

PHYSIOLOGY OF BLOOD PRESSURE REGULATION

Salt Sensitivity and Hypertension

¹Anuj Maheshwari, ²Harish Basera

ABSTRACT

Enough evidence is there to link excess salt intake with cardiovascular and renal risks through hypertension though substantial evidence is also there to support that blood pressure is not always responding to salt. A lot of metabolic and neurohormonal factors determine this salt sensitivity in addition to genetic factors that determine substantial excretion of salt, so it may not increase blood pressure despite high intake. Salt-sensitive hypertensives have reduced levels of urinary endothelin, contributing to impaired natriuresis in response to a salt load. Salt load also increases free radicals and paradoxically decreases excretion of nitric oxide metabolites in salt-sensitive individuals. Type 2 diabetic patients with microalbuminuria are more salt sensitive as they have lower urinary excretion of nitric oxide. Nitric oxide deficiency facilitates endothelial dysfunction causing hypertension in salt-sensitive people, impeding vasodilation after salt load. Sympathetic nervous system plays a significant role in maintenance of blood pressure in response to salt through urinary and plasma levels of catecholamine and renal nerve activity. Apart from this, atrial natriuretic peptides (ANPs) and cytochrome P450-derived metabolites of arachidonic acid play significant roles. Insomnia and menopause increase salt sensitivity. Kidney provides sensitive and specific biomarkers for salt sensitivity in the form of proteomics, and renal proximal tubule cells, microribonucleic acid (miRNA), and exosomes are excreted into the urine apart from genetic biomarkers. A J-shaped curve relationship exists between salt intake and mortality. Salt intakes above and below the range of 2.5 to 6.0 gm/day are associated with high cardiovascular risk. Salt restriction can be a cause of hypertension in inverse salt-sensitive people. Available prevalence studies do not differentiate between salt-sensitive and salt-resistant populations, nor do they include normotensive salt-sensitive people who get their blood pressure raised in response to dietary salt. In these circumstances, salt sensitivity arises as an independent risk factor for cardiovascular mortality and morbidity.

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¹Professor and Head, ²Assistant Professor

¹Department of General Medicine, Babu Banarasi Das University, Lucknow, Uttar Pradesh, India

²Department of Medicine, Doon Medical College, Dehradun Uttarakhand, India

Corresponding Author: Anuj Maheshwari, Professor and Head Department of General Medicine, Babu Banarasi Das University Lucknow, Uttar Pradesh, India, e-mail: dranujm@gmail.com

Many clinical observational studies¹⁻³ and clinical trials on animals^{4,5} and humans⁶⁻⁸ have supported a causal relation between hypertension and dietary salt. High salt intake is well correlated with high cardiovascular risk. At the same time, substantial evidences are there to support that blood pressure does not respond to dietary salt always. This phenomenon is described as salt sensitivity.⁹

Undoubtedly, dietary salt is an important environmental factor for hypertension, but genetic factors play a significant role also in the causation of hypertension apart from environmental factors. Many a times, the presence of other associated environmental factors also makes the response a bit complicated.⁹

Dietary salt enhancement increases blood pressure which is associated with greater cardiovascular and renal risk. It is known as salt-sensitive hypertension. Bulks of evidences are there to support a significant role of metabolic and neurohormonal factors which determine the salt sensitivity of blood pressure together with genetic factors. Genetic factors determine substantial excretion of salt, so it may not increase blood pressure, after high dietary salt intake. Rest of the people cannot do it, without rise in arterial blood pressure.¹⁰ So, in this way, blood pressure response to variation in dietary salt intake produces significant rise and fall.

MECHANISMS OF SALT SENSITIVITY

It seems complex, ranging from genetic to environmental effects on blood pressure. Excess dietary salt intake impacts vasculature functionally and pathologically independent of blood pressure. The phenotype of salt sensitivity is heterogeneous to link excess salt intake through multiple mechanisms to increased blood pressure, though we have enough epidemiological evidences to support the role of excess salt intake in mediating cardiovascular and renal risks.

Fifty years back, Guyton and Coleman¹¹ proposed that a raised arterial pressure coupled with pressure natriuresis increases sodium and water excretion till it loses the volume sufficiently to reduce arterial blood pressure up to baseline. This hypothesis suggests that hypertension is a result of impaired sodium excretory ability of kidneys. However, current evidences favor nonosmotic accumulation of salt in the skin interstitium and endothelial dysfunction playing important role in salt storage. Endothelial dysfunction seems to be occurring due to

vascular endothelial glycocalyx layer destruction and the loss of epithelial sodium channel on the endothelial luminal surface. Thus, it suggests that sodium homeostasis and salt sensitivity give rise not only to kidney malfunction but also to endothelial dysfunction.⁹ As per this theory, the excretion ability of the kidney determines the occurrence of hypertension in response to high sodium intake by shifting the balance between sodium excretion and arterial pressure on the higher side.¹² Beyond the integral role of kidney in blood pressure regulation, a genetic factor for salt sensitivity causing mutations in various genes related to salt transport has been explored to cause monogenic forms of hypertension.¹³

