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Opposing effects of sodium intake on uric acid and blood pressure and their causal implication

Stephen P Juraschek, MD, PhD¹, Hyon K Choi, MD, DrPH², Olive Tang, BS¹, Lawrence J Appel, MD, MPH¹, and Edgar R Miller III, MD, PhD¹

¹ The Johns Hopkins University School of Medicine, The Johns Hopkins Bloomberg School of Public Health, and The Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore MD

² Harvard Medical School, Gout and Crystal Arthropathy Center, and Massachusetts General Hospital

Abstract

Reducing uric acid is hypothesized to lower blood pressure, although evidence is inconsistent. In this ancillary of the DASH-Sodium trial, we examined whether sodium-induced changes in serum uric acid (SUA) were associated with changes in blood pressure. One hundred and three adults with pre- or stage 1 hypertension, were randomly assigned to receive either the DASH diet or a control diet (typical of the average American diet) and were fed each of 3 sodium levels (low, medium, and high) for 30 days in random order. Body weight was kept constant. SUA was measured at baseline and following each feeding period. Participants were 55% women and 75% black. Mean age was 52 (SD, 10) years, and mean SUA at baseline was 5.0 (SD, 1.3) mg/dL. Increasing sodium intake from low to high reduced SUA (-0.4 mg/dL; $P < 0.001$), but increased systolic (4.3 mm Hg; $P < 0.001$) and diastolic blood pressure (2.3 mm Hg; $P < 0.001$). Furthermore, changes in SUA were independent of changes in systolic ($P = 0.15$) and diastolic ($P = 0.63$) blood pressure, regardless of baseline blood pressure, baseline SUA, and randomized diet, as well as sodium sensitivity. While both SUA and blood pressure were influenced by sodium, a common environmental factor, their effects were in opposite directions and were unrelated to each other. These findings do not support a consistent causal relationship between SUA and BP.

Elevated uric acid levels often accompany high blood pressure (1,2) and are associated with cardiovascular disease risk (3–7). Recently, several trials of urate-lowering therapy have shown that short-term reductions in uric acid are associated with a reduction in blood

Stephen P. Juraschek, M.D., Ph.D., Johns Hopkins Medical Institutions, 2024 East Monument Street, Suite 1-500, Baltimore, MD 21205, Phone: 410-502-6444, Fax: 410-502-6446, spj@jhmi.edu.

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Conflicts of interest

The authors have no conflicts of interest to report.

pressure (8–11). These studies have contributed to the hypothesis that hyperuricemia is a causal determinant of hypertension.

The DASH-Sodium trial was an isocaloric, controlled feeding study of the effects of the DASH diet and sodium intake on blood pressure (12). This study showed definitively that both the DASH diet and lower sodium consumption lowered blood pressure. However, in a recent ancillary study, we reported that while the DASH diet lowered uric acid, the lower sodium diet increased uric acid (13).

Thus the purpose of this study was to compare the within-person changes in uric acid with their changes in blood pressure following increased sodium intake. We hypothesized that short-term changes in uric acid would be independent of changes in blood pressure.

Methods

The original DASH-Sodium study was an investigator-initiated, multicenter, randomized trial sponsored by the National Heart, Lung, and Blood Institute between September 1997 through November 1999 (12). This study randomized adults with prehypertension or stage 1 hypertension (not taking antihypertensive medications) and compared the effects of three levels of sodium intake on blood pressure in two distinct diets. The control diet reflected a typical American diet, while the intervention diet, the DASH diet, was rich in fruits, vegetables, and low-fat dairy foods and reduced in saturated fat, total fat, and cholesterol (14). The DASH diet also emphasized whole grains, poultry, fish, and nuts, and de-emphasized red meat, sweets, and sugar-containing beverages than the typical American diet. In both diets, participants were fed each of three sodium levels: low (a target of 60 mmol per day), medium (a target of 120 mmol per day), and high (a target of 180 mmol per day). These targets were based on consumption of 2600 kcal of food per day, where the high sodium level (180 mmol/d) reflected typical sodium intake of a United States adult. The daily sodium intake was adjusted to reflect the total energy requirements of each participant, based on estimated need. As a result, larger or more active participants received more food and sodium compared to smaller and less active participants. Detailed descriptions of the diets are in **Supplement Table S1**.

