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## Novel paradigms linking salt and health

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## Novel paradigms linking salt and health

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**Abstract.** Although sodium is an essential nutrient, conclusive scientific evidence suggests the association between excessive salt intake and various negative health outcomes. One of the health consequences with the greatest public health impact is the increase in population blood pressure with a consequent increase of cardiovascular disease risk. There is ample evidence linking high salt intake with other health outcomes: stomach cancer, impaired renal function, osteoporosis, obesity, severity of asthma, but also with novel health risks established with advanced molecular and metagenomics technology: autoimmunity, immunity in various organs and systems. Some recent studies have reported that a high salt diet modulates the gut-microbiome, interacting with both the host's gastrointestinal tract environment and its genome and metabolism. The newest evidence indicates possible novel pathophysiological mechanisms of obesity, including high fasting ghrelin in healthy individuals consuming a high-salt diet, as well as endogenous fructose production and leptin resistance in mice. This revealing new evidence links high salt intake with obesity and consequently, with further metabolic complications. As a country with high prevalences of obesity and hypertension, and high salt intake, Serbia would greatly benefit from adopting and implementing a national sodium reduction program that minimize risks through education, regulation, and enforcement.

### 1. Sodium

Sodium is an essential nutrient for the physiology of the human body, interrelated with potassium, playing vital roles to maintain physiological homeostasis. It is the principal extracellular cation, corresponding to the leading intracellular cation, potassium (K<sup>+</sup>). Their interaction generates transmembrane electrochemical potentials, fundamental for electrical signaling in the nervous system, muscle, and heart. One of the most important roles of sodium is its involvement in extracellular fluid volume control and systemic distribution of total body water, and thus in blood pressure (BP) regulation. The amount of sodium required for all these demanding physiological roles is very small [1]. Sodium transport and co-transport systems of water and solutes are energy demanding processes consuming around 25% of the resting metabolic rate [2]. There is also new evidence suggesting that sodium metabolism is closely related to energy metabolism, linking high salt intake with non-



communicable chronic diseases (NCD's) such as obesity, diabetes mellitus, osteoporosis, and increased cardiovascular and neurovascular disease risk [3].

Blood concentration of both cations is tightly regulated by multiple homeostatic mechanisms maintaining plasma sodium and potassium concentrations of healthy individuals within a narrow range [4]. During the process of evolution, *Homo sapiens* has developed a high survival capacity in extreme sodium intake ranges, developing adaptive physiological mechanisms that reduce the losses of sodium in urine, feces, and sweat, and maintain blood sodium concentrations at low levels [5]. In the contemporary food environment, the dietary sodium intake from multiple sources far exceeds the physiological minimum and puts pressure on the homeostatic mechanisms. Novel evidence suggests the existence of biological clock in sodium and potassium kinetics, a circadian rhythm of urinary excretion of sodium and potassium, affecting water balance, glomerular perfusion, and filtration rate, and BP [4,5,6].

The nephron in the kidney is the leading “organ” regulating retention and excretion of sodium and, therefore, water homeostasis. In conditions of low dietary sodium intake, it efficiently saves sodium, and, conversely, in response to high dietary intakes, excretes the excess sodium [7]. Almost all ingested sodium (92.8%) is excreted in urine (ranging from 76% to 122% across studies), so 24-h urine collection is appropriate to measure dietary sodium intake [8, 9]. After the kidneys filter out all dietary sodium, more than 99% is reabsorbed in the renal tubules [7]. The number of nephrons and the glomerular filtration rate decreases with age, which reduces the efficiency of the regulatory system and partially explains the physiological occurrence of increasing BP with age in populations with high sodium intake [10]. While the loss of sodium *via* feces is relatively stable, losses *via* sweat vary widely and can be considerably higher in situations of extreme exercise and heat [11]. After excessive sodium intake, renal sodium excretion is established after about 24 h. A state of balance between sodium intake and urinary sodium excretion is considered to be achieved within a few days [12].

## 2. Dietary salt

The leading source of sodium in human nutrition is dietary salt, or sodium chloride (NaCl). One gram of sodium chloride provides 0.4 g of sodium and 0.6 g of chloride (17 mmol sodium and chloride) [2]. Humans are genetically predetermined to eat a diet with small quantities of salt, mainly naturally present in animal and plant food [13]. The role of salt in food preservation led to its long and very influential role in the history of humanity. Since the dawn of civilization, it has been one of the key factors in economic, social, spiritual, religious and political development. Salt is still highly valued, because of its microbiological, technological and sensory significance, primarily in food preservation [14].

