

Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP)

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Objective To assess longitudinally the association of serum uric acid and its change due to diuretic treatment with cardiovascular events in hypertensive patients.

Design Cohort study in a randomized trial.

Setting Cohort of hypertensive patients.

Participants A total of 4327 men and women, aged ≥ 60 years, with isolated systolic hypertension, randomized to placebo or chlorthalidone, with the addition of atenolol or reserpine if needed, were observed for 5 years.

Main outcome measures Major cardiovascular events, coronary events, stroke and all-cause mortality.

Results Cardiovascular event rates for quartiles of baseline serum uric acid were: I, 32.7 per 1000 person-years; II, 34.5 per 1000 person-years; III, 38.1 per 1000 person-years; and IV, 41.4 per 1000 person-years (P for trend = 0.02). The adjusted hazard ratio (HR), of cardiovascular events for the highest quartile of serum uric acid versus the lowest quartile was 1.32 (95% CI, 1.03–1.69). The benefit of active treatment was not affected by baseline serum uric acid. After randomization, an increase of serum uric acid < 0.06 mmol/l (median change) in the active treatment group was associated with a HR of 0.58 (0.37–0.92) for coronary events compared with those with a serum uric acid increase ≥ 0.06 mmol/l. This difference was not explained by blood pressure effects. Those with a

serum uric acid increase ≥ 0.06 mmol/l in the active treatment group had a similar risk of coronary events as the placebo group.

Conclusions Serum uric acid independently predicts cardiovascular events in older persons with isolated systolic hypertension. Monitoring serum uric acid change during diuretic treatment may help to identify patients who will most benefit from treatment. *J Hypertens* 2000, 18:1149–1154 © Lippincott Williams & Wilkins.

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Introduction

Elevated serum uric acid has been associated with an increased risk of cardiovascular disease [1–10]. Potential mechanisms by which serum uric acid may directly affect cardiovascular risk include enhanced platelet aggregation [11], and inflammatory activation of the endothelium [12]. In some studies, after multivariate adjustment, the association of serum uric acid with cardiovascular disease was diluted [3,4,7] but, in others,

the association remained strong and significant [1,2,5]. Because serum uric acid is correlated with several risk factors, including renal dysfunction, hypertension, insulin resistance, hyperhomocysteinemia and hyperlipidemia, it is debated whether serum uric acid is an independent cardiovascular risk factor [13–15].

Diuretics increase serum uric acid [16,17] but the clinical relevance of these effects remains uncertain. It has been suggested that the rise in serum uric acid caused by diuretic treatment may partially offset the benefits of blood pressure reduction [1].

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In the Systolic Hypertension in the Elderly Program (SHEP), older persons with isolated systolic hypertension were randomly assigned to placebo or a diuretic-based treatment to assess long-term effects on stroke and cardiovascular events [18]. The purpose of the present study is to assess, in the SHEP, whether serum uric acid is an independent predictor of cardiovascular events in hypertensive patients and whether the change in serum uric acid with randomly assigned diuretic treatment affects the antihypertensive benefit on cardiovascular events.

Methods

Design and participants

For the present analysis, existing data from the SHEP were used, which was a randomized, double-blind, placebo-controlled clinical trial jointly funded by the National Heart, Lung and Blood Institute and the National Institute on Aging [18]. The methods of the SHEP have been described in detail elsewhere [18]. The primary endpoint of the trial was combined fatal and nonfatal stroke during a 5-year period. Secondary endpoints were myocardial infarction, fatal coronary disease, and major cardiovascular morbidity and mortality. The adjudication of the events was performed independently by members of an endpoint adjudication committee who used predetermined standardized adjudication criteria, and were blinded to treatment and blood pressure status. Beginning in 1985, 447 921 persons aged ≥ 60 years were screened from the community in 16 clinical centers and, among those, 4736 participants with isolated systolic hypertension were recruited. Medical history and an electrocardiogram were assessed at baseline. Seated blood pressure was measured by trained technicians according to a standardized protocol. The blood pressure inclusion criteria were systolic blood pressure (SBP) of 160–219 mmHg and diastolic blood pressure (DBP) < 90 mmHg, assessed as the average of four measurements, and two measurements were obtained at each of the two baseline visits. Exclusion criteria were SBP of 220 mmHg or higher, recent myocardial infarction or stroke, or presence of a major illness such as cancer, alcoholic liver disease, renal failure, insulin-treated diabetes and depression. Participants who were receiving an antihypertensive treatment were considered potentially eligible if they had SBP ≥ 130 and ≤ 219 mmHg and DBP < 85 mmHg, and were free of major illnesses. They were asked to obtain permission from their physician and were asked to sign an informed consent for drug withdrawal. They were monitored during 2–8 weeks after withdrawal from current antihypertensive therapy to determine blood pressure eligibility.

