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SALT SENSITIVITY AND BLOOD PRESSURE RESPONSE IN ESSENTIAL HYPERTENSION: A DIETARY INTERVENTION STUDY

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Abstract:

Background: Salt sensitivity (SS) affects 50-60% of hypertensive patients and increases cardiovascular risk beyond blood pressure elevation alone. Mechanisms underlying individual variability in salt sensitivity remain incompletely understood.

Objective: To assess prevalence of salt sensitivity in essential hypertension patients, examine associated metabolic and renal factors, and evaluate blood pressure response to dietary sodium modification.

Methods: Prospective interventional study of 184 patients with untreated essential hypertension (mean age 54.7±8.9 years, 58% male) and 92 normotensive controls. Participants underwent standardized salt-loading (300 mmol/day sodium for 7 days) followed by salt-restriction (50 mmol/day for 7 days) protocols with 24-hour ambulatory blood pressure monitoring (ABPM). Salt sensitivity defined as mean arterial pressure (MAP) increase ≥5 mmHg from low-salt to high-salt diet. Plasma renin activity (PRA), aldosterone, urinary sodium excretion, and metabolic parameters were measured. Linear regression identified predictors of salt sensitivity magnitude.

Results: Among hypertensive patients, 106 (57.6%) were salt-sensitive (SS) versus 78 (42.4%) salt-resistant (SR). Controls showed 18.5% SS prevalence ($p<0.001$ vs. hypertensives). SS hypertensives demonstrated greater MAP increase during salt-loading (14.8±5.2 mmHg vs. 2.1±1.8 mmHg in SR, $p<0.001$) and larger decrease with restriction (12.6±4.8 mmHg vs. 2.4±1.6 mmHg, $p<0.001$). Baseline characteristics differing between SS and SR groups included: age (57.4±8.2 vs. 51.2±8.8 years, $p<0.001$), BMI (29.8±4.6 vs. 26.4±3.8 kg/m², $p<0.001$), fasting glucose (108.6±18.4 vs. 96.2±12.8 mg/dL, $p<0.001$), and insulin resistance (HOMA-IR: 4.2±2.1 vs. 2.4±1.2, $p<0.001$). SS patients showed suppressed PRA during high-salt (0.8±0.4 vs. 1.6±0.7 ng/mL/h in SR, $p<0.001$) and elevated aldosterone during low-salt (268±94 vs. 186±68 pg/mL, $p<0.001$). Urinary sodium excretion was paradoxically lower in SS patients during high-salt loading (242±68 vs. 284±52 mmol/24h, $p=0.001$), suggesting enhanced renal sodium retention. Multiple regression revealed independent predictors of SS magnitude: age ($\beta=0.24$, $p=0.002$), BMI ($\beta=0.31$, $p<0.001$), HOMA-IR ($\beta=0.28$, $p=0.001$), and baseline PRA ($\beta=-0.22$, $p=0.006$), explaining 48% of variance. African ancestry showed higher SS prevalence (72.3% vs. 51.2% in Europeans, $p=0.008$). During 6-month follow-up on low-sodium diet (<100 mmol/day), SS patients achieved greater BP reduction (-18.4/10.2 mmHg) than SR patients (-6.8/4.2 mmHg, $p<0.001$).

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Conclusions: Salt sensitivity is prevalent in essential hypertension and strongly associates with obesity, insulin resistance, and renin-aldosterone dysregulation. Identifying SS individuals enables targeted dietary sodium restriction with enhanced therapeutic benefit. Findings support personalized approaches to hypertension management based on individual salt sensitivity status.

Keywords: salt sensitivity, hypertension, dietary sodium, blood pressure, renin-angiotensin system, insulin resistance

Introduction

Essential hypertension affects over 1.3 billion adults globally and represents the leading modifiable risk factor for cardiovascular disease, stroke, and kidney disease (1, 2). While sodium intake correlates with blood pressure at population levels, individual blood pressure responses to dietary sodium vary substantially (3).

Salt sensitivity (SS) describes the phenomenon wherein blood pressure increases with sodium loading and decreases with restriction, while salt-resistant (SR) individuals maintain relatively stable blood pressure despite sodium intake changes (4, 5). Approximately 50-60% of hypertensive patients and 25-30% of normotensive individuals demonstrate salt sensitivity (6). Importantly, SS independently predicts cardiovascular events and mortality beyond blood pressure elevation itself, suggesting distinct pathophysiological mechanisms (7, 8).

Despite clinical significance, salt sensitivity assessment remains uncommon in practice due to absence of standardized protocols and time-intensive evaluation requirements (9). Better understanding of SS prevalence, mechanisms, and predictive factors could enable targeted interventions maximizing benefit from dietary sodium modification—a cornerstone of hypertension management often undermined by variable individual responses (10, 11).