Participants

The original study recruited adult men and women, aged 22 years and older, with an average systolic blood pressure (based on three screening visits) of 120 to 159 mm Hg and an average diastolic blood pressure of 80 to 95 mm Hg. We excluded persons with a prior diagnosis of heart disease, renal insufficiency, poorly controlled dyslipidemia, or diabetes mellitus. Furthermore, persons using antihypertensive agents, insulin, or drinking more than 14 alcoholic drinks a week were not eligible for this study (12).

The ancillary study presented here was limited to participants from the Johns Hopkins University clinical center in Baltimore, Maryland, based on uric acid measured at the time the study was performed. The Institutional Review Board at Johns Hopkins University approved the original study protocol. Written, informed consent was provided by all participants.

Controlled feeding

Participants were provided all of their food, including meals and snacks. All participants underwent an 11-14 day, run-in period during which they ate the high sodium, control diet. Subsequently, they were randomized to either the DASH or control diet according to a parallel-arm design. Within the context of either diet, participants ate each of three sodium levels for 30 days in random order. Sodium levels were separated by a 5-day break. Caloric intake was adjusted to maintain a constant weight throughout the trial.

Serum uric acid measurement

Fasting blood was collected from fasting participants at the Baltimore clinical center between 1997-1999. Specimens were centrifuged, aliquoted, and analyzed by Quest Diagnostics (Madison, New Jersey) for analysis without freezing or storage. Uric acid was measured via spectrophotometry.

Other covariate measurements and definitions

Baseline characteristics were gathered via questionnaires, laboratory specimens, and physical measurement. The primary outcome of the original DASH-sodium trial was blood pressure, measured in triplicate by protocol using random-zero, mercury sphygmomanometers after a 5 minute rest, while participants were seated, at three screening visits, twice during the run-in period, weekly during the first three weeks of each of the three 30-day intervention periods, and at five clinic visits during the last nine days (at least two during the final four days) of each intervention period. A high blood pressure at baseline was defined as having a mean, systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg of the three screening visits.

In addition to blood pressure, standard laboratory assays and techniques were used to measure serum total protein and albumin levels.

Statistical analysis

The study population was characterized with means (SD) and proportions. Mean uric acid and blood pressure measured at the end of each sodium period were compared to baseline measurements within each participant, using generalized estimating equation (GEE) regression models with a Huber and White robust variance estimator (15), which assumed an exchangeable working correlation matrix.

We also compared changes in uric acid with changes in systolic or diastolic blood pressure while going from a low to high sodium diet, using Pearson's coefficient and linear regression. These comparisons were performed in strata of baseline hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg), elevated baseline systolic blood pressure (< 140 mm Hg), elevated baseline diastolic blood pressure (< 90 mm Hg), salt sensitive participants (defined based on an absolute increase in mean arterial pressure ≥ 5 mm Hg or $\geq 5\%$), and baseline hyperuricemia (≥ 6 mg/dL). Interaction terms were used to compare effects across strata.

Finally, prior studies have reported that higher sodium intake can increase intravascular volume, artificially lowering biomarkers in blood specimens (16). To minimize this effect, we performed a sensitivity analysis, dividing the uric acid measures by either total protein or albumin (markers thought not be influenced by short-term changes in sodium) as a way to account for intravascular volume change, and compared within person change from baseline or from increasing sodium intake from low to high levels.

All analyses were performed with STATA version 14.0 (Stata Corporation, College Station, TX, USA). Statistical significance was defined as $P < 0.05$. Only 2 SUA values were missing from the control diet with medium sodium intake level, which were excluded from the analysis.

Results

Baseline characteristics

The mean age of participants was 51.5 ± 9.7 years, 55% were women, 75% were black, 42% were obese, and 34% had hypertension (**Table 1**). The mean SUA level at baseline was 5.0 ± 1.3 mg/dL. Mean alcohol consumption among study participants was low, just 1.3 g/d.

Change from Baseline

We determined mean uric acid levels, systolic blood pressure, and diastolic blood pressure at baseline and after each of the three feeding sodium periods for both the control and DASH diets (**Table 2**). We further determined change in uric acid levels, systolic blood pressure, and diastolic blood pressure from baseline at the end of each sodium level period by diet (**Figure 1 & Supplement Table S2**). Adopting the low sodium, control diet significantly increased uric acid level (0.4 mg/dL; $P < 0.001$); while the medium or high sodium and DASH diets, lowered uric acid levels, -0.2 mg/dL ($P = 0.07$) and -0.3 mg/dL ($P = 0.01$) respectively. Both diets lowered systolic blood pressure and diastolic blood pressure from baseline at all sodium levels.

