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Interindividual Variation in Serum Sodium and Longitudinal Blood Pressure Tracking in the Framingham Heart Study

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Abstract

Background—Recent cross-sectional studies have suggested that higher serum sodium levels may be a marker of elevated blood pressure. It is unclear whether serum sodium levels are related to the risk of developing hypertension in the community.

Methods—We investigated the association of serum sodium with longitudinal blood pressure tracking and incidence of hypertension in 2172 non-hypertensive Framingham Offspring Study participants (mean age 42 years, 54% women). We defined an increase in blood pressure as an increment of ≥ 1 category (as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure), and incident hypertension as a systolic pressure of ≥ 140 or a diastolic pressure ≥ 90 mm Hg, or use of antihypertensive medications. Serum sodium was analyzed as a continuous variable, and as categories.

Results—Cross-sectionally, serum sodium was not associated with systolic or diastolic blood pressure (p exceeded 0.10). On follow-up (mean 4.4 years), 805 participants (37 %; 418 women) progressed by ≥ 1 blood pressure category, and 318 (15%; 155 women) developed new-onset hypertension. In multivariable logistic regression analyses (adjusting for age, sex, baseline blood pressure, diabetes, body mass index, weight gain and smoking), serum sodium was not associated with blood pressure progression (Odds ratio [OR] per SD increment 0.93, 95% confidence limits [CI] 0.85–1.03), or with hypertension incidence (OR per SD increment 0.94, 95% CI 0.82–1.08).

Conclusions—In our large community-based sample, serum sodium was not associated with blood pressure cross-sectionally, or with blood pressure tracking or hypertension incidence longitudinally.

Keywords

Hypertension; blood pressure; serum sodium; metabolism; epidemiology; longitudinal studies

Introduction

A large body of scientific evidence links dietary sodium consumption to the pathogenesis of hypertension [1,2]. More recently, investigators have highlighted the potential relations of

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serum (or plasma) sodium concentrations to high blood pressure (BP), a hitherto less-studied association. Wardener and colleagues have suggested that higher serum sodium levels may be a marker of higher BP [3,4]. Several lines of scientific evidence support this possibility. First, acute intervention studies in individuals with hypertension suggest that a reduction in dietary salt intake results in a fall in serum sodium (~3 mmol/L) paralleled by a fall in systolic BP (~17 mm Hg) [4]. Second, salt loading in nonhypertensive people results in a modest rise in serum sodium (~3 mmol/L) accompanied by a rise in pulse pressure [4]. Third, chronic interventions reducing dietary salt in patients with hypertension results in more modest falls in serum sodium (~0.5 mmol/L), but such a reduction is accompanied by modest sustained reductions in systolic BP (~8 mm Hg) [4]. Last, in some cross-sectional studies serum sodium has been associated positively with systolic BP (especially in those with hypertension) [5–8], although other investigations that have evaluated larger samples have reported a lack of association [8,9], or noted an inverse relation to diastolic BP [8].

Wardener and colleagues have proposed two potential mechanisms by which serum sodium may influence BP [3,4]. They postulate that changes in serum sodium may drive extracellular volume responses, which can alter BP. Alternatively, they speculate that “small changes in plasma sodium may directly affect the hypothalamus, the local renin-angiotensin system, and the heart and vasculature, all of which may play a role in changing blood pressure” [3,4].

The studies noted above raise the interesting possibility that interindividual variation in serum sodium may be associated with variation of BP in the community. However, prior studies do not establish a causal relation because the changes in serum sodium in the intervention studies may simply be an epiphenomenon of alterations in BP. Also, cross-sectional studies by design cannot establish causality. Furthermore, both interventional and cross-sectional studies may be limited by referral bias. Therefore, it is unclear if an association between serum sodium and BP exists in community-dwelling individuals in a ‘steady state’ and who are on a random sodium diet, and if serum sodium may serve as a biomarker of future hypertension risk in the general population. Accordingly, we evaluated the relations of the serum sodium level to the incidence of hypertension and to longitudinal changes in BP in a large community-based sample of nonhypertensive individuals.

