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Review Article

How Much of Salt is too Much for You? Let Your Genes Say...

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Abstract

May it be fluid-electrolyte balance, keeping the heart beat/rhythm normal, neuromuscular function or a sensory attribute like palatability, common salt or sodium chloride has its role manifold. Salt, isn't this the prime component making our meal delicious? Of course YES! But will its excess still make the meal delicious? Absolutely NOT! Like our meal our health also struggles to handle excess salt. And this definition of excess can vary between individuals based on genetic make-up. Let's find out how and why...

Keywords: Salt; Sodium; Blood Pressure; Hypertension; Salt Sensitivity; Gene; Allele; Renin-angiotensin-Aldosterone System (RAAS); Renin-Angiotensin Converting Enzyme (ACE); Angiotensinogen (AGT); Angiotensin II Type 1 Receptor (AGTR); Epithelial Sodium Channel (ENaC); 11-Beta Hydroxy Steroid Dehydrogenase (11-BHSD); Sympathetic Alpha Receptor; Beta Receptor Gene; Endothelial Nitric Oxide Synthase; Adducin Gene; ACE Inhibitors

Introduction

Salt holds an important place in our diet because it is rich in sodium which helps maintain the fluid levels and pH balance of our body. Sodium helps maintain a normal blood volume and blood pressure. This in turn keeps our blood vessels in good health, avoiding undue stress and inflammation on them. Moreover our heart is also healthy as the blood flow and blood vessel flexibility is desirable with an optimal sodium intake. However, sodium intakes around the world are well in excess of physiological need (i.e. 10-20 mmol/day). Most adult populations have mean sodium intakes >100 mmol/day, and for many (particularly the Asian countries) mean intakes are >200 mmol/day (200 mmol of sodium is approximately equivalent to 12 grams of salt) [1]. Excess sodium intake through salt can cause an undesirable rise in blood pressure, and the risk for heart attack is 8% higher in people with high blood pressure. Alarmingly, 15% of deaths from heart attack and stroke are attributed to a high salt intake.

What is the recommended level of intake for salt?

International recommendations suggest that average population salt intake should be less than 5-6 g per day [2]. The American Heart Association (AHA) recommends a maximum intake of no more than 2.3 grams (g) or 2,300 milligrams (mg) of sodium a day, or around 1 teaspoon, and preferably no more than 1,500 mg [3,4].

Apart from the salt added while cooking or at table, processed and packaged foods are also responsible for most of the salt people eat. Hence reading a food label for salt content and sodium is also important. Choose products with the lowest Percent Daily Value for sodium: 5 percent or less is low, and 20 percent or more is high [5].

Salt and Hypertension, what's the link?

- Blood pressure is determined by the amount of blood pumped by heart and the resistance to blood flow exerted by blood vessels (mainly arteries). Narrower the space in blood vessels, greater is the resistance to blood flow and henceforth a higher blood pressure. Sustained increase in blood pressure can lead to blood vessel damage.

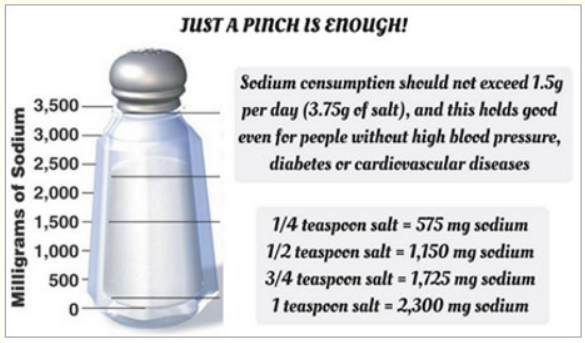

Figure 1: How much of sodium in salt.

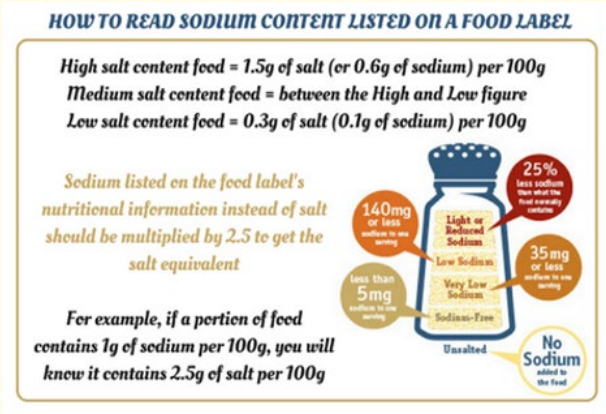

Figure 2: How to read sodium content listed on a food label.