High versus Low Sodium Intake

Overall, increasing sodium intake (from low to high) lowered serum uric acid (-0.4 mg/dL; $P < 0.001$), but increased systolic and diastolic blood pressure, 4.3 mm Hg and 2.3 mm Hg, respectively (both P -values < 0.001) (**Table 2**). Similar reductions in uric acid with concurrent increases in systolic and diastolic blood pressure were observed when stratified by DASH and control diets as well. Standardizing uric acid measures with total protein or albumin did not meaningfully change our findings (**Supplement Table S3**).

Comparison with changes in blood pressure

The effects on uric acid of increasing sodium intake (from low to high levels) were compared with effects on systolic and diastolic blood pressure via linear regression (**Figure 2**). Ultimately they were unrelated (systolic blood pressure: $P = 0.15$; diastolic blood pressure: $P = 0.63$). This lack of association was observed regardless of baseline blood pressure, blood pressure response to sodium, or baseline uric acid level (**Table 3**).

Discussion

In this ancillary study of the DASH-sodium trial, we report that sodium intake significantly affects uric acid and blood pressure in opposite directions. Increasing sodium intake decreased uric acid while increasing systolic and diastolic blood pressure. Furthermore, these changes were independent of baseline blood pressure or uric acid values. These findings suggest that uric acid is not a meaningful causal determinant of blood pressure in the context of changes in dietary sodium intake.

While the relationship between sodium intake and hypertension is well-established, its relationship with uric acid is controversial. It has been hypothesized that higher uric acid levels represent an evolutionary advantage in *homo sapiens* species, allowing them to maintain blood pressure when access to sodium was scarce (17). This theory was demonstrated in uricase-deficient rat models showing an increase in blood pressure from hyperuricemia in the context of a low sodium diet (18). Additional rat models have supported this hypothesis, showing that uric acid causes upregulation and activation of epithelial sodium channels in the nephron (19). This was also observed in an ecological study of acculturation of the Solomon Islands conducted in the 1970s. Uric acid levels were higher among island populations consuming a low salt diet (20). Subsequent observational studies, did not support this hypothesis, however, showing that higher sodium intake was associated with higher uric acid levels cross-sectionally (21,22) as well as with an increased risk of hyperuricemia in the future (23). There is a paucity of clinical trials examining this relationship. One trial performed in 27 men showed that reducing sodium from 200 meq/d to 20 meq/d increased uric acid levels by 1 mg/dL ($P < 0.001$) (24). Further, a crossover trial of 147 non-obese, normotensive adults found that 7 days of high versus low sodium intake (300 versus 20 mmol/d), significantly decreased SUA approximately by 1 mg/dL (25).

We can speculate as to the mechanism by which higher sodium intake decreases uric acid. While increased sodium intake has been noted to cause increased intravascular volume (16), which could cause a hemodilutional effect of sodium on uric acid, adjusting for volume status did not negate the results of our study. It is also possible that the relationship between sodium intake and uric acid reduction results from effects of sodium intake on glomerular filtration rate and excretion or absorption of urate. Previous physiology studies have shown that reabsorption of sodium and urate accompany one another (26,27) at different sites in the nephron (28–30). Thus, it is possible that decreased renal reabsorption of sodium from excess sodium intake, contributes to a decrease in urate reabsorption. Finally, this relationship may reflect action of the renin-angiotensin system, as uric acid is inversely related to vascular resistance (31) and renal blood flow (32).

Our study showed that at least in the short-term, uric acid and blood pressure not only changed significantly in opposite directions, but these changes were not related to each other. This was observed in at least one other study of 21 healthy subjects, in which change in mean arterial pressure was not associated with uric acid levels (33). Our findings contribute to the ongoing debate regarding the role of uric acid in the pathogenesis of hypertension. Several animal studies have demonstrated that hyperuricemia precedes hypertension (18) and contributes to histologic changes known to elevate blood pressure

(34). This association has further been demonstrated in a large number of observational studies (3–6,35–38). Moreover, there is emerging evidence that reducing uric acid with pharmacologic agents like allopurinol, reduces blood pressure (8–11). However, this relationship has not been observed in all trials of urate-lowering therapy (39–41). Meanwhile, Mendelian randomization studies of genes known to influence uric acid levels have shown that while a genetic predisposition toward hyperuricemia is associated with high risk of gout, it is not associated with higher risk of hypertension (42). However, even these findings are inconsistent with some gene studies showing an association (43,44) and others showing no association (45–47).