Methods

Study Sample

The design and the selection criteria of the Framingham Offspring Study have been described previously [10]. Serum sodium levels were measured on attendees at their second examination cycle (1979 to 1982), and a follow-up examination at the Heart Study (third examination cycle, 1984–1987) was performed to reclassify the subjects according to their BP stage. Participants were eligible for the present investigation if they: were not hypertensive (defined as a systolic BP of <140 mmHg and a diastolic BP of <90 mm Hg and were not taking anti-hypertension medications) [11] had available serum sodium concentrations at the second examination cycle, and attended the follow-up third examination cycle approximately four years later. Thus, of the 3863 eligible participants, we excluded 1691 from the investigation for the following reasons: hypertension at baseline (n=914); prevalent cardiovascular disease (n=66), or cancer (n=30); serum creatinine level at or above 2.0 mg/dl (n=4); missing covariates (n= 47) or serum sodium (n=125); hypo- or hyperosmolality suggesting altered total water body content (n= 207; defined by values <280 or >300 mosm/kg respectively, as estimated by the formula: $\text{osmolality} = 2 [\text{serum sodium mEq/l}] + \text{blood glucose in mg/dl}/18 + \text{BUN in mg/dl}/2.8$); use of diuretics for indications other than hypertension (n=30); and nonattendance at third examination cycle (n= 268). After these exclusions, 2172 subjects (mean age 42 years; 54% women) remained eligible for the present investigation. All participants provided written

informed consent, and the institutional review board at the Boston University School of Medicine approved the study protocol.

Baseline Examination

At the baseline examination, all the participants underwent a standardized physical examination, anthropometry, electrocardiography, and laboratory testing for assessment of vascular risk factors.

Blood pressure was measured on the left arm of seated participants by a physician, using a mercury-column sphygmomanometer, a cuff of appropriate size, and a standardized protocol. Participants had rested in a chair for about five minutes before BP was measured, and the average of two physician-obtained readings was considered the examination BP. The examination BP was considered for classification of BP stages, according to Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) criteria [11]. When systolic and diastolic BP readings belonged to different categories, the higher of the two categories was used. Thus, eligible subjects were categorized into the following BP stages: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal (systolic 120 to 129 or diastolic 80 to 84 mm Hg), or high-normal (systolic 130 to 139 or diastolic 85 to 89 mm Hg) [11]. We chose this classification system as opposed to that recommended more recently in the JNC VII [12] because progression of BP stage was one of the outcomes defined a priori, and the JNC VI classification yields more BP groups, thereby facilitating assessment of changes in BP category on follow-up associated with more modest BP changes. Additionally, the JNC VI classification permitted consistency with prior Framingham investigations that evaluated BP progression [13,14].

Venous blood was drawn from fasting participants, typically between 8 AM and 9 AM, and serum electrolytes and creatinine were measured. Serum sodium was measured by flame-emission spectrophotometry [15]. Serum creatinine was determined by an autoanalyzer [16].

Blood Pressure Outcomes on Follow-up

At follow-up, approximately four years after the baseline examination, participants attended the third examination cycle, at which time they underwent a routine examination including measurement of their BP (average of two measurements using the same standardized protocol as the baseline examination).

Four BP endpoints on follow-up were evaluated in the present investigation: i. progression in BP by one or more categories (as defined by the JNC VI) [11]; ii. development of hypertension [11]; iii. change in systolic BP; and, iv. change in diastolic BP. We have used these BP outcomes in several prior Framingham investigations [13,14].

Statistical Analysis

Cross-sectional Relations of Serum Sodium—Multivariable linear regression was used to evaluate the clinical correlates of serum sodium at the baseline examination: sodium (dependent variable) was related to age, sex, systolic and diastolic BP, body mass index, diabetes, smoking and serum creatinine (all independent variable).

