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DIETARY SODIUM INTAKE AND HYPERTENSION

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Introduction

Hypertension is a heterogeneous disease in which both genetic and environmental factors play a role. Among the major environmental determinants of high blood pressure (BP) are high alcohol consumption, physical inactivity, and dietary factors, in particular dietary salt and potassium intakes. In recent years, the benefits of lowering sodium and increasing potassium intakes have been reinforced by the demonstration that these non-pharmacological approaches to hypertension management enable the lowering of blood pressure and the reduction of target organ damage as well as cardiovascular events [1]. However, despite accumulating experimental, epidemiological, and clinical evidence from patients with genetic diseases or from interventional studies, the need and pertinence of promoting a low sodium intake in the management of hypertensive patients remains regularly disputed. When combined with the difficulty to implement such non-pharmacological strategies in clinical practice, unless national initiatives are taken, this scientific dispute has led to a general underuse and lack of promotion of these preventive approaches in favour of therapeutic drug strategies.

Association between dietary salt intake and blood pressure

Experimentally, numerous studies involving various species and genetically modified animals have demonstrated that a prolonged increase in salt intake leads to an increase in blood pressure. Convincing evidence of a link between sodium intake and the level of blood pressure has been obtained in chimpanzees, which are genetically very close to humans [2, 3]. A study conducted on chimpanzees showed that increasing dietary salt intake substantially (> 15 g of salt per day) increased BP during a 20-month period. Blood pressure returned to pre-intervention levels within 3–4 months in the high-salt intake group after salt intake was returned to baseline. Another study was conducted in chimpanzees to analyze BP alterations in response to smaller changes in dietary salt intake [3]. In this study, BP closely followed changes in dietary salt intake. An important piece of information from this study is that BP changes were as large for sodium intakes at or below current guidelines (*i.e.* 2–6 g/day mmol/24 h) as for higher intakes (6–15 g/day).

In humans, a weak association between salt intake and the level of BP has also been demonstrated. The most frequently cited study is the INTERSALT study [4], which showed that 24-hour urinary sodium excretion, a proxy of sodium intake, was significantly associated with both systolic and diastolic blood pressure in individual subjects. More importantly, the results of this study demonstrated a greater rise in blood pressure with age among subjects with higher salt intake. In the 1990s, an overview of data collected for 47,000 non-African subjects from 24 communities confirmed the positive association between BP and urinary sodium excretion across and within populations, and its strengthening with age [5, 6]. Of note, in the INTERSALT study, populations with low dietary salt intakes (*i.e.* < 50 mmol/24 h for sodium or 3 g/24 h for salt) had little BP increase with age. In the EPIC-Norfolk study involving 23,104 individuals, BP was also higher among subjects with a high sodium intake, the prevalence of an elevated BP (systolic > 160 mm Hg) being 12% when the salt intake was > 12.9 g/day and only 6% in those with a salt intake of 4.7 g/day [7].

Dietary salt intake and target organ damage

A high sodium intake has also been associated with left ventricular hypertrophy (LVH), and the structure and function of large arteries and of the kidney in part independently of its impact on blood pressure.

Left ventricular hypertrophy is recognized as an independent predictor of cardiovascular complications and mortality [8]. Its prevalence is particularly elevated among hypertensive patients because BP is a major determinant of left ventricular mass. However, there are good experimental data suggesting that a high salt intake can promote left ventricular hypertrophy even in the absence of an elevated systemic BP. Experimentally, sodium is a necessary co-factor for the development of LVH and cardiac fibrosis in animals receiving an excess of mineralocorticoids [9]. Moreover, an increase of sodium concentration directly exerts growth stimulating intracellular signals. In humans, several cross-sectional studies have reported a positive association between urinary sodium excretion and left ventricular mass, both in normotensive subjects and hypertensive patients [10, 11]. Careful assessment of dietary salt intake confirmed such a blood pressure independent relation of sodium intake with left ventricular mass. In these studies, salt intake was found to be a powerful determinant of left ventricular mass. In hypertensive patients, a reduction in salt intake is associated with a reduction of left ventricular mass, concomitant to the reduction in blood pressure.