Multiple mechanisms has been suggested by various workers:

- MacGregor has suggested that the prevalence of salt-sensitive blood pressure rises from normotensive to mild hypertensives to severe hypertensives. It is inversely related to plasma renin response to salt depletion. Actually impaired renin response to salt depletion is responsible for lowering of blood pressure in salt-sensitive people.¹⁴ Reduced renin angiotensin II and aldosterone response to salt depletion are more commonly seen in hypertensives than in normotensives. Blacks are more prone to get this impaired renin response to salt depletion.¹⁵ Endogenous angiotensin II levels rise with salt deficiency and diminish sensitivity to exogenous angiotensin II in normal subjects. On the contrary, in salt-sensitive subjects, sensitivity to exogenous angiotensin II is maintained or even rises with salt loss.¹⁶
- Routinely, urinary endothelin follows a circadian rhythm and correlates negatively with blood pressure in normal and hypertensive subjects but positively with Na⁺ excretion during a salt load. Salt-sensitive hypertensives have reduced levels of urinary endothelin, contributing to impaired natriuresis in response to a salt load.¹⁷
- Nitric oxide and oxidative stress also play an important role in salt-sensitive hypertensives. A salt load increases free radicals and paradoxically decreases excretion of NO metabolites in salt-sensitive hypertensives, which normally increase in response to salt loading. This suggests that in such subjects, NO is diverted to the scavenging of salt-induced free radicals in salt-sensitive hypertensives. Type 2 diabetic patients with microalbuminuria are more salt sensitive than those who do not have microalbuminuria. They have lower urinary excretion of nitric oxide which can be raised by valsartan.¹⁸ It is not only nitric oxide scavenging but defect in production is also seen in salt-sensitive subjects e.g., salt-sensitive blacks can tolerate more lowering of blood pressure and lesser increase in renal blood flow on giving intravenous arginine as compared with salt-resistant or normotensive controls. This nitric oxide deficiency may contribute to endothelial dysfunction, which in turn may be responsible for salt-sensitive hypertension by impeding vasodilation after a salt load.¹⁹
- Sympathetic nervous system plays a significant role in the maintenance of blood pressure in response to salt, especially in genetically determined salt-sensitive individuals.²⁰ In majority of them, high level of catecholamines in plasma and urine together with renal nerve activity determine blood pressure response to salt. Decreased central sympathetic inhibition of peripheral sympathetic outflow is reflected in reduced hypothalamic norepinephrine content.²¹ In salt-sensitive individuals, increase in blood pressure in response to salt is usually not associated with a decrease in plasma catecholamines in contrast to normotensive or salt-resistant hypertensive subjects.²² On the contrary, plasma catecholamine response to salt depletion is more in salt-sensitives compared with salt-resistant hypertensives caused by sympathetic stimulation in response to low blood pressure.²³ In a nutshell, in salt-sensitive subjects, vascular reactivity to catecholamines remains high because of sympathetic hyperactivity. Sympathetic innervations of the heart determine the hemodynamic adaptation to high salt intake in diet. Increased autonomic reactivity in response to mental stress has its impact on salt handling and its effect on arterial pressure.²⁴
- Atrial natriuretic peptides play an important pathogenic role in some salt-sensitive individuals while it remains compensatory in rest of the hypertensive and normotensive people.²⁵ Again, it is genetically determined. A lower level of circulating N-terminal ANP predicts salt-sensitive blood pressure while in normal volunteers and prehypertensives, it remains high.²⁶
- Cytochrome P450-derived metabolites of arachidonic acid play significant role through their two major products of this pathway, the vasoconstrictor 20-hydroxyeicosatetraenoic acid (produced by omega hydroxylases) and the vasodilator epoxyeicosatrienoic acids (produced by epoxygenases). They act as natriuretic agents in different parts of the renal tubule acting on different transporters.²⁷
- Salt sensitivity is determined by multiple gene variants but only variants of G protein-coupled receptor kinase 4 (GRK4) have been found to be highly associated with salt sensitivity in human beings. Experimentally they have been shown to cause salt-sensitive and salt-resistant hypertension in mice with the same genetic background.²⁸

Table 1: Hypertension and salt sensitivity testing²⁸

| | Low salt intake | High salt intake |
|------------------------|-----------------|------------------|
| Salt sensitive | Normal MAP | High MAP |
| Salt resistant | Normal MAP | Normal MAP |
| Inverse salt sensitive | High MAP | Normal MAP |