- High levels of dietary sodium (consumed as common salt, sodium chloride) may provoke water retention, thus leading to a condition of high flow in arterial vessels which eventually causes adverse changes in vascular resistances.
- Excessive sodium intake induces hypertrophy of vascular smooth muscles and reduces the availability of nitric oxide. Nitric oxide is vital in regulating blood vessel tone, helping them to relax and dilate.
- Excessive salt intake may cause microvascular endothelial inflammation, and functional abnormalities, even in normotensive subjects.
- Changes in sodium plasma levels exert their effects on small resistance arteries, and also affect the function and structure of large elastic arteries.
- An increase in BP in the renal arteries causes increased salt and water excretion. This hemodynamic load, may lead to an adverse microvascular remodeling by the effects of increased BP levels. A desirable balance between sodium and potassium is needed for optimal kidney function, and this gets disrupted by excess of sodium [6-8].

Excessive sodium consumption (defined by the World Health Organization as >5 g sodium per day) has been shown to produce a significant increase in BP and has been linked with onset of hypertension and its cardiovascular complications [9-13]. Conversely, reduction in sodium intake not only decreases BP levels and hypertension incidence, but is also associated with a reduction in cardiovascular morbidity and mortality [14-21]. These scientific facts are explained in the following illustrations.

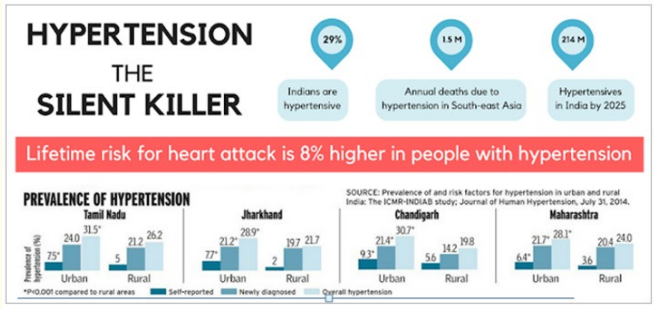

Figure 3: Impact of excess salt on heart and blood vessels [22].

Figure 4: Salt reduction can work wonders for the heart and blood vessels [23,24].

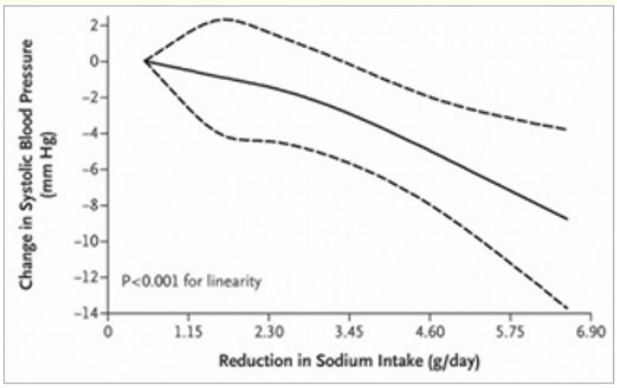

Figure 5: Effect of reduced sodium intake on BP [22].

Your genes can tell you how much of salt is too much for you

Blood pressure is mainly regulated by Renin-angiotensin-aldosterone system (RAAS) which also acts as a key regulator of electrolyte balance. The RAAS is a group of related hormones that act together to regulate blood pressure by maintaining vascular tone and the balance of water and sodium [25].

- Angiotensinogen, a protein, is the vital part of the RAAS system, which regulates blood pressure and the balance of fluids and electrolytes in the body.
- Renin secreted by kidneys (juxtaglomerular cells) is also known as angiotensinogenase as it cleaves Angiotensinogen (AGT) to produce angiotensin I.
- The angiotensin converting enzyme (ACE) converts angiotensin-I to angiotensin-II, a potent vasoconstrictor. The enzymatic activity of ACE inactivates bradykinin, a potent vasodilator.
- Angiotensin II binds to its receptors (AGTR1 and AGTR2, predominantly), exerting physiologic effects on the sodium homoeostasis and vascular resistance, thus regulates the blood pressure.
- Angiotensin II causes blood vessels to narrow (constrict), which results in increased blood pressure. This molecule also stimulates production of the hormone aldosterone, which triggers the absorption of salt and water by the kidneys. The increased amount of fluid in the body also increases blood pressure.