Western diets are characterized by a high dietary intake of processed food, and even more, with ultra-processed food. When used in small quantities, those products are harmless. However, processed foods have intense taste and palatability, and are subject to sophisticated and aggressive marketing (reduced price for super-sized serving, free refill, social media). These factors contribute significantly to high intake of energy, fat, saturated fat, added sugar, additives, and salt, along with low fiber, vitamin, and mineral intake on consuming processed foods [15]. Epidemiological studies have found associations between consumption of processed food and the risk of cardiovascular diseases (CVD), a higher risk of dyslipidemia and higher incidences of overweight and obesity, as well as a higher risk of overall cancer and breast cancer [16].

High dietary salt intake consumed with processed foods or by adding salt during cooking or at the table, has long been associated with high BP, a major risk factor for CVD and cerebrovascular diseases [17]. New evidence also connects high dietary salt intake with other health risks [18].

### 2.1. Dietary salt intake

Dietary sodium/salt intake can be measured using different methods (2.5g of salt contains 1g of sodium) [9]. Blood sodium concentration is not a reliable indicator of usual dietary sodium intake

reflecting most often inadequate water balance, rather than salt intake. A number of different ways of measuring dietary sodium (salt) intake are currently available, including dietary (24-h dietary recall, Food Frequency Questionnaires, diet records) and urinary assessment (24-h urinary sodium excretion, spot urine). Selection of the appropriate method must be in accordance with the research interests, the profile of the respondents and their environment, and available resources. Population sodium intake should be a valid estimate of the range and frequency of dietary salt intake across the population, and must provide a valid estimate of mean population level intake in the representative population sample [19]. The World Health Organization (WHO) recognized 24-h urine collection as a standard method appropriate to measure dietary sodium intake [20, 21]. Sodium intake assessed by dietary records could lead to underreporting of salt intake by 29-41% [22].

One of the biggest systematic reviews, conducted as part of the 2010 Global Burden of Diseases (GBD), Injuries and Risk Factors Study, estimated the mean level of sodium consumption during 2010 in 187 nations (covering almost 74.1% of adults worldwide) was 3.95 g per day (corresponding to 9.88 g of salt), and regional mean levels ranged from 2.18 to 5.51 g per day. Estimated sodium intake level is nearly twice the WHO recommended reference intake of 2.0 g of sodium per day (5g of salt per person per day) [23; 24]. Similarly, according to data collected by the European Commission, salt intake in European adults ranges from 7 to 13 g per day [25]. While a national study of population salt intake has not yet been carried out in Serbia, salt intake measured by the reference 24-h urinary sodium excretion method was reported in Novi Sad. Average salt intake of 12.12 g per person per day was measured [26], similar to other countries in the sub-region, like Montenegro with an average salt intake of 11.6 g/day [27], and Slovenia with 11.3 g/day [28].

## 2.2. *Dietary sources of salt*

The leading dietary source of salt/sodium in developed countries, about 75-80%, is processed food, and 5-10% is obtained from sodium naturally present in the foods. These are non-discretionary salt sources that occur inherently in food or are due to salt being added during food production, manufacture or processing. The remaining 10-15% comes from salt added during cooking or at the table [29, 30]. In some countries, like many Eastern countries, the predominant source of salt in food is discretionary salt, from added condiments (soy sauce) to food, comprising 76% of total salt intake [22].

Despite some regional differences, in most European countries, four food categories are the main contributors to salt intake: bread, cereals and bakery products as a staple food, then meat and meat products, cheese and dairy products and canned and pickled vegetables [22]. Similar results were found in a study on the student population in Novi Sad, Serbia [31]. Those food groups are also targeted for reformulation in most countries where salt reduction actions occur.

## 3. **Salt and health**

Although sodium is an essential nutrient, conclusive scientific evidence systematically reviewed by leading health authorities suggest the association between excessive salt intake and various negative health outcomes [1,21,32]. Epidemiological data show that in 2017, more than half (3 million) of diet-related deaths and two-thirds (70 million) of diet-related DALYs (disability adjusted life years) globally were attributable to sodium intake greater than 3g per day (7.5g of salt per day), the leading dietary risk factors for deaths and DALYs globally [33].