Proposed mechanisms underlying salt sensitivity include: impaired renal sodium handling with enhanced tubular reabsorption, endothelial dysfunction with reduced nitric oxide bioavailability, dysregulated renin-angiotensin-aldosterone system (RAAS), sympathetic overactivity, and insulin resistance (12, 13, 14). The relative contributions of these pathways and their interrelationships require further characterization.

Racial/ethnic differences in SS prevalence are documented, with African ancestry populations demonstrating higher rates—potentially related to genetic variants affecting sodium transport, different RAAS activity profiles, or socioeconomic factors (15, 16). Age, obesity, and metabolic syndrome also associate with increased SS, but comprehensive evaluations in well-characterized cohorts remain limited.

Study Objectives: (1) Determine SS prevalence in essential hypertension patients versus normotensive controls using standardized salt manipulation protocol; (2) Compare clinical, metabolic, and hormonal characteristics between SS and SR individuals; (3) Identify independent predictors of salt sensitivity magnitude; (4) Evaluate blood pressure response to prolonged sodium restriction in SS versus SR patients.

Methods

Study Population

We prospectively enrolled 184 patients (107 male, 77 female; mean age 54.7±8.9 years) with newly diagnosed, untreated essential hypertension from three outpatient clinics between January 2021 and December 2022. Hypertension defined as office BP ≥140/90 mmHg on ≥3 occasions or 24-hour ABPM mean ≥130/80 mmHg (17). Inclusion criteria: age 30-70 years; untreated hypertension; estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m². Exclusion criteria: secondary hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease stage ≥3, medications affecting sodium balance or BP, inability to follow dietary protocols.

Normotensive controls (n=92; 54 male, 38 female; mean age 52.3±9.2 years) were healthy volunteers with office BP <130/80 mmHg and normal ABPM, matched for age and sex distribution.

All participants provided written informed consent. The institutional review board approved the protocol.

Salt Sensitivity Assessment Protocol

Participants underwent supervised dietary sodium manipulation (Figure 1):

Baseline Period (7 days): Usual diet with 24-hour urinary sodium measurement to assess baseline intake.

High-Salt Period (7 days): Standardized diet providing 300 mmol (6.9g) sodium daily through controlled meals plus sodium chloride tablets. Compliance verified by 24-hour urinary sodium excretion.

Low-Salt Period (7 days): Standardized diet providing 50 mmol (1.2g) sodium daily with potassium supplementation (100 mmol/day) to prevent hypokalemia.

ABPM Measurements: 24-hour ambulatory blood pressure monitoring performed on days 6-7 of each dietary phase using validated oscillometric devices (SpaceLabs 90217). Readings obtained every 20 minutes daytime, every 30 minutes nighttime. Mean arterial pressure (MAP) calculated as: DBP + (SBP-DBP)/3.

Salt Sensitivity Classification: SS defined as MAP increase ≥5 mmHg from low-salt to high-salt period (18). Secondary classification: SS if ≥10 mmHg increase (highly salt-sensitive), intermediate SS if 5-9.9 mmHg, SR if <5 mmHg.

Biochemical Assessments

Blood samples collected after overnight fast on final day of each dietary period:

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- **RAAS markers:** Plasma renin activity (PRA, radioimmunoassay), aldosterone (chemiluminescence)
- **Metabolic parameters:** Fasting glucose, insulin, lipid panel, HbA1c
- **Renal function:** Creatinine, eGFR (CKD-EPI equation), electrolytes
- **Insulin resistance:** HOMA-IR = (fasting insulin × fasting glucose) / 22.5

24-hour urine collections: sodium, potassium, creatinine, microalbumin.

Anthropometric and Clinical Data

Baseline evaluation included: detailed medical history, physical examination, body composition analysis (bioelectrical impedance), office BP (triplicate readings after 5-minute rest), echocardiography (left ventricular mass index), and pulse wave velocity (arterial stiffness assessment).

Follow-up Intervention

After SS assessment, hypertensive patients received individualized dietary counseling recommending sodium intake <100 mmol/day (2.3g). Participants were followed at 3 and 6 months with ABPM, urinary sodium measurement, and clinical assessment. Antihypertensive medication was initiated if BP remained uncontrolled (≥140/90 mmHg) despite dietary intervention.

Statistical Analysis

Continuous variables: mean±SD or median (IQR). Categorical variables: frequencies (%). Independent t-tests or Mann-Whitney U tests compared groups. Chi-square tests compared categorical variables. Pearson/Spearman correlations examined relationships.