Blood pressure responses to dietary salt intake may be influenced by various genetic factors. These include important candidate genes like renin-angiotensin converting enzyme (ACE) gene, angiotensinogen (AGT) gene, angiotensin II type 1 receptor (AGTR), epithelial sodium channel (ENaC) genes, 11-beta hydroxy steroid dehydrogenase (11-BHSD) genes, sympathetic alpha receptor gene, beta receptor gene, endothelial nitric oxide synthase gene, adducin gene, among others [26-28].

A few examples to understand better

- The AGT gene encodes the production of angiotensinogen. Angiotensinogen being among the activators of RAAS cascade, a variation in this gene (rs699) is shown to impact the susceptibility for hypertension. People who carry C allele (threonine variant in place of methionine) are more likely to have an increase in blood pressure due to higher levels of angiotensin II [28,29].
- The angiotensin converting enzyme (ACE) gene is the key gene in RAAS which encodes the Angiotensin converting enzyme (ACE). A commonly studied genetic variation at rs4340 of ACE gene is associated with increased levels of ACE in plasma which eventually increases Angiotensin II levels, a key factor enhancing peripheral resistance. An individual with deletion pattern at rs4340 of ACE gene is likely to have greater angiotensin II formation in cardiac and vascular tissue, predisposing him to cardiovascular risk compared to individuals carrying insertion pattern [27,30,31].
- The Angiotensin II Receptor type 1 (AGTR1) gene mediates the vasoconstrictive and salt-conserving actions of the RAAS, via its action with angiotensin II, and may be an important regulator of BP response to salt intake. The prohypertensive effect of angiotensin II occurs by occupation of AGTR1, resulting in vasoconstriction and sodium retention. Hence the response of AGTR1 gene expression may be relevant in determining the ability to adapt to salt intake. A single nucleotide polymorphism (rs2638360) in this gene is significantly associated with salt sensitivity. C allele of rs2638360 could significantly increase the risk of essential hypertension. Moreover, their carriers may have less favourable results in BP reduction after the existing salt restriction norms. This clearly demands a revised recommendation [32,33].

- The ability of aldosterone to increase BP is caused mainly by increasing renal sodium transport and by increasing vascular smooth muscle contractility. Aldosterone synthase, which is needed to synthesize aldosterone, has a genetic polymorphism, CYP11B2 (Cytochrome P450 Family 11 Subfamily B Member 2) rs1799998 that is associated with hypertension. C allele carriers of rs1799998 have higher plasma aldosterone-to-renin (ARR) ratios and hence may have an increased susceptibility for high blood pressure. Their BP response to salt restriction may be comparatively poor than T allele carriers [34-36].

How to manage such genetic variations and have Blood pressure under control?

The above examples clearly reveal that there are individuals who need a revision in the existing salt restriction norms to maintain their blood pressure levels optimally. Individuals with a not-so-favourable variation in BP-impacting genes may need a revised salt intake limit. Revised salt restriction norms (not more than 3.5 grams of table salt as against <5 grams given by WHO) are recommended to maintain optimal sodium levels and prevent hypertension in these individuals [37].

Discussion

Why is it needed to understand the genetics behind salt and hypertension?

In many individuals, when salt intake increases, the excess amount is excreted through kidney or as sweat. However, there are some individuals where this mechanism is faulty and increased salt is retained and manifests as high BP. There is an inter-individual difference in the BP response to changes in dietary sodium chloride intake which could be attributed to salt sensitivity. Overall, salt sensitivity appears to be a major public health problem with estimated incidence of 51% in patients with hypertension and 26% in normotensive people. While not all hypertensives are salt sensitive and not all salt sensitive people are hypertensive, the available evidence suggests that even normotensive salt sensitive individuals are at high cardiovascular (CV) risk as BP eventually rises later in life with high salt diet [38].