Longitudinal Relations of Serum Sodium to BP Outcomes—We used multivariable logistic regression models to examine the association of serum sodium with incidence of BP progression and hypertension on follow-up. The serum sodium level was examined in separated models, being treated both as a continuous variable (with natural logarithmic transformation to normalize the skewed distribution), and as a categorical variable (in 4 categories of sodium concentrations). The 4 categories of serum sodium did not have equal numbers of participants

(i.e., were not exact quartiles) because serum sodium concentrations were reported as whole numbers and the values had a narrow distribution. When modeled as 4 categories (cutpoints were identical in the two sexes), the second and third categories of serum sodium were used as referent, and the lowest and top categories were compared with the middle categories. The use of the middle two categories as referent permitted us to elucidate any potential U-shaped relations of serum sodium to HTN. Covariates in the multivariable models were: age, sex, baseline BP category, baseline systolic and diastolic BP, smoking, diabetes mellitus, body mass index (all defined at the baseline examination), and weight gain (between the baseline and the follow-up examinations). We tested for effect modification by age, sex, baseline BP category, diabetes mellitus, and body mass index by incorporating corresponding interaction terms into multivariable models with serum sodium as a continuous variable.

We performed additional analyses examining the relations of serum sodium levels to longitudinal systolic and diastolic BP changes analyzed as continuous variables. For these analyses, we used censored normal regression [17] to account for treatment for high BP at the follow-up examination. Multivariable models were adjusted for the covariates noted above for analyses of categorical BP outcomes. Additionally, we repeated all analyses using a standard-deviation (SD)-based categorization of serum sodium levels ($<\text{mean}-1\text{SD}$; between mean and mean-1 SD; between mean and mean+1SD; $>\text{mean}+1\text{SD}$) because the classification we initially used based on ranking people did not result in an equal number of people in each category. In these analyses, we compared the odds of developing BP endpoints in the lowest and highest categories using the middle two categories (serum sodium within 1 SD of the mean) as referent.

Results

The baseline characteristics of our study subjects are displayed in Table 1. A higher proportion of women had optimal BP at the baseline examination, compared to men. Cross-sectionally, serum sodium was positively related to age ($\beta=0.12$ per 10 year increment, $p=0.02$), but inversely related to diabetes ($\beta=-2.56$; $p<0.0001$) and serum creatinine ($\beta=-0.59$ per mg/dl increment, $p=0.01$) in multivariable models. Serum sodium was not related to either systolic or to diastolic BP, or to sex or body mass index ($p>0.10$).

At the follow-up examination approximately four years from baseline, 805 participants (37%; 418 women) experienced progression of BP by one or more JNC VI stage, and 318 individuals (15%; 155 women) developed new-onset hypertension. Ranges of serum sodium in the 4 categories are shown in Table 2, along with the 4-year rates of progression of BP and hypertension incidence. There was no consistent pattern for BP progression in relation to serum sodium categories. A lower proportion of participants in the highest serum sodium category developed new-onset hypertension.

Table 3 displays the results of multivariable analyses relating log-serum sodium and serum sodium categories to BP progression and hypertension incidence. Serum sodium was not related to either of these BP outcomes. None of the interactions terms evaluated were statistically significant. In additional analyses, serum sodium was not related to longitudinal changes in systolic (mean change 3.1 mm Hg, SD 10.8) and diastolic BP (mean change 2.0 mm Hg, SD 7.0) evaluated as continuous outcomes ($p=0.74$ and 0.53 , respectively).

Because we did not observe statistically significant associations of serum sodium with BP outcomes prospectively in any of our analyses, we evaluated our statistical power to detect modest associations. Based on the width of the confidence intervals presented in Table 3, we can exclude (with 95% confidence) a $>3\%$ increase in the odds of blood pressure progression or a $>8\%$ increase in odds of developing hypertension per 1 SD increase in serum sodium.

More modest associations of serum sodium with BP outcomes would require analyses of much larger samples.

