortality [31]. In the NHANES II study reported in 2006, the same group confirmed their earlier findings, but no such association was detected for subjects aged <55 years, obese subjects and non-whites within a follow-up period of 13.7 years [32]. In a very recent longitudinal study conducted in 40 547 Japanese men and women aged 40–79 years and followed up for 7 years, Shimazu et al. [33] observed that the ‘Japanese dietary pattern’ (quite rich in salt) was associated with a decreased risk in cardiovascular mortality, as compared to ‘high-fruit and vegetable diet’. Only in overweight subjects, He et al. [34] reported that a 100 mmol increase in sodium intake (as estimated by dietary recall) was associated with an increase in stroke incidence of 32%, coronary heart disease mortality of 44% and overall cardiovascular mortality of 35%.
mortality of 61%. In a Finnish population of 2436 individuals aged 25–74 years, with a remarkably high sodium intake (24-h natriuresis above 159 and 119 mmol/day in 75% of men and women, respectively), dietary sodium predicted mortality and risk of coronary heart disease, independent of blood pressure and other cardiovascular risk factors. These findings were restricted to obese men in whom for a 100 mmol increase in sodium intake, cardiovascular morbidity increased by 45%; however, no influence on acute stroke was detected [35]. The same group later reported that the risk of developing type 2 diabetes within a period of 18 years in 35- to 64-year-old Finnish people was markedly increased (RR 2.8) only in subjects of the fourth quartile (natriuresis >253 in men and >189 mmol/day in women) as compared to the lowest quartile associated [36].

Is sodium reduction associated with reduction in cardiovascular risk in interventional studies?

In the TONE study (Trial of Nonpharmacologic Interventions in the Elderly) [37] conducted in 681 treated hypertensive patients aged 60–80 years with blood pressure <145/85 mmHg while taking one medication, reduction of 24-h natriuresis to 80 mmol/day or less, alone or combined with body weight reduction, was proposed. After 3 months of dietary intervention, the medication was discontinued. Within a mean follow-up period of 27.8 months, the primary endpoint of blood pressure ≥150/90 mmHg or resumption of antihypertensive medication or a cardiovascular event occurred in 59% of subjects submitted to sodium reduction versus 73% in the group maintained on usual diet (HR of 0.68, P < 0.001). Resumption of antihypertensive treatment was necessary in 64% of the sodium-reduced versus 79% in the control group. However, no information on cardiovascular outcome was provided. The TOHP study (Trials for Hypertension Prevention) was conducted in subjects aged 30–54 years with ‘high-normal’ blood pressure. From baseline to 18 months, a net decrease in urinary sodium of 44 mmol/day (from a baseline value of 155 mmol/day) was associated with a significant change in blood pressure of −1.7/−0.8 mmHg, and a reduction by 26% of the incidence of denovo hypertension. In addition, the risk of a cardiovascular event was 25% lower in the sodium reduction intervention group after adjustment for age, gender and baseline natriuresis and body weight [38]. Nevertheless, there are some limitations of these studies, including post hoc analysis of two studies, no repeat assessment of compliance to dietary sodium restriction and finally the absence of any difference in mortality between low and normal salt intake.

Although in favour of a moderate reduction (by at least 30–40%) of dietary sodium, the results of the above-mentioned studies deserve to be confirmed.

Putative mechanism(s) involved in the deleterious effect of salt

Beyond an even minimal increase in systemic pressure and circulating or extracellular volume, several non-pressure-dependent consequences of increased sodium intake on widely accepted predictors of deleterious cardiovascular events, such as LVH and MA [24] as well as pulse pressure [28] and arterial stiffness [29], may explain an unfavourable effect of sodium on cardiovascular disease. The mechanisms of the prohypertrophic effects of dietary sodium on the cardiovascular system are still unclear. In rat studies, upregulation of type 1-angiotensin II receptors with prohypertrophic action [39] as well as downregulation of type 2-angiotensin II receptors with antihypertrophic properties [40], and an increase in the cardiac production of aldosterone, aldosterone synthase activity and CYP11B2 expression [41], together with the correction of salt-associated cardiovascular abnormalities by spironolactone [42] were demonstrated. Only in subjects with salt-sensitive hypertension, it was shown that plasma concentration of isoprostan (as markers of superoxide generation) [43] or the endogenous inhibitor of nitric oxide synthesis (asymmetrical dimethyl arginine, ADMA) [44] were consistently increased after sodium loading; thus suggesting that high salt intake may exacerbate the generation of free radicals.

Conclusion

Until now, most debates have focused on the pressure effect of dietary sodium. Taking into consideration the presently reported findings on the non-pressure-related effects of salt on widely accepted markers of cardiovascular risk, such as left ventricular geometry, albuminuria or pulse pressure and the reduction by moderate and reasonable reduction of dietary sodium of the progression from pre- to sustained hypertension, it may be wise to favour a modest (30–40%) reduction in sodium intake to 5–7 g sodium chloride. Since no unpleasant effect of such a proposition has been reported, this could be achieved through education and ‘comprehensible labelling’ of processed foods (the main source of sodium).

Conflict of interest statement. None declared.

(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. Dr¨ueke. Aphrodite, sex and salt—from butterfly to man. Nephrol Dial Transplant 2008; 23: 2154–2161.)

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