Salt and Hypertension Hypothesis - Still Relevant
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Abstract
Dietary salt intake is a common and important risk factor for hypertension. There has been a shift in the understanding of the pathogenesis of hypertension and the role that salt plays in its development - from the centrality of kidney, to the concept of salt sensitivity and more lately, hypertension as a disorder of endothelial function. There remains much heated debate and controversy about the relation between salt and hypertension, with both proponents and opponents pointing to observational, experimental, and epidemiological evidence supporting their claims. Other dietary factors such as refined sugars and potassium have also been identified as important contributory factors to hypertension, raising the question of whether the role of salt was as central as it was purported to be. While few would challenge the evidence showing the benefit of a low-salt diet in hypertensive patients, the contention is whether the same strategy of salt restriction should apply to normotensive populations to prevent hypertension, given observational data that low-salt intake may be associated with increased cardiovascular risk. With increasing prevalence of hypertension and burden of metabolic diseases worldwide, more evidence in the form of randomized controlled trials is required to determine whether a low-salt intake should be recommended as policy, which must strive to benefit majority of the population without causing harm to the minority. Until then, the salt and hypertension hypothesis is likely to remain relevant in the foreseeable future.

Key words: Controversy, endothelial function, hypertension, salt sensitivity

Introduction
The Evolving Understanding of Salt and Hypertension

Essential hypertension accounts for >90% of cases of hypertension.[1,2] The pathogenesis of essential hypertension is multifactorial, with involvement of multiple pathophysiologic factors. THESE include increased sympathetic nervous system activity, activity of the renin-angiotensin-aldosterone system, and vascular tone due to inappropriate levels of vasoconstrictors, vasodilators and alterations in adrenergic receptors; inadequate dietary intake of potassium and calcium; diabetes mellitus and insulin resistance; and altered cellular ion transport.

In addition to these, dietary sodium, or salt, intake has been found to play a key player, and the most common and important risk factor for hypertension.[3] Numerous clinical trials have shown a direct association and causal relation between salt intake and the pathogenesis of hypertension. In particular, sodium retention due to the overproduction of sodium-retaining hormones or inappropriate renal salt handling due to alterations in expression of the Kallikrein–Kinin system have been implicated as mechanisms in hypertension.[2]

In the last half a century, there has been a gradual shift in the understanding of the role of salt in hypertension. The traditional view emphasized the centrality of the kidney and its malfunction in the development of hypertension. It was proposed that hypertension was a consequence of impaired sodium and water excretion due to a failure of pressure diuresis in regulating blood volume to return arterial pressures to control values.[4,5] The hypothesis that renal salt handling plays a role in hypertension has also been supported by studies which show that genetic mutations affect blood pressure in Mendelian or monogenic forms of human hypertension and hypotension.[6,8]
The concept of salt sensitivity developed around the same time, with observations that blood pressure responses to dietary salt intake varied among both hypertensive and normotensive individuals due to differing abilities and extents of salt excretion.\(^9\) Salt sensitivity was subsequently characterized by an alteration of kidney function that necessitates higher arterial pressure to excrete a given amount of salt. While there is no universal definition of salt sensitivity, it is usually arbitrarily defined as an increase in blood pressure of 10% or greater during a high-salt diet than that during a low-salt diet. Dahl et al. demonstrated the concept of salt sensitivity and salt resistance by producing from the Sprague-Dawley line two strains of rats that were either susceptible or resistant to the hypertensive effects of a high-salt (8% sodium chloride) diet; salt-sensitive rats rapidly and uniformly developed hypertension and died by 12 weeks of age.\(^{12}\)

In a recent scientific statement, the American Heart Association succinctly summarized salt sensitivity as not a single disease, but an entity that is superimposed on a constellation of disorders\(^\text{13}\) - multiple inherited or acquired disorders of the endothelium, exacerbated by long-term consumption of a high-salt diet disrupt endothelial responses to high-salt intake and promote a complex syndrome of salt sensitivity.\(^{14}\)

However, recent studies suggest alternative and novel paradigms of salt and hypertension. Heer et al. in a randomized controlled trial involving healthy males showed that instead of increasing total body water, high-salt intake increased plasma volume dependently, suggesting non-osmotic sodium storage resulting in fluid shift from the interstitial to intravascular compartments.\(^{15}\) In support of this hypothesis, it has been subsequently demonstrated in rats that skin is a major site for osmotically inactive sodium storage without accompanying water retention,\(^{16}\) and rats receiving a high-salt diet developed hypertonicity of the skin interstitium.\(^{17,18}\)

Feng et al. in a recent review proposed that a central feature of hypertension may be a fine balance of endothelial homeostatic function in response of extracellular fluid volume expansion.\(^{14}\) The understanding of the pathogenesis of hypertension has thus gradually shifted from kidney malfunction to endothelial dysfunction\(^3\) and has been supported with evidence showing the role of salt in generating oxidative stress,\(^{19-22}\) increasing asymmetrical dimethylarginine,\(^{23}\) and transforming growth factor beta-1,\(^{24,25}\) with the common pathway being their effects on a net reduction of bioavailable nitric oxide and resultant endothelium-dependent dilatation.