At the vascular level, increased sodium intake has been reported to induce pronounced structural alterations of arteries, such as cerebral or renal arteries, independently of BP levels [12, 13]. Through changes in shear stress and endothelial function, high sodium intake can induce pressure-independent effects on the vascular wall, affecting the vascular content of collagen and elastin fibres. Clinically, there is also evidence that salt affects arterial stiffness and hence systolic and pulse pressure. In a Chinese study, the age-associated increase in pulse wave velocity was lower in the community with a lower salt intake [13]. Interestingly, salt consumption was double in the urban Chinese population than in the rural population, and the age-related changes in systolic BP and aortic stiffness occurred 30 years of age later in the rural than in the urban community. A reduction in dietary salt intake reduced pulse pressure, suggesting an improvement in arterial distensibility [14].

Experimentally, a low sodium diet prevents renal alterations in several models of hypertension and renal diseases. In rat models of hypertension and reduced renal mass, salt restriction prevents an increase in proteinuria, compensatory kidney growth, and glomerulosclerosis [15]. Similarly, in diabetic animals, long-term salt restriction attenuates the progressive rise in albuminuria and the development of renal hypertrophy. A low sodium intake may also induce renal protection by reducing glomerular hyperfiltration [16]. In humans, the long-term benefits of a low sodium intake on the progression of non-diabetic or diabetic nephropathies are less well documented. However, in a retrospective analysis of chronic kidney disease progression, the rate of decline in creatinine clearance over a 43-month period was two-fold greater in patients on a high sodium intake (> 200 mmol/day) when compared to patients on a low sodium intake (< 100 mmol/day) [17]. Several short-term studies have shown that a high sodium intake increases glomerular filtration and may have a detrimental effect on glomerular haemodynamics, as reflected by an increase in filtration fraction and hence in intraglomerular pressure. The most significant impact of dietary salt intake on renal function is certainly its effect on urinary albumin excretion. In a cross-sectional study including untreated subjects with a wide range of BP levels, the prevalence of microalbuminuria was markedly higher in subjects with a sodium intake higher than 12 g/day [18]. This finding is corroborated by the results of the Groningen population-based study including 7850 subjects, in which an interaction between sodium intake and obesity on the prevalence of microalbuminuria was found [19]. Lowering salt intake in proteinuric patients is associated with a significant reduction in urinary protein excretion, and salt restriction increases the antiproteinuric effect of blockers of the renin-angiotensin system, an effect that can be mimicked by the administration of a thiazide diuretic in combination with an RAS blocker.

Dietary salt intake and the incidence of cardiovascular events

Several prospective observational studies have analyzed the association of dietary sodium intake and all-cause mortality. Tuomilehto et al. reported that dietary sodium intake is associated with a 32% increase in all-cause mortality in men, but the association was only observed in overweight men [20]. Other studies [21] found a positive

association between dietary sodium intake and cardiovascular mortality, in particular in overweight subjects, whereas other studies found no such association. In the Scottish Heart Health Study, a positive association between dietary sodium intake and coronary death was found in women, but not in men [22]. In the NHANES I follow-up study, a negative association was found between dietary salt intake and cardiovascular mortality, but the association was positive when sodium excretion was corrected for calorie intake [23]. Several prospective studies examined the association of dietary sodium intake and the risk of stroke. The data gathered so far are inconsistent. However, based on the changes in blood pressure from the meta-analysis of randomized salt-reduction trials and the relationship between BP and stroke and ischaemic heart disease, it has been estimated that a 3 g/day reduction of dietary salt intake would reduce stroke by 13% and ischaemic heart disease by 10% [24].

Interventions to lower dietary salt intake reduce BP and cardiovascular events

Numerous interventional studies have been conducted to investigate the clinical impact of lowering dietary sodium intake on BP. Several of them were limited either by the short duration of the intervention or by the very small or excessive changes in sodium intake obtained during the study. The last meta-analysis of randomized studies which took into account only studies with a duration of at least one month and modest reductions of sodium intake that can be achieved in daily life practice (mean 4.4–4.6 g of salt/day) demonstrated that a reduction in salt intake is associated with a significant decrease in BP, both in normotensive and hypertensive individuals [25].