In analyses using SD-based categories of serum sodium, neither the lowest category of serum sodium ($<\text{mean}-1\text{SD}$), nor the highest category ($>\text{mean}+1\text{SD}$) were associated with BP progression (p values exceeded 0.10) or with hypertension incidence (p values exceeded 0.55), compared to the referent group (serum sodium at or between mean -1SD and mean $+1\text{SD}$). These results suggest that our results were not sensitive to the method used to categorize serum sodium.

Discussion

Principal Findings

Our principal findings are three-fold. First, cross-sectionally, serum sodium was positively associated with age, but inversely related to diabetes and to serum creatinine. Second, serum sodium was not related to systolic or diastolic BP in cross-sectional analyses of our sample of non-hypertensive individuals. Third, longitudinal analyses did not demonstrate any association of serum sodium with BP progression, hypertension incidence or with longitudinal changes in systolic or diastolic BP.

Comparison with the Published Literature

Our observation of a positive cross-sectional relation of serum sodium to age is consistent with prior reports demonstrating a very modest increase in sodium concentrations in older people, in part related to aging-associated changes in renal regulation of sodium homeostasis with a resultant increase in total body sodium [7].

Recent reports highlighted the potential relations of serum sodium to high BP, suggesting that higher serum sodium levels may be a marker of elevated BP development [3,4]. In the present investigation of a large community-based sample of nonhypertensive individuals, there was no statistically significant association between serum sodium concentration and the development of hypertension or BP progression. The hypothesis that prolonged small changes in plasma sodium would correlate with development of hypertension or with modest longitudinal changes in BP was not confirmed in this study.

There are several potential explanations for the lack of association between serum sodium concentrations and hypertension incidence or BP progression in our investigation. First, the concentration of serum sodium is closely and rapidly regulated by the modulation of renal sodium excretion, the movement of fluid between the intra- and the extracellular space, and by the activity of the hypothalamic thirst center [18]. Thus, the dynamic equilibrium between the extracellular fluid volume and serum osmolality maintains serum sodium levels within a very narrow range [18]. Second, it is likely the habitual dietary intake of sodium and not the highly regulated serum sodium concentration that determines blood pressure levels (as reviewed elsewhere) [1,2]. Third, genetic influences may modulate renal sodium handling based on the variations in dietary sodium intake, quite independent of serum sodium levels [19]. Fourth, it is conceivable that excess dietary salt intake may cause small elevations in serum sodium levels in genetically predisposed individuals with concomitant changes in BP, but such effects are not discernible in a large group of individuals in the community all of whom may not be so predisposed. Finally, hypertension is a multifactorial disease, related to the combinatorial influences of genetic, environmental, and behavioral factors [20]. Therefore, the link between a specific factor (such as serum sodium) and the development of hypertension may be difficult to demonstrate in the community.

Strengths and Limitations

Strengths of the present investigation include the large, community-based sample of non-hypertensive individuals, the standardized BP assessments at baseline and on follow-up, and the multivariable analyses adjusting for several confounders known to influence BP and serum sodium levels. Limitations include the predominantly white sample that limits the generalizability of our findings to other ethnicities.

Perspectives

A large body of experimental and clinical observational data link dietary salt intake to the mean BP, the age-BP slope and the prevalence of high BP in the general population.(1, 2) Randomized controlled trials have demonstrated that long-term modest reductions in dietary salt intake can be associated with small reductions in mean BP of populations, which can translate into potentially substantial public health benefits [1,2]. The lack of association of serum sodium levels with BP in the present investigation do not negate a critical role for dietary sodium and sodium homeostasis in the regulation of BP. Rather, these observations likely indicate that the tight regulation of serum sodium within a narrow physiological range would render serum sodium concentration an inadequate biomarker of the propensity to develop high BP.

Conclusions

Our observations on a large community-based sample suggest that serum sodium concentrations was not associated with BP cross-sectionally or related to longitudinal changes in BP (including hypertension incidence). These findings may reflect the multifactorial determinants of interindividual variability in BP levels [20].

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Table 1

Baseline Characteristics of the Participants.