**The Controversy - For and Against the Low-Salt Diet**

Despite the understanding of the pathophysiology of hypertension above pointing clearly to salt as a key player in the pathogenesis of hypertension, there remains heated debate and controversy about the relation between salt and hypertension.\(^{26}\)

Proponents of the salt-hypertension hypothesis point to overwhelming observational, experimental, and epidemiological evidence. It had been observed that hypertension was not prevalent in societies that thrived on a hunter-gatherer diet, until they became urbanized and were exposed to a high-salt diet.\(^{27,28}\) A classic study is the Yi Migrant study, where the Yi population, who lived in a salt inaccessible remote mountain region of China, had a very low prevalence of hypertension in their community until they migrated and adopted salt-rich diet, after which the incidence of hypertension started to increase.\(^{29,30}\)

The INTERSALT study, a worldwide epidemiology study with a sample size of more than 10,000 participants found a significant positive and independent linear relationship between 24-h sodium excretion and systolic blood pressure, concluding strongly that its results agree with findings from other diverse studies, including data from clinical observations, therapeutic interventions, randomized controlled trials, animal experiments, physiologic investigations, evolutionary biology research, anthropologic research, and epidemiologic studies, support the judgment that habitual high-salt intake is one of the quantitatively important, preventable mass exposures causing the unfavorable population-wide blood pressure pattern that is a major risk factor for epidemic cardiovascular disease (CVD).\(^{31}\)

Low-salt diets, such as the Kempner’s rice diet\(^\text{32}\) and dietary approaches to stop hypertension (DASH) diet\(^\text{33}\) showed the benefit of a salt-restricted diet on blood pressure in hypertensive and even normotensive individuals (in the case of the DASH diet). Systematic reviews including a Cochrane review\(^\text{34,35}\) and one conducted by the World Health Organization’s nutrition policy and scientific advice unit\(^\text{36}\) support the efficacy and beneficial effects of a very low-salt diet in a non-acute illness, normal population.

Opponents of the salt-hypertension hypothesis dispute the benefits of salt restriction, pointing to inconsistent outcomes in observational studies.\(^\text{37,38}\) Particular concerns and reservations include methodologies of the epidemiological studies, inadequate consideration of harmful effects of salt deprivation and lack of attention and weight attributed to studies on salt loading (as opposed to salt-deprivation), and measurement of total body sodium.\(^\text{39}\)

Critiques of the Yi Migrant study argued that the increase in hypertension incidence coincided and was confounded by the adoption of a sedentary lifestyle and weight gain among other factors. Detractors of the INTERSALT study criticized it on the basis of its generalization that a reduced sodium intake will decrease hypertension across ethnic groups and for using epidemiological and biostatistical methods that did not adequately reduce error.\(^\text{40}\) Statisticians Freedman and Petitti subsequently also published an article arguing that the results in INTERSALT were driven mainly by four outlying populations, and across the 48 other populations, blood pressures actually decrease with salt intake.\(^\text{41}\)

It has also been observed that numerous populations that consume a high-salt diet that is low in refined sugar do not actually develop hypertension. These include the Kotyang inhabitants in Nepal, Kuna Indians off the coast of Panama and Buddhist farmers in Thailand.\(^\text{42}\) An analysis of 27 populations indicated that six populations including Java, Thailand, parts
of Taiwan with an agricultural population, North India, rural Bantu, and Okyama had an average blood pressure that was not hypertensive despite eating a high-salt diet (mean daily salt intakes ranging from 9 to 19 g of salt).\(^{43}\)

DiNicolantonio \textit{et al.} suggested that dietary salt is more of an Innocent Bystander in the phenomenon of salt and fluid overload and that added dietary sugar, fructose, in particular, is the main culprit and primary cause of hypertension.\(^{44,45}\) Overconsumption of refined carbohydrates has been shown to reduce nitric oxide, possibly leading to increased peripheral vascular resistance, increase oxidative stress, activate the renin-angiotensin-aldosterone system, and cause hyperinsulinemia and insulin resistance.\(^{46-48}\)

The contributory role of a diet low in potassium to the development of hypertension has been well established, with a meta-analysis by Whelton in 1997 concluding that increased potassium intake be considered as a recommendation for prevention and treatment of hypertension, especially in those who are unable to reduce their intake of sodium.\(^{49}\) 20 years on, a meta-analysis by Poorolajal finds that potassium supplementation has a modest, but significant positive impact on blood pressure and may be recommended as an adjuvant antihypertensive agent for patients with essential hypertension, without significant adverse effects.\(^{50}\) Data from the Third National Health and Nutrition Examination Survey indicate that a higher sodium-to-potassium ratio is associated with significantly increased risk of CVD and all-cause mortality in the general US population.\(^{51}\)

Identification of these dietary factors which contribute to the development of hypertension has raised the question of whether the role of salt was as central and important as it was purported to be.

