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Serum Sodium in Hypertension

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Summary

High salt intake assessed by 24-hours urinary excretion of sodium is associated with increased blood pressure. Certain hypertensive subjects may have reduced renal excretion of sodium. Both factors might lead to a positive association between serum sodium and blood pressure. The present analysis was undertaken to test this hypothesis. Seven hundred and ninety-six individuals (331 females and 465 males) who presented for executive health check over 18 months from January 2004 were included in the study. Relationship between blood pressure and serum sodium was investigated using multivariable linear regression analysis including age, gender, body-mass index, and plasma glucose in the model. Systolic and diastolic pressures were significantly related to serum sodium in both men and women. Systolic pressure increased significantly (mean ± SD 130.1 ± 18.3 and 135.8 ± 19.8 mm Hg, P <0.005) with increasing levels of serum sodium (1st and 4th quartiles); similar increase was noted in diastolic pressure (80.0±10.3 and 84.1±10.8, P<0.005). Increase in serum sodium from 130 to140 mmol/L increased the systolic blood pressure by 5.7 mm of Hg (95% confidence interval 2.6-8.8 mm Hg). Corresponding increase in diastolic pressure was smaller (3.4, 95% confidence interval 1.6-5.2 mm Hg). Serum sodium and blood pressure are positively correlated in affluent subjects with high prevalence of life-style disorders including hypertension.

Key words: blood pressure - body mass index - plasma glucose

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Introduction

Systemic hypertension is a major cause of death and disability due to ischemic heart disease, cerebrovascular disease and renal failure all over the world. The prevalence of hypertension in adults in India is high (1-7) in both urban (30-50%) and rural areas (15-20%). It is often under-diagnosed and inadequately treated even in highly developed countries (8). Essential hypertension is recognized to result from a complex interplay of several genetic and environmental factors. Its association with advancing age, obesity and glucose intolerance is well established.

High dietary salt intake is associated with elevated blood pressure (9). Further, certain individuals may have abnormal handling of sodium load at the renal tubular level resulting in impaired capacity to excrete salt (10). Both factors lead to mild increase in serum sodium level which is largely compensated by expansion of the extra-cellular fluid volume via the thirst mechanism. Increased extra-cellular fluid volume is believed be responsible for increase in systemic blood pressure (11). High sodium may also reduce compliance of the conduit vessels contributing to further rise in blood pressure (12).

High salt intake has usually been assessed by dietary history or measurement of 24-hours urinary sodium excretion. Only a few studies have investigated the relationship between serum sodium and blood pressure after adjustment for important confounders. In this communication we report the association of age, body mass index, plasma glucose, and serum sodium on blood pressure in a cross-sectional study of adults undergoing preventive health check-up.

Material & Methods

1. Participants

Over a period of 18 months starting January 2004, we screened 1,701 individuals (637 females and 1,064 males) who presented themselves for general health check-up at the Sitaram Bhartia Institute of Science and Research, New Delhi. Most of them were apparently healthy adults and free from symptoms except for common life-style disorders. They were drawn from relatively higher socio-economic group and a majority had some health insurance cover provided by their employers. The objective of their medical examination was to recognize existing diseases, disorders and risk factors, and to offer appropriate interventions.

2. Procedures

All participants underwent clinical evaluation by a thorough history and physical examination. Blood pressure was measured on two occasions in the sitting posture using Hawksley random-zero mercury sphygmomanometer and appropriate cuff size. Subjects also had several laboratory investigations including plasma glucose (fasting and 2 hours after 75 G of oral glucose, PP), lipid profile, liver and kidney function tests, serum electrolytes, and uric acid using standard analytical methods and

external quality control. Serum sodium was measured using ion sensitive electrode (AVL, Austria). The coefficient of variation for duplicate measurement during the period of study was 1.5%. All subjects, however, did not have the complete work-up with all investigations enumerated above. The results of plasma glucose (fasting and 2 hours after ingestion of 75 G glucose), lipid profile, renal and liver function tests, and serum electrolytes were available in 796 individuals (331 females and 465 males). This group of subjects formed the material for our analysis. The analysis of data was approved by the institutional review board.

3. Statistical analysis

All data were entered on excel spread sheet and analyzed using Stata version 6. Apart from summary statistics, we used t-test for comparison between two groups, with modification for groups with unequal variance. Dichotomous variables were compared using ÷2 statistic. Multivariable linear regression analyses were performed with blood pressure as the dependent variable and age, gender, body mass index, plasma glucose, and serum sodium as the predictor variables. Subgroup analysis for male and female subjects was also undertaken. Subgroup analyses were also undertaken for subjects with or without metabolic syndrome, and after exclusion of 46 subjects receiving diuretics. All data were used without transformation. Certain variables, particularly triglycerides and PP were skewed to the right. Using log transforms of these variables did not influence model selection, main results and conclusions.