Our study has unclear implications on risk for cardiovascular outcomes. While higher blood pressure has been unequivocally associated with increased risk for cardiovascular disease (48,49), the role of uric acid has remained unclear, with some studies showing strong associations (35,36,50) and other showing no association with cardiovascular disease (51). In this regard, the Systolic Hypertension in the Elderly Program (SHEP) trial was informative, showing that small increases in uric acid from thiazides did not influence the benefit achieved by better blood pressure control; whereas large increases in uric acid did attenuate the risk reduction from blood pressure reduction (52). It is possible that these small, acute changes have little impact on the subsequent development of cardiovascular disease. However, the utility of uric acid as a marker of cardiovascular disease risk should not be discounted on the basis of our study, given the relatively short duration of the intervention.

Our study has limitations. First, this study was not conducted in persons with prior cardiovascular disease, advanced kidney disease, or medication-treated diabetes, all conditions associated with both hyperuricemia and hypertension. Further, we did not measure urinary excretion of uric acid, which could provide additional clarity as to whether higher excretion was responsible for reducing uric acid. Third, while our findings do not suggest a causal relationship between uric acid levels and blood pressure, it should be noted that such a relationship could still exist, but perhaps is overwhelmed or negated by the opposing effects of dietary sodium on uric acid or blood pressure. It is also important to note that participants of the DASH-Sodium trial were less obese and had a lower proportion of participants with hypertension (34%) than some of the initial studies showing relationships between uric acid and blood pressure. Thus, our findings should be interpreted as non-casual in the context of dietary changes in sodium among a population similar to participants in the DASH-Sodium trial. Fourth, our sample size is potentially underpowered to see a significant relationship between uric acid and blood pressure. Nevertheless, it should be noted that the direction of the association is inverse, even though non-significant. Finally, the parallel design of the dietary intervention precluded examination of within person changes in uric acid and blood pressure across diets (DASH versus control).

This study also has important strengths. Each person consumed the three sodium diets in random order. Thus, they served as their own control, allowing us to determine the effects of sodium on uric acid and blood pressure within each participant. Further, weight did not change during the trial and the study population was diverse. Finally, diets were highly regulated with excellent compliance from study participants throughout the trial.

In conclusion, our findings show that higher sodium intake decreases uric acid, but increases blood pressure. These effects are not only in opposing directions, but independent of each other. Ultimately, these findings are not consistent with a causal relationship between SUA and blood pressure, and do not support use of urate-lowering therapies as an intervention to lower blood pressure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

DASH	Dietary Approaches to Stop Hypertension
GEE	generalized estimating equation
CI	confidence interval

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Highlights

- Higher dietary sodium intake increases blood pressure yet decreases serum uric acid
- Changes in blood pressure associated with increased sodium intake are independent of changes in uric acid
- These findings do not support a causal relationship between serum uric acid and blood pressure

Figure 1.

Within person, baseline changes in (A) uric acid, (B) systolic blood pressure, and (C) diastolic blood pressure levels after the low sodium feeding period, the medium sodium feeding period, and the end of the high sodium feeding period for either the control (diamonds, blue) or DASH (circles, green) diets. Vertical lines represent 95% confidence intervals.

Figure 2.

Scatter plots of change in systolic or diastolic blood pressure (y-axes) versus change in uric acid (x-axis). Dashed line represents linear regression. *P*-value corresponds to the slope of the line.

Table 1

Baseline characteristics overall and by diet

	Overall (N = 103)	Control Diet (N = 52)	DASH Diet (N = 51)
Age, yr	51.5 (9.7)	53.0 (9.7)	49.9 (9.7)
Women, %	55.3	48.1	62.7
Black, %	74.8	69.2	80.4
High Blood Pressure [*] , %	34.0	38.5	29.4
Salt Sensitive (absolute) ^{**} , %	32.0	40.4	23.5
Salt Sensitive (percent) ^{***} , %	35.9	46.2	25.5
Blood pressure, mm Hg			
Systolic	135.6 (8.7)	136.6 (8.8)	134.6 (8.7)
Diastolic	85.6 (3.8)	85.6 (3.7)	85.6 (4.0)
Body mass index, kg/m ²	29.5 (4.4)	30.0 (4.8)	29.1 (3.9)
Body mass index 30, %	41.7	46.2	37.3
eGFR _{Cys} , mL/min/1.73 m ²	93.7 (21.0)	93.9 (19.2)	93.4 (22.8)
Fasting glucose, mg/dL	99.8 (18.5)	99.1 (20.3)	100.6 (16.6)
Fasting triglycerides, mg/dL	122.1 (151.7)	116.5 (65.4)	127.8 (206.2)
Total protein, g/dL	7.2 (0.4)	7.2 (0.4)	7.3 (0.4)
Albumin, g/dL	4.1 (0.2)	4.1 (0.2)	4.1 (0.2)
Uric acid, mg/dL	4.96 (1.29)	5.02 (1.30)	4.90 (1.29)
Alcohol intake, g/d	1.3 (2.5)	1.5 (2.6)	1.2 (2.3)

