Sodium Intake induece Cardiovascular damages

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Sodium (Na+), contained in dietary salt, is essential for human homeostasis. For millions of years, our ancestors ate less than 0.25 g of salt per day, while the current average daily consumption approaches 10 g in most countries. Such an increase over a comparatively modest time span imposes a significant physiological challenge in evolutionary terms.

Keywords: salt ; sodium ; blood pressure ; hypertension ; cardiovascular

1. Introduction

Sodium (Na+), contained in dietary salt, is essential for human homeostasis. For millions of years, our ancestors ate less than 0.25 g of salt per day, while the current average daily consumption approaches 10 g in most countries [1][2]. Such an increase over a comparatively modest time span imposes a significant physiological challenge in evolutionary terms. Excessive sodium intake is thought to adversely affect our health through effects on blood pressure (BP) and cardiovascular damages. Consequently, three million deaths were attributed to high salt intake in 2017 [3]. Given that the majority of cardiovascular burden affects individuals with high-normal BP or mild hypertension, dietary and lifestyle programs including salt reduction constitute attractive and simple public health measures [4]. Despite general agreement that excessive sodium consumption is globally harmful, controversies still exist on the net benefit of sodium intake reduction on a population level and the levels that should be targeted [5]. Moreover, far from a simplistic cause–effect relationship, pathophysiological mechanisms linking sodium intake and cardiovascular outcomes are diverse and intricate.

2. Sodium Intake, Blood Pressure and Cardiovascular Outcomes

Although the beneficial effect on BP is clear, it has been previously suggested that sodium intake reduction could potentially lead to harmful consequences. A meta-analysis of 167 trials randomizing patients to low versus high sodium diets concluded that sodium reduction resulted in an increase in renin, aldosterone, catecholamine and cholesterol levels [6]. However, this report included studies involving large reductions in sodium intake over a very short period of time. Such an abrupt decrease in sodium consumption is expected to enhance several compensatory mechanisms, in contrast to what has been described with a modest reduction over longer periods [7]. Second, a dose-response relationship between sodium intake and BP has consistently been shown across observational as well as interventional trials, suggesting that benefits of sodium reduction could extend to very low values [8][9][10][11]. Third, studies have generally shown that sodium reduction allowed a significantly greater BP fall in older, hypertensive and Afro-American individuals [8][12]. Such findings can be linked to varying sensitivities of the renin–angiotensin–aldosterone system (RAAS) regulation in different populations [13][14]. Finally, sodium reduction has synergistic effects with pharmacological and conservative measures on BP control. The DASH-sodium trial showed that a combination of low sodium and a healthy diet has a greater effect on BP reduction than individual measures [9]. The TONE and TOHP-II trials reported similar additive effects of sodium reduction with weight reduction [15][12]. Taking into account such compensatory mechanism, a randomized controlled trial showed that sodium reduction allowed for a further reduction of BP in hypertensive individuals treated with captopril as compared to normal sodium intake [16].

Globally, the causal relationship between sodium intake and BP control is, thus, well established, and modest reduction in salt consumption is associated with a meaningful reduction in BP on a population level. However, as the full effect of sodium intake reduction on BP control is not reached until several weeks, results of interventional trials could have underestimated the magnitude of this effect as most studies lasted a few weeks only [17][18]. On the other hand, the few existing long-term interventional trials showed that maintaining a lower salt intake on a prolonged time period is challenging from an individual perspective given the societal food environment [15][19].

As sodium intake reduction lowers BP in normotensive and hypertensive individuals, it could also be expected to improve cardiovascular outcomes. However, evidence from large, long-term, randomized controlled trials on an individual level is currently lacking.

Considering the available evidence, it is reasonable to assume a direct and continuous relationship between sodium intake, BP control and cardiovascular outcomes from a population standpoint. However, as definite evidence from long-term randomized controlled trials is still lacking, a consensus has yet to be reached on the effectiveness, safety and feasibility of sodium intake reduction on an individual level. Until then, it seems judicious to routinely evaluate sodium intake in patients at high cardio-renal risk and recommend adherence to low sodium diet as part of a multifaceted treatment approach in an effort to reduce morbidity and mortality in those patients [20][21].