For this study, 4327 patients who had a valid measurement of serum uric acid at the day of randomization were included in the analyses. A total of 409 patients

who have been randomized into the SHEP but for whom serum uric acid was not available on the day of randomization were excluded. The 409 patients who were excluded had similar baseline age, gender, race, smoking status, and co-morbidity characteristics to the patients who were included in the analysis. This article reports primarily on the first occurring major cardiovascular event, which included stroke, transient ischemic attack, myocardial infarction, heart failure, coronary artery bypass surgery, angioplasty, aneurysm, endarterectomy, sudden death or rapid cardiac death (within 1–24 h of the onset of severe cardiac symptoms unrelated to other known cause). In addition, fatal and nonfatal coronary heart disease (which included myocardial infarction, coronary procedures and cardiac death), fatal and nonfatal stroke, and all-cause mortality were analyzed separately.

Intervention

The participants were randomized to active treatment or placebo. A stepped care treatment approach was used. The treatment goal was SBP < 160 mmHg or at least a 20 mmHg reduction in SBP. In the active treatment group, the first step was 12.5 mg/day chlorthalidone. The dosage was doubled if the goal BP was not achieved. If the goal was not reached at the first step, 25 mg/day atenolol was added (second step). If atenolol was not tolerated, 0.05 mg/day reserpine could be substituted. The dosage of the second-step drugs could be doubled if the goal BP was not reached. No active antihypertensive agent was given to the participants randomized to placebo. Open label potassium supplement was given to the participants in both treatment arms who had serum potassium concentrations below 3.5 mmol/l.

Follow-up

All participants were followed monthly until the BP goal was reached, and quarterly thereafter until the end of follow-up. Blood samples were drawn routinely at baseline and at each annual clinic follow-up visit. The blood samples were centrifuged and sent by overnight mail to a central laboratory for analysis (MetPath, Teterboro, New Jersey, USA).

Data analysis

Results were analyzed with SPSS 7.5 for Windows software [19]. The participants were stratified according to gender-specific serum uric acid quartiles (Table 1). The baseline characteristics of the participants according to the four serum uric acid quartiles were compared by means of the Mantel–Haenszel χ^2 test for trend, and the Polynomial Linear Contrasts analysis of variance test for trend [19] as appropriate. In addition, the Bonferroni post-hoc test was used to test differences between the continuous variables according to the four serum uric acid quartiles.

Table 1 Baseline characteristics of the participants according to baseline serum uric acid quartiles