Results

The basic characteristics of the participants with normal (<140 mm Hg systolic and <90 diastolic) and high blood pressure are given in Table I. Subjects with hypertension had higher body mass index (BMI), plasma glucose (following oral glucose administration), serum sodium, triglycerides and uric acid. Distribution of subjects in the study sample according to grade of hypertension as per JNC 7 criteria is given in Table II. This categorization is based on the prevalent blood pressure irrespective of concurrent anti-hypertensive medication. Only 56% of women and 49% of men had blood pressure <140 mm Hg systolic and < 90 mm Hg diastolic; the rest had various grades of hypertension. Three hundred and forty-eight individuals (43.7%) had been diagnosed to have hypertension in the past; of these 115 had taken no treatment in the past one month. Eighty of these 115 individuals had blood pressure in the hypertensive range (>139 systolic or >89 diastolic). The remaining 233 diagnosed to have hypertension were taking diuretics (46), angiotensin converting enzyme inhibitors or receptor blockers (102), calcium channel blockers (99), ß-blockers (74) or centrally acting drugs (3) either singly or in various combinations. Amongst the previously diagnosed hypertensive subjects, 246 still had blood pressure in the hypertensive range (grade I or above). Further, 134 of the 448 subjects without previous

diagnosis of hypertension had blood pressure in the hypertensive range. The number of subjects receiving antihypertensive drugs but having blood pressure in the normal range (68), and those with blood pressure exceeding 139/89 mm Hg was 447 out of 796 individuals (56.2%). Of the 796 individuals, 21.3%

Table I

Basic characteristics of the participants with normal and high blood pressure

Parameters	Normal blood pressure (n=417)	High blood pressure (n=379)	P value¶
Age (years)	50.7±0.50	54.7±0.55	0.0000
Males	231(55.4%)	234(61.7%)	0.072*
Body mass index (kg/M^2)	26.7±3.9	27.7±4.3	0.0004
Plasma glucose§ (mg/dl)	107±52	126±66	0.0000
Serum sodium (mmol/L)	144.1±3.8	144.8±4.1	0.0164
Serum uric acid (mg/dl)	5.68±1.43	5.90±1.56	0.0413
Serum creatinine (mg/dl)	0.87±0.24	0.89±0.28	0.3585
Serum triglycerides (mg/dl)	140±88	156±129	0.0326

*Fisher's exact, ¶Student's two-tailed t-test, §2 hours after ingestion of 75 g glucose

Table II

Distribution of blood pressure graded according to JNC 7 criteria amongst the subjects studied

Hypertension	Blood pressure (mm Hg)	Females Freq (%)	Males Freq (%)
Normal blood pressure	<120/<80	50 (15.1)	50 (10.8)
Pre-hypertension	120-139/80-89	136 (41.1)	181 (38.9)
Hypertension gr I	140-159/90-99	98 (29.6)	159 (34.2)
Hypertension gr II	160-179/100-109	36 (10.9)	62 (13.3)
Hypertension gr III	180-199/110-119	10 (3.0)	12 (2.6)
Hypertension gr IV	>199/>119	1 (0.3)	1 (0.2)
Total		331	465

had metabolic syndrome according to ATP III criteria[13], 16.2% had diabetes mellitus and 18.7% had impaired glucose tolerance (IGT).

1. *Systolic blood pressure (SBP)*

Combined multivariable linear regression analysis for males and females showed that SBP was significantly related to age, body mass index, post-glucose blood sugar, and serum sodium, whereas gender was not a significant predictor (Table III). Subgroup analysis according to gender gave similar results.

2. *Diastolic blood pressure (DBP)*

Male sex, BMI and serum sodium were positively related to DBP (Table IV).

Table III

Linear regression of age, gender, body mass index (BMI), plasma glucose (PP), and serum sodium on systolic blood pressure.