Faulty salt genes can be managed with gene-specific nutrients

Gene-nutrient interactions determine a broad array of health outcomes, such as vascular problems and hypertension [39]. Two major players in hiking blood pressure levels are angiotensin II and nitric oxide. When chronically elevated, angiotensin II promotes excessive vasoconstriction and hypertension. While Nitric oxide causes vasodilation, and hence it is antihypertensive. Gene-nutrient interactions should therefore aim at increasing nitric oxide availability and decreasing the effects of angiotensin II [40].

Gene-specific nutrients that help in blood pressure control [40].

Nutrient(s)	Effect
Vitamin B_6, taurine, and magnesium	Work well together as diuretics. Diuretics help the body in getting rid of excess fluid and salt
Taurine, vitamin B_6, and potassium	When consumed together act as Central alpha agonists. Central alpha agonists regulate brain signals in such a way that they prevent increased heart rate and narrowing of blood vessels.
Omega-3 fatty acids, magnesium, and co-enzyme Q10 (CoQ10)	This combination renders direct vasodilator effect, hence relaxes blood vessels bringing down blood pressure
Alpha-lipoic acid, magnesium, and omega-3 fatty acids (mainly eicosapentaenoic acid and docosahexaenoic acid)	Act together as Calcium channel blockers to lower blood pressure. They work by slowing the movement of calcium into the cells of the heart and blood vessel walls, which makes it easier for the heart to pump and widens blood vessels.

Table 1

Food-derived Angiotensin-Converting Enzyme or ACE inhibitors

The concept of viewing food as a remedy has been existent since ancient times, mainly because of the role of its disease-preventive components. Bioactive Peptides from food are specific protein fragments that have a positive impact on health outcomes. Peptides known as ACE inhibitors are derived from food proteins, and their bio-functionality makes them a great option for blood pressure control. Antihypertensive activity of long-chain ACE inhibitors can result from the process of their hydrolysis into shorter, active fragments. Shorter fragments, such as di- or tripeptides, are absorbed from the intestine and then directly interact with the appropriate receptors [41]. Food-originated anti-ACE biopeptides bind to the enzyme and hinder its activity, bringing the blood pressure under control [42,43]. Following are important food sources of ACE inhibitory peptides-

- Milk proteins have a leading role as a source of ACE inhibitors. Yoghurt has ACE inhibitory peptides which are produced during fermentation.
- The proteins present in sunflower seeds undergo extensive hydrolysis by pepsin and pancreatin generating the release of ACE inhibitory peptide
- Whole grain cereals like wheat, oat, barley and red rice have ACE-inhibitor peptides that exhibit hypotensive, anti-thrombotic and antioxidant activity.
- Wheat germ has tripeptide which is a potent ACE inhibitor
- Mung-bean protein is a good precursor of ACE inhibitors
- The risk of developing CVD is lowered by 50% in hypertensives through blood pressure reduction (a 20 mmHg reduction in high systolic BP, SBP>140 mmHg or a 10 mmHg reduction in high diastolic BP, DBP>90 mmHg). Dipeptides present in garlic bring down the activity of ACE. S-allylcysteine of garlic is shown to reduce systolic blood pressure by about 10 mmHg, which is associated with a risk reduction in cardiovascular disease/CVD by 16 to 40%. A dosage of 240-960 mg of aged garlic extract containing 0.6-2.4mg of S-allylcysteine significantly lowered blood pressure by about 12 mmHg over 12 weeks [44,45].
- An example of a soybean commercial product known for its antihypertensive effect is douchi.
- Various fish species such as tuna, sardine, herring and salmon contain bioactive peptides that have ACE inhibitory effects. Consumption of oily fish two to three times week helps in blood pressure control

Conclusion/Summary

Salt is the prime component that makes our meal delicious. The sodium chloride of salt has manifold roles in our body. And this includes, maintenance of fluid-electrolyte balance, keeping the heart beat/rhythm normal, neuromuscular function and sensory attribute like palatability. The recommended level of intake for salt is not more than 5 grams in a day. Like our meal our health also struggles to handle excess salt. And this definition of excess can vary between individuals based on genetic make-up. High-salt intake is one of the major dietary determinants of increased blood pressure. Some individuals, due to unfavorable genetic changes, are more prone to be salt sensitive, that is, their excess salt intake results in a parallel rise in blood pressure. An insight on genes related to salt sensitivity will bring out our tendency for salt-induced hypertension/high blood pressure. This will guide in deciding how much of salt is too much for an individual through a personalized approach.

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