

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.

Keywords: Dietary salt, Hypertension, Salt sensitivity.

How to cite this article: Maheshwari A, Basera H. Salt Sensitivity and Hypertension. *Hypertens J* 2017;3(4):178-182.

Source of support: Nil

Conflict of interest: None

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.

REFERENCES

1. Ambard L, Beaujard E. Causes de l'hypertension artérielle. *Arch Gen Med* 1904;1:520-533.
2. Kempner W. Treatment of hypertensive vascular disease with the rice diet. *Am J Med* 1948 Apr;4(4):545-577.
3. Ball CO, Meneely GR. Observations on dietary sodium chloride. *J Am Diet Assoc* 1957 Apr;33(4):366-370.
4. Dahl LK, Heine M, Tassinari L. Effects of chronic salt ingestion. Evidence that genetic factors play an important role in susceptibility to experimental hypertension. *J Exp Med* 1962 Jun;115(6):1173-1190.
5. Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixon A, Moisson P, Pingard AM, Shade R, Carey D, Ardaillou R, et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med* 1995 Oct;1(10):1009-1016.
6. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988 Jul;297(6644):319-328.
7. The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA* 1992 Mar;267(9):1213-1220.
8. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997 Mar;157(6):657-667.
9. Choi HY, Park HC, Ha SK. Salt sensitivity and hypertension: a paradigm shift from kidney malfunction to endothelial dysfunction. *Electrolyte Blood Press* 2015 Jun;13(1):7-16.
10. Majid DS, Prieto MC, Navar LG. Salt sensitivity hypertension: perspective of intrarenal mechanism. *Curr Hypertens Rev* 2015;11(1):38-48.
11. Guyton, AC.; Coleman, TG. Long-term regulation of the circulation: inter-relationship with body fluid volumes. In: Reeve E, Guyton AC, editors. *Physical basis of circulatory transport: regulation and exchange*. Philadelphia (PA): Saunders; 1967. pp. 179-201.
12. Cowley AW Jr. Long-term control of arterial blood pressure. *Physiol Rev* 1992 Jan;72(1):231-300.
13. Lifton R, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001 Feb;104(4):545-556.
14. Cappuccio FP, Markandu ND, Sagnella GA, MacGregor GA. Sodium restriction lowers high blood pressure through a decreased response of the renin system: direct evidence using saralasin. *J Hypertens* 1985 Jun;3(3):243-247.
15. He FJ, Markandu ND, Sagnella GA, MacGregor GA. Importance of the renin system in determining blood pressure fall with salt restriction in black and white hypertensives. *Hypertension* 1998 Nov;32(5):820-824.
16. Williams GH, Dluhy RG, Lifton RP, Moore TJ, Gleason R, Williams R, Hunt SC, Hopkins PN, Hollenberg NK. Non-modulation as an intermediate phenotype in essential hypertension. *Hypertension* 1992 Dec;20(6):788-796.
17. Hoffman A, Grossman E, Goldstein DS, Gill JR Jr, Keiser HR. Urinary excretion rate of endothelin-1 in patients with essential hypertension and salt sensitivity. *Kidney Int* 1994 Feb;45(2):556-560.
18. Imanishi M, Okada N, Konishi Y, Morikawa T, Maeda I, Kitabayashi C, Masada M, Shirahashi N, Wilcox CS, Nishiyama A. Angiotensin II receptor blockade reduces salt sensitivity of blood pressure through restoration of renal nitric oxide synthesis in patients with diabetic nephropathy. *J Renin-Angiotensin-Aldosterone Syst* 2012 Aug;14(1):67-73.
19. Campese VM, Amar M, Anjali C, Medhat T, Wurgaft A. Effect of L-arginine on systemic and renal haemodynamics in salt-sensitive patients with essential hypertension. *J Hum Hypertens* 1997 Aug;11(8):527-532.
20. Chen YF, Meng QC, Wyss JM, Jin H, Oparil S. High NaCl diet reduces hypothalamic norepinephrine turnover in hypertensive rats. *Hypertension* 1988 Jan;11(1):55-62.
21. Oparil S, Yang RH, Jin HK, Wyss JM, Chen YF. Central mechanisms of hypertension. *Am J Hypertens* 1989 Jun;2 (6 Pt 1):477-485.
22. Campese VM, Romoff MS, Levitan D, Saglikes Y, Friedler RM, Massry SG. Abnormal relationship between sodium intake and sympathetic nervous system activity in salt-sensitive patients with essential hypertension. *Kidney Int* 1982 Feb;21(2):371-378.
23. Eljovich F, Laffer CL, Amador E, Gavras H, Bresnahan MR, Schiffrin EL. Regulation of plasma endothelin by salt in salt-sensitive hypertension. *Circulation* 2001 Jan;103(2):263-268.
24. Zimmermann-Viehoff F, Weber CS, Merswolken M, Rudat M, Deter HC. Low anxiety males display higher degree of salt sensitivity, increased autonomic reactivity, and higher defensiveness. *Am J Hypertens* 2008 Dec;21(12):1292-1297.
25. Lieb W, Pencina MJ, Jacques PF, Wang TJ, Larson MG, Levy D, Kannel WB, Vasani RS. Higher aldosterone and lower N-terminal proatrial natriuretic peptide as biomarkers of salt sensitivity in the community. *Eur J Cardiovasc Prev Rehabil* 2011 Aug;18(4):664-673.
26. Melander O, von Wöhrn F, Frandsen E, Burri P, Willsten G, Aurell M, Hulthen UL. Moderate salt restriction effectively lowers blood pressure and degree of salt sensitivity is related to baseline concentration of renin and N-terminal atrial natriuretic peptide in plasma. *J Hypertens* 2007 Mar;25(3):619-627.
27. Laffer CL, Laniado-Schwartzman M, Wang MH, Nasjletti A, Eljovich F. Differential regulation of natriuresis by 20-hydroxy-eicosatetraenoic acid in human salt-sensitive versus salt-resistant hypertension. *Circulation* 2003 Feb;107(4):574-578.
28. Felder RA, White MJ, Williams SM, Jose PA. Diagnostic tools for hypertension and salt sensitivity testing. *Curr Opin Nephrol Hypertens* 2013 Jan;22(1):65-76.
29. Sullivan JM. Salt sensitivity. Definition, conception, methodology, and long-term issues. *Hypertension* 1991 Jan;17 (1 Suppl):I61-I68.
30. de la Sierra A, Giner V, Bragulat E, Coca A. Lack of correlation between two methods for the assessment of salt sensitivity in essential hypertension. *J Hum Hypertens* 2002 Apr;16(4):255-260.
31. Yatabe MS, Yatabe J, Yoneda M, Watanabe T, Otsuki M, Felder RA, Jose PA, Sanada H. Salt sensitivity is associated with insulin resistance, sympathetic overactivity, and decreased suppression of circulating renin activity in lean patients with essential hypertension. *Am J Clin Nutr* 2010 Jul;92(1):77-82.
32. Weinberger MH, Fineberg NS, Fineberg SE, Weinberger M. Salt sensitivity, pulse pressure, and death in normal and hypertensive humans. *Hypertension* 2001 Feb;37(2 Pt 2):429-432.