Variable	ß coefficient	95% confidence interval	t value	P value
Age	0.55	0.43 – 0.66	9.235	0.000
Gender	0.74	-1.74 – 3.22	0.584	0.559
BMI	0.52	0.22 – 0.82	3.377	0.001
PP	0.053	0.032 – 0.074	4.974	0.000
Sodium	0.57	0.26 – 0.88	3.627	0.000

Number of observations = 796, F(5,790) = 30.38, Probability >F = 0.0000, adjusted R^2 = 0.16

Table IV

Linear regression of age, gender, body-mass index (BMI), post-glucose plasma sugar (PP) and serum sodium on diastolic blood pressure

Variable	ß coefficient	95% confidence interval	t value	P value
Age	-0.03	-0.09 – 0.04	-0.761	0.447
Gender	3.38	1.94 – 4.82	4.600	0.000
BMI	0.48	0.31 – 0.66	5.454	0.000
PP	0.002	-0.01 – 0.01	0.264	0.792
Sodium	0.34	0.16 – 0.52	3.682	0.000

Number of observations = 796, F(5, 790) = 13.61, Probability > F = 0.0000, Adjusted R^2 = 0.07

Notably, age and plasma glucose were not significant predictors of diastolic pressure. These associations were maintained in sub-group analysis according to gender.

Table V gives the ß coefficient for the change in systolic and diastolic pressure per 10 mMol/L change in serum sodium in different subgroups. The ß coefficient for change in diastolic pressure per 10 mMol/L change in serum sodium was smaller than the corresponding ß coefficient for systolic pressure in all analyses. Further, the ß coefficient was greater in females compared to males. The relationship between blood pressure and serum sodium appeared consistent after exclusion of individuals receiving diuretics or those with metabolic syndrome. The regression models for systolic and diastolic pressure explained greater amount of variability in the females as compared to males.

Table V

Coefficients of regression of blood pressure per 10 mMol/L change in serum sodium

Subjects	Observations	Adjusted R^2	ß coefficient	95% confidence interval
Systolic pressure:				
All subjects*	796	0.16	5.7	2.6 - 8.8
Females	332	0.24	6.9	2.0 - 11.8
Males	464	0.10	4.6	0.6 - 8.7
Excluding subjects receiving diuretics*	750	0.15	4.8	1.6 - 8.1
Excluding subjects with MS*	626	0.15	6.1	2.7 - 9.6
Diastolic pressure:				
All subjects*	796	0.08	3.4	1.6 - 5.2
Females	332	0.10	3.5	0.7 - 6.4
Males	464	0.03	3.1	0.7 - 5.4
Excluding subjects receiving diuretics*	750	0.07	3.1	1.3 - 5.0
Excluding subjects with MS*	626	0.06	3.5	1.5 - 5.4

* Core model: Systolic blood pressure = age + gender + BMI + PP + sodium + constant

Three hundred and eighty three individuals with hypertension (grade I and above according to JNC 7 criteria) had serum sodium (mean ± SD) 144.8 ± 4.1 mmol/L compared to 144.1 ± 3.8 in 424 individuals with blood pressure in the normal or pre-hypertensive range (P = 0.0164, Table I). Table VI gives mean (±SD) of systolic and diastolic blood pressure according to quartiles of serum sodium. Both pressures increased with increase in serum sodium, the difference between the 1st and 4th quartile being highly significant (P<0.005). Figure 1 shows the scatterplot of blood pressure regressed on serum sodium with lowess smoother. There is a considerable degree of scatter but both systolic and diastolic pressure begin to increase after serum sodium exceeds 144 mmol/L. Marked scatter is also reflected in low adjusted R^2 (0.16 and 0.07 for systolic and diastolic pressures) noted in multivariable regression analysis.

3. Factors influencing serum sodium

In multivariate linear regression model, serum sodium was significantly positively related to diastolic blood pressure and uric acid, and negatively related to plasma glucose and serum creatinine. Exclusion of 46 subjects receiving diuretics did not affect the results.

Discussion

The study sample used in this analysis is not representative of urban population of India but represents the educated executive class in high income group. The participants generally had a sedentary life-style with high prevalence of overweight and obesity. The prevalence of all grades of hypertension was also high, and higher than in other reports from urban India. Lack of heterogeneity in certain risk factors in a cross sectional analysis is likely to underestimate their influence on blood

Table VI

Systolic and diastolic blood pressure amongst subjects categorized according to serum sodium levels

Sodium category	No of observations	Sodium mean±SD	Systolic pressure mean±SD	Diastolic pressure mean±SD
1st quartile	205	139.5 ± 2.6	130.1 ± 18.3	80.0 ± 10.3
2nd quartile	194	143.6 ± 0.5	132.4 ± 20.2	81.1 ± 10.8
3rd quartile	236	145.9 ± 0.8	134.1 ± 18.1	82.8 ± 10.3
4th quartile	161	149.7 ± 2.1	135.8 ± 19.8*	84.1 ± 10.8*