\textbf{Salt - One Man’s Meat, Another Man’s Poison?}

While few would challenge the evidence showing the benefit of a low-salt diet in hypertensive patients, the contention is whether the same strategy of salt restriction should apply to normotensive populations to prevent hypertension, given the potential harms as postulated above.

In 2003, a technical report by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations recommended a population-wide daily salt intake of no more than 5 g. Several nations, including the United States, Canada, Finland, Ireland, and the United Kingdom, have taken steps to reduce the sodium intake of their populations.\(^{52}\)

The World Action on Salt and Health, a global group which aims to emulate the success of the United Kingdom salt reduction strategy, was launched in 2005 with the mission of improving the health of populations throughout the world by achieving a gradual reduction in salt intake.\(^{53}\)

The Salt Intake study in Singapore comprised 800 subjects aged 18–79 years of age and was conducted as part of the National Nutrition Survey 2010. It was found that among adult Singapore residents, the estimated salt intake was 8.3 g (or 3265 mg sodium) per day, based on a mean urinary sodium excretion of 142.2 mmol/24 h. About eight in 10 Singapore residents (80.2%) exceeded the recommended dietary limit for salt. Moreover, 27.7% of the population consumed double the recommended limit.\(^{54}\)

This finding has led to the introduction of the “FINEST (Functional, Innovative, Nutritious, Effective, Science-based, and Tasty) Food Programme,” a multiagency collaboration between the Health Promotion Board’s Centre of Excellence for Nutrition, private sector food industry Singapore Food Manufacturers Association, and knowledge institutions including the Agency for Science, Technology, and Research (A*STAR) and various polytechnics, to develop healthier salt and other functional food products.\(^{55,56}\)

The effectiveness and success of this endeavor will be evaluated in the upcoming National Health Survey and National Nutrition Surveys. It will be hoped that the latest government effort taking a multipronged approach to the “War on Diabetes,” which includes reducing sugar in Singaporean’s diet by 25% in 2020\(^ {57}\) will have a synergistic effect to reduce the prevalence of hypertension further.

Several studies, including Cochrane reviews, in the early 2000s and 2010s\(^ {58-61}\) have observed that the magnitude of the effect of reduced sodium intake does not warrant support for a general or universal recommendation for dietary salt restriction, and may even be questionable in view of marginal benefit and suggestion of possible deleterious effects on cardiovascular outcomes.

A recent large population-based observational cohort study by Stolarz-Skrzypek \textit{et al.} concluded that lower sodium excretion was associated with higher cardiovascular mortality,\(^ {62}\) leading to the extrapolation that a low-salt diet is associated with increased mortality. The main risk is attributed to the expected activation of the renin-angiotensin-aldosterone system along with increased sympathetic nervous system activity.\(^ {63}\) Although this study was criticized and dismissed by The Lancet,\(^ {64}\) another large population study by O’Donnell \textit{et al.} subsequently followed shortly confirming the association between low-salt intake with increased cardiovascular risk.\(^ {65}\)

In 2014, the PURE study conducted also by O’Donnell \textit{et al.} was published, showing that a J-shaped association curve exists, with both higher (>5 g/day) and lower levels (<3 g/day) of sodium excretion being associated with increased risk of CVD.\(^ {66}\) A subsequent meta-analysis showing that low-sodium intakes and high-sodium intakes are associated with increased mortality\(^ {66}\) supported this finding as well. The PREVEND cohort study also showed no association between sodium excretion and risk of coronary artery disease.\(^ {67}\) Most recently in 2016, O’Donnell \textit{et al.} published a pooled analysis from four studies concluding that high-sodium intake is associated with an increased risk of cardiovascular events and death in hypertensive populations, without an association in normotensive populations, while the association of low-sodium intake with increased risk of cardiovascular events and death is observed in those with or without hypertension.\(^ {64}\)
Conclusion

It might be argued that the salt and hypertension hypothesis remains controversial - with strong evidence of benefit for salt restriction in hypertensives, even though it is uncertain whether salt deprivation in normotensives confers more risks than benefit. With increasing prevalence of hypertension and burden of metabolic diseases worldwide, many of which have common biochemical pathways in their pathogenesis, most nations continue to adopt a strategy of reduction in their populations' salt intakes. It would also be important to look at salt intake in the context of other dietary and environmental factors which affect blood pressure, which include but are not limited to obesity and intake of potassium and fat. Nevertheless, the relevance of the salt and hypertension hypothesis is likely to remain in the foreseeable future.

Although a population-based randomized controlled trial may not be feasible to better support causality between salt intake and health outcomes, a pilot randomized controlled trial (Sodium Intake in Chronic Kidney Disease, ClinicalTrials.gov Identifier: NCT02458248) is underway to determine whether recommending a low-salt intake, compared to average/moderate intake, is associated with a slower rate of decline in kidney function in patients with chronic kidney impairment.

As in most policies, there is probably no one-size-fits-all approach, especially in the salt and hypertension debate given the effect of sodium on multiple physiological systems and processes. The sweet spot would be crafting an approach which benefits the majority of the population without causing harm to the minority.

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