One of the health consequences with the greatest public health impact is the increase in population BP with a consequent increase of CVD risk [17]. There is numerous evidence linking high salt intake with other health outcomes: stomach cancer, impaired renal function, osteoporosis, obesity, severity of asthma, but also with novel health risks established with advanced molecular and metagenomics technology: autoimmunity, and immunity in various organs and systems (brain, kidney, skin, and vasculature) [18]. Some studies have reported that high salt diet modulates the gut-microbiome interacting with both the host's gastrointestinal tract environment and its genome and metabolism,

revealing new evidence linking high salt intake and obesity, one of the major public health concerns, and consequently, with further metabolic complications [34].

### 3.1. Salt and cardiovascular diseases

It is indisputable that high salt intake is a determiner for individual and population BP [1, 21, 10]. Raised BP (greater than 140/90 mmHg) is the leading cause of mortality and disability in adults worldwide, mainly due to CVD [9]. With increasing BP, the risk for CVD outcomes increases progressively, and starts even at suboptimal BP levels 115/75 mmHg [35;36]. The public health significance is even greater having in mind there are so many individuals in the population with these BP values and the fact that clinical guidelines do not recommend any treatment for the majority of these individuals. It is well established that a reduction in BP causes a significant reduction in vascular events, and therefore, a wide population-approach through non-pharmacological measures (diet and lifestyle) is the most feasible option, recommended by the WHO and adopted under a UN Resolution of the 66th World Health Assembly in 2013 [36;37].

One of the latest epidemiological studies estimates that 9.5% (1.65 million) of all deaths annually from CVD worldwide in 2010 were attributed to sodium intake above the recommended level, 2.0 g of per day. Four of every 5 deaths (84.3%) occurred in low- and middle-income countries, and 2 of every 5 deaths (40.4%) were before 70 years of age [23].

Despite the many advances in our understanding, the precise mechanisms of how dietary salt elevates BP are still poorly understood. Besides mechanisms by which the kidneys retain salt, mechanisms that promote the expansion of extracellular fluid volume and increased cardiac output, many researchers are focused on molecular and biochemical events following endothelial dysfunction and peripheral vascular resistance [39;40]. Excess dietary salt and dietary or endogenous fructose also can play a synergistic role in the development of high sodium-induced hypertension. Several mechanisms promote salt and water retention, and sensitization to the renin-angiotensin system, while promotion of insulin resistance and nitric oxide (NO) deficiency are involved [41].

Gut bacteria could also affect the ability of the kidneys to excrete sodium, contributing to the BP level and control of hypertension. This can be partially explained by the beneficial or non-beneficial effects of short-chain fatty acids (SCFAs) (acetate, butyrate, and propionate/lactate), or by modulation of immunity and inflammation, cell metabolism, and proliferation [42]. High salt intake could additionally drive autoimmunity by inducing T helper (TH)17 cells, which could also contribute to hypertension. Induction of TH17 cells depends on the gut microbiota, yet the effect of salt on the gut microbiome is unknown [43].

### 3.2. Salt and obesity

Obesity has also become a leading public health concern. Recent evidence suggest that, independent of energy intake and high intake of macronutrients (fats, carbohydrates and/or proteins), intake of high non-caloric nutrients, such as micronutrient dietary sodium, could be associated with increased overweight and obesity risk, contributing significantly in metabolic and diabetes risk [44].

Several epidemiological studies have already shown that salt intake, by increasing thirst, promotes passive overconsumption of food and sugar-sweetened beverages [45,46]. A 1 g/d increase in salt intake was associated with an increase in consumption of sugar-sweetened soft drink of 27 g/d in children and adolescents [44,45]. Excessive consumption of processed food that is high in both calories and salt contributes to higher incidences of overweight and obesity [16]. Salty foods are often more palatable, encouraging consumption of greater quantities of these foods.

Dietary fructose intake has been undoubtedly linked to increased *de novo* lipogenesis, when newly synthesized fatty acids are either secreted into the blood as very low density lipoproteins – triglycerides – or temporarily stored as intrahepatic triglycerides, decreased insulin sensitivity and increased visceral adiposity in overweight and obese adults [47].