3. Pathophysiological Considerations

Multiple mechanisms are responsible for the association between sodium intake and BP. The key role of the kidney in this relationship has been clearly demonstrated in several transplant experiments [22][23]. Guyton formalized the basic principle of kidney BP regulation as the pressure natriuresis response [24]. In its simplest form, this concept states that when BP increases, the excess pressure causes the kidney to excrete more sodium and water. This, subsequently, decreases extracellular blood volume and, thus, preload as well as cardiac output, thereby restoring BP to lower levels. On the other hand, variations in sodium intake induce parallel changes in plasma sodium content, both in hypertensive and normotensive individuals [25][26]. A rise in plasma sodium increases osmolarity, thus inducing a fluid shift from the intracellular to the extracellular compartment. A small increase in plasma osmolarity also stimulates vasopressin secretion, thus resulting in water retention. Both these mechanisms restore plasma sodium to its original level but also increase extracellular fluid volume thereby increasing BP [27]. Importantly, evidence exists that a variation in plasma sodium can influence BP regulation independently of blood volume variation [28]. Such additive effects could be mediated by the direct influence of plasma sodium on the hypothalamus; the vasculature as well as the immune system [29][30][31].

Excessive sodium has been shown to be involved in different pathways such as oxidative stress, inflammation and fibrosis, which are determinant in target organs being damaged. In patients with non-diabetic chronic kidney disease, sodium restriction increases the concentration of anti-inflammatory and anti-fibrotic peptides on top of RAAS blockade, providing pathophysiological insights into the synergistic benefit of sodium reduction and RAAS blockade [32]. Animal studies confirmed a direct pro-fibrotic effect of sodium on glomeruli mediated via an increased local expression of transforming growth factor (TGF) β [33][34]. Additionally, sodium intake directly influences nitric oxide (NO) generation and local oxidative stress in rats' kidneys [35][36]. Thus, in middle-aged hypertensive adults, dietary sodium restriction largely reversed macro- and microvascular endothelial dysfunction by enhancing NO bioavailability and decreasing oxidative stress, thus supporting a direct vascular protective effect of sodium restriction beyond any influence on BP regulation [37].

The adverse effect of sodium on target organs could be partially mediated by hormonal interactions. In a case-control study including 21 patients with primary aldosteronism and 21 hypertensive control patients, 24 h sodium excretion was associated with left ventricular mass and thickness only in patients with primary aldosteronism [38]. Aldosterone excess may thus play a permissive role in sodium induced target organ damage. Another study prospectively investigated the influence of sodium intake on cardiac outcomes of patients both before and after treatment of primary aldosteronism [39]. Interestingly, sodium intake interacted with aldosterone in inducing cardiac changes over time, while left ventricular mass was associated with both sodium intake and aldosterone levels before treatment. The decrease in ventricular mass obtained after treatment was greater in patients whose sodium intake also decreased. Change of ventricular mass was also associated with sodium intake independently of BP and other potential confounders. In another study including 90 adults with essential hypertension, left ventricular mass was associated with plasma aldosterone level after, but not prior to, intravenous saline load, implying that a limited ability of sodium to supress aldosterone production could contribute to organ damage [40]. Finally, in a longitudinal study, 182 adults with essential hypertension and left ventricular hypertrophy were treated with RAAS blockade [41]. The observed decrease in left ventricular mass over time was correlated with change in BP, 24-h sodium urinary excretion and plasma aldosterone concentration. At the end of the follow-up, the combination of high sodium intake and high aldosterone levels was associated with increased left ventricular mass. In contrast, in patients with low sodium intake, no influence of aldosterone levels was detected. These results together suggest that persistence of organ damage despite adequate BP control may result from the combined effect of excessive sodium intake and breakthrough of aldosterone despite pharmacological blockage. Basic research studies also support the interplay between sodium and aldosterone in organ damage physiopathology as aldosterone-induced superoxide over-production and vascular smooth muscle hypertrophy in cell culture, a phenomenon synergistically augmented with sodium chloride [42].

Altogether, the available evidence suggests that sodium not only affects target organs via its indirect effect on BP but, clearly, also through complex interconnected pathways involving oxidative, inflammatory, endocrine, immune and microbiological mechanisms.

4. Conclusions

The available evidence points toward a causal role of sodium intake on BP and cardiovascular prognosis. While the pathophysiological link between hypertension and cardiovascular events is relatively straightforward, a large body of data now suggests that sodium directly damages target organs independently of BP control via multiple intricate pathways. Although gaps in knowledge still exist, reduction in sodium intake on a population level represents a feasible strategy to reduce the burden of cardiovascular morbidity and mortality worldwide.

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