Several large clinical trials have investigated the impact of lowering salt intake alone or in association with other dietary or non-pharmacological interventions on blood pressure and cardiovascular events. The trial of non-pharmacologic interventions in the elderly (**TONE**) [26] implemented weight loss and/or sodium reduction in obese patients or sodium reduction in non-obese hypertensive subjects aged 60–80 years treated with one antihypertensive drug. The goal was to obtain and maintain a urinary sodium excretion of less than 80 mmol/24 h (< 4.7g salt/24 h) in addition to a weight loss of at least 4.5 kg. A usual care group was compared to an active intervention group. The combined outcome measures (incident hypertension and/or cardiovascular events) were less frequent among those assigned vs not assigned to reduced sodium intake (relative hazard ratio 0.69). Relative to usual care, hazard ratios among the obese participants were 0.60 for reduced sodium intake alone, 0.64 for weight loss alone, and 0.47 for reduced sodium intake and weight loss combined after a median follow-up of 29 months. In the Trial of Hypertension Prevention I (**TOHP I**), multiple lifestyle changes were compared in parallel, including dietary sodium reduction and weight reduction [27]. The target population were healthy men and women aged between 30 and 54 years, with high normal diastolic blood pressure, who were not taking antihypertensive treatment. A significant 55-mmol reduction in urinary sodium excretion was achieved in the sodium reduction group, but not in the control group at 18 months. Systolic and diastolic BPs were significantly reduced in the active group versus the control group for the sodium reduction and weight loss interventions. In the sodium reduction group, there was a non-significant 16% reduction in the incidence of hypertension (RR: 0.84, 95% CI: 0.62–1.13), whereas in the weight loss group, there was a significant 36% reduction in the incidence of hypertension (RR: 0.66, 95% CI: 0.46–0.94). The aim of the Trial of Hypertension Prevention II (**TOHP II**) (2 × 2 factorial randomized, open multicenter trial) was to determine whether weight loss alone, dietary sodium reduction alone, or a combination of both interventions could lower BP and reduce the incidence of hypertension in subjects with high-normal BP [28]. Participants in this trial had high normal diastolic BP (83–89 mm Hg) with systolic BP < 140 mm Hg. Blood pressure was significantly lower in the intervention groups in each time period. The large effects observed at 6 months greatly diminished during follow-up, indicating that long-term interventions for sodium reduction are difficult to maintain. At 48 months of follow-up, the incidence of hypertension was significantly lower in every intervention groups as compared to the usual care group. The results of the long-term follow-up (10–15 years) of patients enrolled in the THOP1 and THOP II trials showed a non-significant 20% lower all-cause mortality in the group of subjects assigned to the sodium restriction intervention but a significant 30% lower incidence of cardiovascular disease (defined as myocardial infarction, stroke, coronary artery bypass graft, coronary angioplasty, or death of any cardiovascular cause) as compared to persons of the control groups.

The **DASH** study is a landmark trial, which compared a control diet with a diet rich in fruit, vegetables, and low-fat dairy products (*i.e.* DASH diet). The DASH diet significantly reduced blood pressure at 1 month. In the subsequent DASH-sodium trial, three different dietary sodium intakes were compared, 150, 100, and 50 mmol/24 h, which correspond to approximately 8.8, 5.8, and 2.9 g of salt per day, respectively, with and without DASH diet [29]. Blood pressure was significantly lower when going to a lower group of dietary salt intake in both the control diet or the DASH diet groups. The results of low sodium — DASH diet trial further strengthen the conclusion that reduction of dietary sodium intake through low-salt diet lowers BP effectively and adds to the benefits conferred by the DASH diet. More recently, a large interventional study was conducted to examine the association between metabolic syndrome and salt sensitivity, defined as the BP response to low (50 mmol/day) and high (300 mmol/day) salt intake [30]. The results of this study performed in non-diabetic Chinese subjects revealed that the presence of metabolic syndrome increases the BP response to salt intake. Hence, sodium restriction could be an important component of the strategy to lower BP in subjects with the metabolic syndrome.

Conclusions

Non-pharmacological dietary interventions promoting low salt intake should be more systematically considered in the prevention and management of essential hypertension and prevention of hypertensive target organ damage. Although these approaches are considered difficult to implement and sustain over a number of years in most subjects, they provide unique cost-effective opportunities to avoid drug treatment in the early stages of hypertension and to reduce drug therapies in patients with established hypertension. In view of the difficulty in achieving long-term changes in dietary habits at the individual level, nationwide interventions aimed at reducing the sodium content of processed foods may provide substantial health benefits to the general population and also to hypertensive patients.

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