The newest evidence indicates possible novel pathophysiological mechanisms of obesity, including high fasting ghrelin in healthy individuals consuming a high-salt diet, as well as endogenous fructose

production and leptin resistance in mice. The mechanism for this effect is still unknown. High salt intake led to an increase in osmolality in the liver which triggers the aldose reductase pathway (polyol pathway), resulting in the development of metabolic syndrome, fatty liver and elevated BP in mice. High salt-induced hyperphagia is driven by fructose-dependent hyperleptinemia and reduced hypothalamic leptin sensitivity [48].

High-salt diets have been associated with a higher risk of developing diabetes mellitus regardless of the calorie intake [49,50]. A clinical study performed to assess findings in animal studies confirmed that high baseline salt intake also predicts metabolic syndrome, diabetes and non-alcoholic fatty liver disease in a healthy population, regardless of the calorie intake [48].

#### **4. Salt debate**

For decades, especially since the salt reduction strategy became part of a global strategy to reduce chronic diseases, the efforts to cut dietary salt were met with fierce resistance by the salt industry and some scientific opponents. Low-quality research with conflicting evidence started a debate over the extent to which elevated salt consumption contributes to death. This challenged clinicians and policy stakeholders to keep informed on the effects of salt on health outcomes.

One of the first studies with results opposed to the official recommendations showed a “J-shaped” association between estimated sodium excretion and cardiovascular events in a cohort with 29000 high-risk patients [51]. Mente and associates, in their re-analysis of data from the Prospective Urban Rural Epidemiology (PURE) study, also produced some controversial results [52,53]. Among them, they stated that intake below 3,000 mg of sodium per day was associated with an increased risk of death and that the strong association between salt and stroke exists only in the highest tertile of salt intake (over 12.7 g/day) [52,53]. Meticulous analysis of these results showed serious methodological gaps, such as inaccurate sodium measurements and sample selection (people eating a low sodium diet might be doing so because they are already sick, making it impossible to attribute low sodium intake as a cause of their poor health outcomes) [54].

#### **5. Salt reduction strategies**

Salt reduction has been recognized as the ‘best buy’ approach to prevent and reduce NCD’s [55]. WHO’s global action plan for the prevention and control of NCDs sets a specific target to reduce mean population salt intake of 30% by 2025, with the aim of achieving a target of less than 5 g per day (approximately 2 g sodium) [37].

Modest, stepwise sodium reduction, as recommended by the leading health authorities [1,2,20-21,37,55] remains an achievable, effective, and important public health strategy to prevent a considerable number of heart attacks and strokes and save costs in health care, globally [56]. The latest cost-effectiveness analysis of different national salt reduction policies shows that government-supported national policy to reduce population sodium intake by 10% over 10 years is recognized as cost effective in all countries, globally [56]. New pathophysiological mechanisms implies that reducing salt intake could be important not only for reduction of BP, CVD and stroke but even more, in promoting weight loss and treatment of metabolic consequences.

National salt reduction strategies combine estimation of population salt intake, monitoring of salt content in foods, food reformulation, consumer education, front of pack labeling, interventions in public institution settings, and tax policies for salty foods [20, 58-59]. Food reformulation is one of the key pillars of salt reduction strategies. It is a long and challenging process, having in mind that salt has numerous technological, sensory, behavior and safety impacts [60]. Many technological interventions could contribute to changes in salt concentrations that are acceptable to consumers. A combination of novel technological treatments such as high hydrostatic pressure and ultrasound technology, changing in salt perception, “stealth” reformulation, salt substitutes and enhancers, interaction of senses and the use of flavorings, changes in salt structure, and using different emulsions, seem to be promising to ensure microbiological safety in low-sodium products [60,61].

## 6. Conclusion

There should be no further delay in issuing a national salt reduction strategy. A public health framework given by leading world health authorities, experience and results from numerous neighboring and countries globally, should lead and facilitate progress in Serbia. The Institute of Public Health of Vojvodina, supported by the local and provincial governments, has implemented some activities regarding salt reduction strategies at local and regional levels [62-65]. As a country with high prevalences of obesity and hypertension, and high salt intake, Serbia would greatly benefit from adopting and implementing a national sodium reduction program that minimize risks through education, regulation, and enforcement.

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