33. Simonetti GD, Farese S, Aregger F, Uehlinger D, Frey FJ, Mohaupt MG. Nocturnal dipping behaviour in normotensive white children and young adults in response to changes in salt intake. *J Hypertens* 2010 May;28(5):1027-1033.
34. Barton M, Meyer MR. Postmenopausal hypertension mechanisms and therapy. *Hypertension* 2009 Jul;54(1):11-18.
35. Fisher ND, Hurwitz S, Jeunemaitre X, Hopkins PN, Hollenberg NK, Williams GH. Familial aggregation of low-renin hypertension. *Hypertension* 2002 Apr;39:914-918.
36. Sanada H, Yatabe J, Midorikawa S, Hashimoto S, Watanabe T, Moore JH, Ritchie MD, Williams SM, Pezzullo JC, Sasaki M, et al. Single-nucleotide polymorphisms for diagnosis of salt-sensitive hypertension. *Clin Chem* 2006 Mar;52(3):352-360.
37. Glazier AM, Nadeau JH, Aitman TJ. Finding genes that underlie complex traits. *Science* 2002 Dec;298(5602):2345-2349.
38. Gildea JJ, Carlson JM, Schoeffel CD, Carey RM, Felder RA. Urinary exosome miRNome analysis and its application to salt sensitivity of blood pressure. *Clin Biochem* 2013 Aug;46(12):1131-1134.
39. Esteva-Font C, Wang X, Ars E, Guillén-Gómez E, Sans L, GonzálezSaavedra I, Torres F, Torra R, Masilamani S, Ballarín JA, et al. Are sodium transporters in urinary exosomes reliable markers of tubular sodium reabsorption in hypertensive patients? *Nephron Physiol* 2010 Feb;114(3):25-34.
40. Centers for Disease Control and Prevention (CDC). Vital signs: awareness and treatment of uncontrolled hypertension among adults—United States, 2003-2010. *MMWR Morb Mortal Wkly Rep* 2012 Sep;61:703-709.
41. Dorresteijn JA, van der Graaf Y, Spiering W, Grobbee DE, Bots ML, Visseren FL; Secondary Manifestations of Arterial Disease Study Group. Relation between blood pressure and vascular events and mortality in patients with manifest vascular disease: J-curve revisited. *Hypertension* 2012 Jan;59(1):14-21.
42. de Wardener HE, MacGregor GA. Harmful effects of dietary salt in addition to hypertension. *J Hum Hypertens* 2002 Apr;16(4):213-223.
43. Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2011 Jul;7:CD009217.