*P vales for Student's t-test 4th quartile versus 1st quartile <0.005

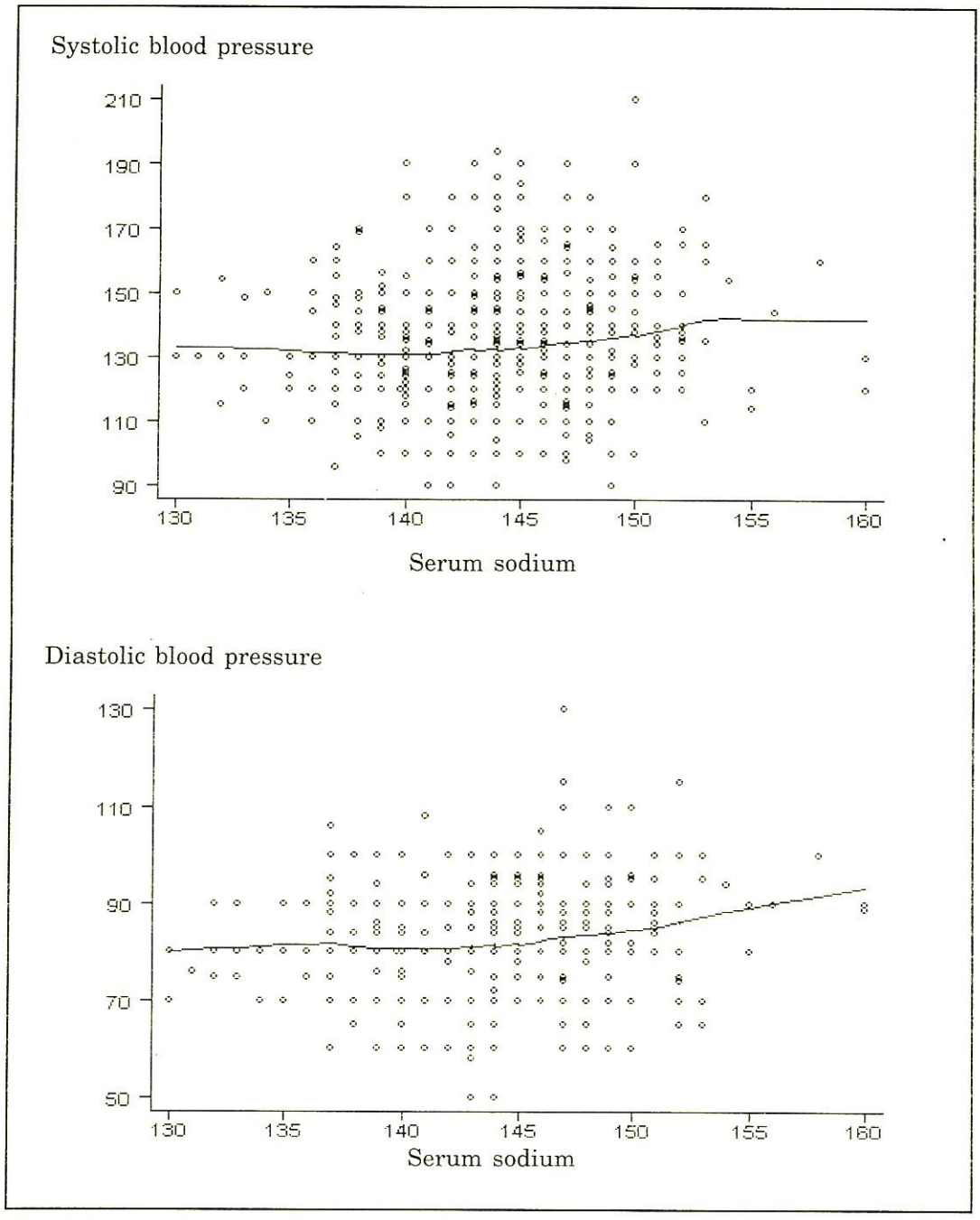

Figure 1. Scatterplot of systolic and diastolic blood pressure on serum sodium. Lowess smoother with bandwidth 0.8 has been used for curve fitting.

pressure and the investigators are aware of this limitation of the study. Nevertheless, large datasets with most of the study variables involving blood sampling are becoming available at several health facilities in large cities of India. We have not come across any published study which looked at the association between blood pressure and serum sodium in individuals seeking routine health check.