DIAGNOSIS OF SALT SENSITIVITY

It can be diagnosed by noticing 5 to 10% variation in blood pressure on office measurement or at least 5 mm Hg in response to a salt intake²⁹ or rise in 4 mm Hg of mean arterial blood pressure (MAP) on 24-hour ambulatory blood pressure monitoring with an increase in salt intake.³⁰

$$\text{Salt sensitivity index}^{31} = \frac{(\text{MAP on high salt} - \text{MAP on low salt})}{\text{MAP on low salt}}$$

It can also be diagnosed by observing at least 10 mm Hg rise in blood pressure after 2 L saline infusion in 4 hours from the blood pressure reading recorded in morning after 1 day of low-salt diet (10 mmol) and a tablet of loop diuretic.³²

Inverse salt sensitivity is defined as increase in blood pressure even on low-salt diet (Table 1).

SURROGATE MARKERS OF SALT SENSITIVITY

As it is always very difficult to measure the response to salt intake, surrogate markers are used often. Salt sensitivity is seen higher in insomnia or if we do not see at least 10 to 20% reduction in blood pressure after sleeping normally.³³ Postmenopausal women are supposed to have more salt sensitivity as a response to estrogen withdrawal.³⁴ Low plasma renin activity indicates salt sensitivity in normotensive and hypertensive population, but has limited sensitivity as well as specificity as a diagnostic marker.³⁵ So, it is not always differentiating between salt-sensitive and salt-resistant individuals. Circulating level of ANP, brain natriuretic peptide, and endogenous ouabain are also supposed to serve as surrogate markers of salt sensitivity, but they all have limitations of sensitivity and specificity as marker.

The diagnostic threshold of three or more single-nucleotide polymorphisms for GRK4 genetic variant yielded 85% sensitivity and 100% specificity.³⁶ This genetic marker has been well correlated with physiological response too.³⁷

ROLE OF KIDNEY IN SALT SENSITIVITY

Undoubtedly, kidney plays an important role in the pathogenesis of hypertension. Salt sensitivity also increases and kidney provides sensitive and specific biomarkers for salt sensitivity in the form of proteomics, and renal proximal tubule cells, miRNA, and exosomes excreted into the urine apart from genetic biomarkers.³⁸ Urinary exosomes which are small 50 to 90 nm vesicles

containing proteins, miRNA, and miRNA serve not only as biomarkers but also as internephron acellular signal for altering sodium homeostasis.³⁹

IMPACT ON ADVERSE HEALTH OUTCOME

As per the Centers for Disease Control and Prevention data in the United States, only 46% patients keep their blood pressure within the target range despite taking treatment.⁴⁰ Salt sensitivity seems to play a major role in creating this gap. Most of the dietary recommendations are universal while every individual has his/her own "salt sensitivity index" and according to which it needs individualized salt intake recommendations.²⁸ There is a J-shaped curve relationship between salt intake and mortality. Salt intakes above and below the range of 2.5 to 6.0 gm/day have been found to be associated with increased cardiovascular risk.⁴¹ Sometimes, salt restriction becomes a cause of hypertension in inverse salt-sensitive people. Therefore, universal guidelines are not desirable for salt intake. Available prevalence studies for essential hypertension do not differentiate between salt-sensitive and salt-resistant populations, nor they include normotensive salt-sensitive people who can get their blood pressure raised in circumstantially excess intake of dietary salt. In these circumstances, salt sensitivity comes up as an independent risk factor for cardiovascular mortality and morbidity. So, this differentiation is needed very much. Apart from cardiovascular mortality and morbidity, salt sensitivity poses a risk for other diseases also, e.g., asthma, gastric carcinoma, osteoporosis, and renal dysfunction.⁴² Salt is an integral part of food and in modern world; it is used as preservatives to prevent spoilage of food. Processed food is coming up as a major source of salt constituting 75% of salt intake in the United States. Apart from that, pizza, burger, pasta, cold cuts, ham, bacon, soups, and many other fast food items provide a huge amount of salt, which is directly related to the health hazards, especially of cardiovascular diseases.⁴³

CONCLUSION

Although more research is to be done to establish the non-linear effect of salt intake on cardiovascular morbidity and mortality, pharmacogenomics can play an important role in suggesting proper therapeutic strategies to treat hypertension. Not only it can suggest appropriate salt intake for individuals who carries specific genetic variant but also it may suggest most effective therapeutic choice with maximum feasibility. Patients having inverse salt sensitivity and high salt sensitivity with normal blood pressure always remain a challenge to diagnose. Urinary surrogate markers like renal proximal tubular cells, exosomes, and miRNA can be predictive for salt sensitivity effectively.

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