* Defined as systolic blood pressure 140 mm Hg and diastolic blood pressure 90 mm Hg.

** Defined as an increase in MAP of >5 mm Hg when going from the low to high sodium intake levels

*** Defined as an increase in MAP of >5% during high versus low salt intake

Table 2
Mean uric acid, systolic blood pressure, and diastolic blood pressure at baseline and by sodium intake

	Baseline		Low Sodium		Medium Sodium		High Sodium		High versus Low Sodium	
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Difference (95% CI)	P
Control Diet										
Uric acid, mg/dL	5.0 (1.3)		5.4 (1.3)		5.1 (1.3)		4.9 (1.4)		-0.5 (-0.7, -0.3)	<0.001
Systolic blood pressure, mm Hg	136.6 (8.8)		127.4 (10.7)		130.2 (11.5)		132.6 (11.3)		5.2 (3.0, 7.5)	<0.001
Diastolic blood pressure, mm Hg	85.6 (3.7)		80.6 (5.2)		81.3 (5.4)		83.7 (6.2)		3.1 (1.7, 4.5)	<0.001
Dash Diet										
Uric acid, mg/dL	4.9 (1.3)		4.9 (1.1)		4.6 (1.1)		4.6 (1.1)		-0.3 (-0.5, -0.1)	0.003
Systolic blood pressure, mm Hg	134.6 (8.7)		126.0 (9.9)		127.0 (10.5)		129.4 (10.8)		3.3 (1.5, 5.2)	<0.001
Diastolic blood pressure, mm Hg	85.6 (4.0)		80.6 (5.4)		80.6 (6.7)		82.0 (6.8)		1.4 (0.2, 2.6)	0.018
Overall										
Uric acid, mg/dL	5.0 (1.3)		5.2 (1.2)		4.9 (1.2)		4.7 (1.3)		-0.4 (-0.6, -0.3)	<0.001
Systolic blood pressure, mm Hg	135.6 (8.7)		126.7 (10.3)		128.6 (11.1)		131.0 (11.1)		4.3 (2.8, 5.8)	<0.001
Diastolic blood pressure, mm Hg	85.6 (3.8)		80.6 (5.3)		81.0 (6.1)		82.8 (6.6)		2.3 (1.4, 3.2)	<0.001

Association between overall within-person change in uric acid with change in systolic or diastolic blood pressure when increasing sodium intake from low to high

Table 3

	N	Change in SBP			Change in DBP		
		r	β	P	r	β	P
Overall	103	-0.14	-1.4	0.15	-0.05	-0.3	0.63
Baseline hypertension							
No	68	-0.22	-1.9	0.07	-0.04	-0.2	0.72
Yes	35	0.09	1.2	0.61	0.07	0.6	0.67
Elevated SBP							
No	74	-0.22	-1.9	0.06	-0.07	-0.4	0.56
Yes	29	0.18	2.5	0.35	0.19	1.6	0.32
Elevated DBP							
No	87	-0.13	-1.2	0.24	-0.03	-0.2	0.79
Yes	16	-0.21	-3.2	0.43	-0.13	-1.3	0.63
Salt Sensitive (absolute) [*]							
No	70	-0.13	-0.9	0.29	0.09	0.4	0.44
Yes	33	0.07	0.4	0.68	0.05	0.2	0.79
Salt Sensitive (percent) [*]							
No	66	-0.11	-0.7	0.39	0.11	0.5	0.39
Yes	37	0.04	0.2	0.84	0.05	0.2	0.75
Hyperuricemia > 6							
No	79	-0.14	-1.4	0.23	-0.06	-0.40	0.62
Yes	24	-0.16	-1.4	0.46	-0.03	-0.1	0.90

**Based on increase in MAP of >5% during high versus low salt intake

*Based on increase in MAP of >5 mm Hg during high versus low salt intake