It is well recognized that advancing age, overweight/obesity and glucose intolerance/diabetes are independently associated with high blood pressure. The prevalence of metabolic syndrome (MS), IGT and type 2 diabetes in the study sample was high but consistent with previous reports of increasing life-style disorders in this segment of the population (1, 15). The present study demonstrates a consistent positive relationship between serum sodium and systolic and diastolic blood pressures in both sexes after inclusion of other explanatory variables, particularly age, body mass index and plasma glucose in the regression model. The relationship persists after exclusion of subjects with MS or those receiving diuretics. The association of increased blood pressure with serum sodium, however, is weak and notable rise in blood pressure is observed only after serum sodium exceeds ~144 mmol/L.

There are no large studies investigating the relationship between daily salt intake, serum sodium, urinary sodium excretion and blood pressure. It has been reported that mild elevations of serum sodium in the physiological range may be associated with elevated blood pressure (15). A recent study (16) investigated the effect on plasma sodium of an acute and large reduction in salt intake, progressive increase in salt intake, and long-term modest reduction in salt intake. Chronic reduction in salt intake reduced plasma sodium by 0.4 mmol/L ($P<0.05$) in 118 patients with untreated essential hypertension. There are no studies relating habitual salt intake to serum sodium levels. Those who habitually consume excessive amounts of salt, or those who are poor salt handlers would be expected to have mild elevation of serum sodium despite expansion of the extracellular fluid volume resulting in elevation of blood pressure. Further, reduction in salt intake has been shown to increase the compliance of large arteries (12) such as carotids and this might partly explain the beneficial effect of low salt diet on systolic blood pressure, particularly in the elderly.

Estimation of serum sodium is much more precise than that of urinary sodium excretion. Moreover it could be a marker not only of excessive salt intake but also of poor salt handling at the renal tubular epithelium. Regression analysis indicates that increase in serum sodium from 130 to140 mmol/L could increase the systolic blood pressure by 5.7 mm of Hg (95% confidence interval 2.6-8.8 mm Hg, Table III). This compares with 3-6 mm higher blood pressure in those who excreted 100

mmol more of sodium in the urine per day in the INTERSALT study (9). There appears to be a reasonable concordance in these results.

Komiya *et al* (17) observed serum sodium to be approximately 2 mmol/L higher in Japanese subjects with hypertension (n=741) compared to 3222 normotensive individuals. We observed a significantly higher serum sodium in hypertensive subjects as compared to normotensive individuals (mean difference 0.7 mmol/L, P=0.0164). The ß coefficient for diastolic blood pressure was smaller than for the systolic pressure (about half of the coefficient for systolic pressure). This observation, again, is consistent with findings of the INTERSALT study. Wannamethee *et al* (18) also observed an association between serum sodium and systolic, but not diastolic blood pressure in 2297 hypertensive subjects.

One can only speculate on the consistent observation of a greater effect of sodium on systolic pressure compared to diastolic pressure. Expansion of extracellular fluid volume triggered by small increase in serum sodium occurs due to redistribution of fluid and activation of the thirst mechanism. This is likely to increase both systolic and diastolic pressures. Disproportionate increase in systolic pressure is likely related to stiffening of the conduit vessels for which considerable evidence has accumulated from different study designs.

Regression models developed in this study showed greater unexplained variability in blood pressure in males compared to females. It is possible that several potential risk factors influencing blood pressure such as sedentary life style, high alcohol intake and mental stress were more prevalent in men. Unexplained variability was greater for diastolic blood pressure. These observations suggest the importance of several risk factors for high blood pressure other than those included in the present study.

Association of hyperuricemia with hypertension and other cardiovascular diseases is well recognized. Uric acid is handled in a manner similar to sodium in the kidney, and decreased fractional excretion of uric acid has been used as a marker for altered sodium re-absorption (19). We also noted significant correlation between serum sodium and uric acid suggesting hypertensive subjects to be poor salt handlers.

In summary, we suggest that the relationship between serum sodium and high blood pressure observed in the present study is valid and generalizable to affluent urban population. There are physiological reasons and limited observational studies to suggest that high serum sodium reflects high salt intake and abnormal sodium handling by the kidneys. We believe that reduction in the dietary salt content in India would help reduce burden from cardiovascular mortality.

Salt content of typical Indian diet ranges from 10-15 g/day (20,21). There is little awareness regarding the adverse effect of high salt intake on blood pressure and cardiovascular events. The findings of the present study considered along with the results of several previous studies support the need for reduction of salt consumption by Indians for better cardiovascular health.

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