Multiple linear regression modeled magnitude of MAP change (high-salt minus low-salt) as function of baseline characteristics using stepwise selection. Logistic regression identified predictors of SS classification (binary outcome).

Subgroup analyses examined SS prevalence across demographic and clinical strata. Repeated-measures ANOVA compared BP changes during follow-up between SS and SR groups. Statistical significance: $p<0.05$ (two-tailed). Analyses used SPSS 28 and SAS 9.4.

Results

Salt Sensitivity Prevalence

Among 184 hypertensive patients, 106 (57.6%) were classified as salt-sensitive (MAP increase ≥5 mmHg). Within SS group: 48 (26.1%) were highly salt-sensitive (≥10 mmHg increase), 58 (31.5%) intermediate SS. Among controls, 17 of 92 (18.5%) demonstrated salt sensitivity ($p<0.001$ vs. hypertensives).

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Blood Pressure Responses

SS hypertensives showed marked BP changes across dietary phases (Table 1):

Table 1: Blood Pressure Responses by Salt Sensitivity Status

Parameter	Baseline	High-Salt	Low-Salt	Δ High-Low
SS Hypertensives (n=106)				
24h MAP (mmHg)	102.4±8.6	112.8±9.2***	98.2±8.4***	14.6±5.1
24h SBP (mmHg)	146.8±12.4	160.2±14.6***	139.4±11.8***	20.8±8.4
24h DBP (mmHg)	88.6±7.8	95.4±8.6***	83.2±7.4***	12.2±5.6
SR Hypertensives (n=78)				
24h MAP (mmHg)	103.2±8.2	104.8±8.6	102.4±8.4	2.4±1.7
24h SBP (mmHg)	147.6±11.8	150.2±12.4	147.8±12.2	2.4±2.8
24h DBP (mmHg)	89.2±7.4	90.6±7.8	88.4±7.6	2.2±2.2

***p<0.001 vs. baseline; MAP=mean arterial pressure

Clinical and Metabolic Characteristics

SS and SR groups differed significantly in multiple baseline characteristics (Table 2):

Table 2: Baseline Characteristics by Salt Sensitivity

Variable	SS (n=106)	SR (n=78)	p-value
Age (years)	57.4±8.2	51.2±8.8	<0.001
Male sex (%)	56.6%	60.3%	0.61
BMI (kg/m²)	29.8±4.6	26.4±3.8	<0.001
Waist circumference (cm)	98.6±11.4	89.2±10.2	<0.001
Fasting glucose (mg/dL)	108.6±18.4	96.2±12.8	<0.001
Fasting insulin (μU/mL)	18.4±8.6	11.2±5.4	<0.001
HOMA-IR	4.2±2.1	2.4±1.2	<0.001
HbA1c (%)	5.8±0.6	5.4±0.4	<0.001
Total cholesterol (mg/dL)	218±38	204±34	0.01
LDL-C (mg/dL)	138±32	126±28	0.01
HDL-C (mg/dL)	46±12	52±14	0.003
Triglycerides (mg/dL)	168±74	132±56	<0.001
eGFR (mL/min/1.73m²)	84.2±14.6	89.8±12.4	0.006
LVMI (g/m²)	118±24	106±22	0.001
PWV (m/s)	9.8±2.2	8.4±1.8	<0.001

SS patients were older, more obese, and demonstrated greater insulin resistance, dyslipidemia, and target organ damage (left ventricular hypertrophy, arterial stiffness).

RAAS and Sodium Handling

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Hormonal profiles revealed distinct patterns (Table 3):

Table 3: RAAS Markers by Dietary Phase

Marker	Baseline	High-Salt	Low-Salt
PRA (ng/mL/h)			
SS	1.4±0.6	0.8±0.4***	4.2±1.6***
SR	1.8±0.8	1.6±0.7	4.8±1.8***
Aldosterone (pg/mL)			
SS	156±64	118±48**	268±94***
SR	164±72	124±56**	186±68***

***$p<0.001$, **$p<0.01$ vs. baseline

SS patients showed greater PRA suppression during high-salt and higher aldosterone during low-salt, suggesting enhanced RAAS sensitivity to sodium status.

Urinary sodium excretion during high-salt phase: SS 242±68 mmol/24h vs. SR 284±52 mmol/24h ($p=0.001$), indicating enhanced renal sodium retention in SS individuals despite identical intake.

Predictors of Salt Sensitivity

Multiple linear regression modeling MAP change magnitude ($R^2=0.48$, $p<0.001$):

Independent Predictors:

- BMI (β=0.31, 95% CI: 0.18-0.44, $p<0.001$)
- HOMA-IR (β=0.28, 95% CI: 0.14-0.42, $p=0.001$)
- Age (β=0.24, 95% CI: 0.11-0.37, $p=0.002$)
- Baseline PRA (β=-0.22, 95% CI: -0.36 to -0.08, $p=0.006$)
- African ancestry (β=0.18, 95% CI: 0.05-0.31, $p=0.02$)

Each 5 kg/m² BMI increase associated with 2.4 mmHg greater MAP change. Each unit HOMA-IR increase associated with 1.8 mmHg greater change.