Characteristics	Men (n=995)	Women (n=1177)
Age, years	42 ± 10	42 ± 9
Body-mass index, kg/m ²	26.4 ± 3.4	24.2 ± 4.1
Diabetes, %	2.4	0.4
Current smoker, %	36.6	35.5
Blood pressure, mm Hg		
Systolic	119 ± 10	113 ± 12
Diastolic	77 ± 7	73 ± 8
Blood-pressure category, % *		
Optimal	40.1	64.0
Normal	34.3	22.7
High-normal	25.6	13.3
Biochemical features		
serum sodium, meq/L	139.3 ± 2.2	139.3 ± 2.3
serum creatinine, mg/dl	1.24 ± 0.22	1.06 ± 0.21

Values are means ± SD or percent.

* Participants were categorized into three groups according to their baseline blood pressure: optimal (systolic <120 and diastolic <80mm Hg), normal (systolic 120 to 129 or diastolic 80 to 84 mm Hg), or high-normal (systolic 130 to 139 or diastolic 85 to 89 mm Hg).

Table 2
Baseline Serum Sodium Concentrations and the Incidence of Blood Pressure Outcomes on Follow-up.

Serum Sodium Categories	Baseline			Follow-up		
	Men		Women	Mean Baseline Blood Pressure (mmHg)		Hypertension [†]
	n	Median serum Sodium, meq/L (minimum, maximum)	n	Median serum Sodium, meq/L (minimum, maximum)	Increase in Blood Pressure Stage [*]	
					No. of events/No. at risk	% (95% CI) [*]
First (lowest)	227	136 (133–137)	278	137 (133–137)	115	75
Second	308	139 (138–139)	366	138 (138–139)	116	75
Third	162	140 (140–140)	188	140 (140–140)	117	76
Fourth (highest)	298	142 (141–145)	345	142 (141–145)	116	75
					197/505	39.0 (34.1, 44.1)
					244/674	37.0 (32.6, 41.6)
					123/350	35.5 (30.1, 41.2)
					241/643	36.5 (32.1, 41.2)
					76/505	15.1 (11.7, 19.1)
					100/674	15.2 (12.1, 19.0)
					54/350	15.7 (11.8, 20.5)
					88/643	13.2 (10.3, 16.7)

The 4 categories of serum sodium did not have equal numbers of participants (i.e., were not exact quartiles) because serum sodium concentrations were reported as whole numbers.

^{*} age- and sex-adjusted %; an increase in blood pressure stage was defined as an increment of at least one blood pressure category (as defined by the sixth report of the Joint National committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).

[†] age- and sex-adjusted %; Hypertension was defined as a systolic blood pressure of 140mm Hg or higher, a diastolic blood pressure of 90mm Hg or higher, or the use of antihypertensive medications.

Table 3
Association of Baseline Serum Sodium with Increase in Blood Pressure Stage and the Development of Hypertension on Follow-up.

Serum Sodium	Increase in Blood Pressure Stage [*]		Hypertension [†]	
	Adjusted Odds Ratio (95% CI)	p value	Adjusted Odds Ratio (95% CI)	p value
A. Continuous variable				
1 SD increase	0.93 (0.85,1.03)	0.159	0.94 (0.82,1.08)	0.389
B. Serum sodium categories				
First (lowest)	1.19 (0.93,1.52)	0.156	1.15 (0.82,1.61)	0.411
Second	1.0	Referent	1.0	Referent
Third	1.0		1.0	
Fourth (highest)	1.01 (0.81,1.26)	0.928	0.92 (0.67,1.26)	0.595

Odds ratios were adjusted for age, sex, baseline blood pressure category, systolic blood pressure, diastolic blood pressure, body-mass index, percentage weight gain, diabetes, and smoking status. CI denotes confidence interval.

^{*} An increase in blood pressure stage was defined as an increment of at least one blood pressure category (as defined by the sixth report of the Joint National committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).

[†] Hypertension was defined as a systolic blood pressure of 140mm Hg or higher, a diastolic blood pressure of 90mm Hg or higher, or the use of antihypertensive medications.