Racial/Ethnic Differences

Among hypertensive patients with African ancestry (n=47), 72.3% were salt-sensitive versus 51.2% among Europeans (n=125, $p=0.008$) and 48.0% among Asians (n=12, $p=0.08$). African ancestry patients showed larger MAP changes: 16.2±5.8 mmHg versus 13.6±4.8 mmHg in Europeans ($p=0.01$).

Follow-up Outcomes

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During 6-month low-sodium dietary intervention (mean achieved intake: 92±28 mmol/day), SS patients demonstrated superior BP reduction (Figure 2):

6-Month BP Changes:

- SS group: -18.4/-10.2 mmHg (systolic/diastolic)
- SR group: -6.8/-4.2 mmHg
- Difference: $p<0.001$

Among SS patients, 68% achieved BP goal (<140/90 mmHg) with dietary modification alone versus 28% of SR patients ($p<0.001$). Antihypertensive medication initiation rates: 32% (SS) versus 72% (SR), $p<0.001$.

Discussion

This study demonstrates that salt sensitivity affects over half of essential hypertension patients and strongly associates with obesity, insulin resistance, and altered renin-angiotensin system regulation. Importantly, identifying SS status enables targeted dietary sodium restriction with substantially greater therapeutic benefit—an average 18.4 mmHg systolic BP reduction in SS individuals.

The 57.6% SS prevalence aligns with previous estimates (19, 20) and was significantly higher than the 18.5% observed in normotensive controls, confirming that salt sensitivity represents a pathogenic mechanism in essential hypertension rather than merely a normal physiological variant.

The strong association between insulin resistance and salt sensitivity supports mechanistic links. Insulin resistance enhances renal sodium reabsorption through multiple pathways: increased epithelial sodium channel (ENaC) activity, enhanced sympathetic activation, and endothelial dysfunction impairing pressure-natriuresis mechanisms (21, 22). The metabolic clustering observed—obesity, dyslipidemia, impaired glucose metabolism—suggests that salt sensitivity may represent a cardiovascular risk phenotype warranting comprehensive intervention beyond sodium restriction alone.

RAAS dysregulation in SS patients—excessive suppression during sodium loading yet paradoxically elevated aldosterone during restriction—indicates altered feedback regulation. Enhanced mineralocorticoid receptor sensitivity or impaired aldosterone metabolic clearance may contribute (23). The lower urinary sodium excretion despite identical intake confirms enhanced renal retention as a key mechanism.

Age-related increases in salt sensitivity likely reflect cumulative vascular and renal aging processes including reduced glomerular filtration, tubular dysfunction, endothelial senescence, and arterial stiffening (24). The higher prevalence among individuals of African ancestry warrants consideration of genetic factors affecting sodium transport, though socioeconomic influences on dietary patterns and healthcare access also contribute (25).

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The dramatic differential response to dietary intervention between SS and SR patients has major clinical implications. Current guidelines recommend sodium restriction for all hypertensive patients (26), but our findings suggest this strategy provides minimal benefit for SR individuals while being highly effective for SS patients. Salt sensitivity testing could therefore guide personalized dietary recommendations, focusing intensive counseling on those most likely to benefit.

Clinical Applications

Several practical approaches emerge: (1) Consider SS screening for hypertensive patients, particularly those with obesity, insulin resistance, or African ancestry; (2) For confirmed SS individuals, emphasize aggressive sodium reduction (<1500 mg/day) with close monitoring demonstrating BP benefit; (3) For SR patients, moderate restriction may suffice, with greater focus on other interventions (weight loss, exercise, medications); (4) Address insulin resistance comprehensively in SS patients through weight management and potentially insulin-sensitizing agents.

Limitations

The study's intensive dietary protocol limits generalizability to real-world settings where compliance varies. Single-center design may affect population characteristics. Follow-up duration (6 months) was insufficient to assess cardiovascular outcomes; longer studies are needed. Genetic analyses were not performed but could elucidate inherited determinants.

Conclusions

Salt sensitivity is prevalent in essential hypertension, strongly associates with obesity and insulin resistance, and predicts substantial blood pressure response to dietary sodium modification. Identifying salt-sensitive individuals enables targeted interventions with enhanced therapeutic efficacy. Findings support developing practical screening tools and personalized dietary approaches based on individual salt sensitivity status to optimize hypertension management.

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