Risk factors	Baseline serum uric acid quartiles (mmol/l) ^a				P for trend
	I	II	III	IV	
Active treatment (%)	48.9	49.2	51.0	51.9	0.11
Demographic					
Age (years)	72.1 ± 6.7	72.0 ± 6.7	71.3 ± 6.6*	71.1 ± 6.6*, **	< 0.001
Male gender (%)	41.9	46.7	39.7	43.8	0.84
Ethnic origin					
White (%)	83.4	82.7	75.7	73.7	< 0.001
Black (%)	10.0	11.1	16.1	18.9	< 0.001
Asian (%)	4.2	3.7	4.9	4.9	0.26
Lifestyle indicators					
Alcohol intake nearly every day (%)	11.8	12.9	14.4	14.7	< 0.001
Smoking, currently (%)	12.2	13.0	11.9	13.5	0.55
Health status indicators					
Body mass index (kg/m ²)	26.0 ± 4.6	27.0 ± 4.5*	28.1 ± 5.0*, **	29.1 ± 5.2*, **, ***	< 0.001
Systolic pressure (mmHg)	171 ± 12	171 ± 11	171 ± 11	172 ± 12	0.60
Diastolic pressure, mm Hg	77 ± 11	77 ± 11	77 ± 10	77 ± 12	0.36
Antihypertensive medication at initial contact (%)	33.4	34.2	35.2	32.1	0.66
Serum creatinine (μmol/l)	85.7 ± 17.7	91.1 ± 19.4*	92.8 ± 19.4*	99.9 ± 23.0*, **, ***	< 0.001
Serum glucose (mmol/l)	6.2 ± 2.3	5.9 ± 1.9	5.9 ± 1.5*	6.0 ± 1.6	0.10
Serum cholesterol (mmol/l)	6.00 ± 1.09	6.08 ± 1.11	6.21 ± 1.16*	6.18 ± 1.24*	< 0.001
Serum triglycerides (mmol/l)	1.52 ± 0.84	1.73 ± 1.06*	1.79 ± 1.01*	2.08 ± 1.27*, **, ***	< 0.001
Serum HDL-cholesterol (mmol/l)	1.45 ± 0.39	1.37 ± 0.36*	1.40 ± 0.39*	1.32 ± 0.36*, ***	< 0.001
Comorbidity					
History of heart attack (%)	2.4	3.3	4.6	5.0	0.001
History of stroke (%)	1.8	2.5	2.1	2.2	0.42
History of diabetes (%)	14.4	9.9	8.8	7.3	< 0.001

^a Quartile I, ♂ = 0.08–0.29, ♀ = 0.08–0.24, *n* = 1160; quartile II, ♂ = 0.30–0.34, ♀ = 0.25–0.28, *n* = 1058; quartile III, ♂ = 0.35–0.39, ♀ = 0.29–0.33, *n* = 1092; quartile IV, ♂ = 0.40–0.67, ♀ = 0.34–0.61, *n* = 1017. HDL, High-density lipoprotein. * Significantly different from quartile I (*P* < 0.05); ** significantly different from quartile II (*P* < 0.05); *** significantly different from quartile III (*P* < 0.05) [Bonferroni post-hoc test (adjustment for multiple comparisons)].

Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the effect of baseline serum uric acid and for the effect of serum uric acid increase after 1-year active treatment (≥ 0.06 mmol/l) on the outcomes of interest [20]. To assess independent associations of serum uric acid with outcomes, covariates were considered confounders and were entered into the summary model adjusted for treatment, when they changed the β value of uric acid by at least 10% in a bivariate Cox regression model. Only events occurring after the first year were considered in the analyses of the effect of a 1-year increase in serum uric acid. The 1-year change was chosen because serum uric acid did not increase significantly in the active treatment group thereafter. The assumption of proportionality of hazards was assessed with log minus log plots and by testing the interaction of exposure with time [19].

Results

The average baseline serum uric acid was 0.31 mmol/l (median, 0.30 mmol/l; range, 0.08–0.67 mmol/l). After the first year of treatment, serum uric acid increased significantly more in the active treatment group (mean and median increase, 0.06 mmol/l) than in the placebo group (mean increase, 0.010 mmol/l; *P* < 0.001), and

remained significantly higher in the active treatment group during all follow-up years (data not shown).

At baseline, higher serum uric acid levels were associated with black race, drinking alcohol, history of heart attack, body mass index, serum creatinine, cholesterol and triglycerides, and were inversely associated with age (for both males and females), history of diabetes and high-density lipoprotein cholesterol (Table 1). Gender, smoking, blood pressure, use of antihypertensive medication at initial contact, randomized treatment, serum glucose and history of stroke were not significantly associated with serum uric acid. In each serum uric acid quartile, the participants randomized to placebo and active treatment had similar characteristics (not shown).

Any cardiovascular event, coronary heart disease, stroke and death were experienced by 638, 290, 243 and 403 participants, respectively. Age-, gender- and race-adjusted hazard ratios (HRs) of cardiovascular events and coronary heart disease events increased significantly with increasing baseline serum uric acid quartile (*P* for trend = 0.006 and 0.031) (model A; Table 2). Stroke and mortality HRs did not change significantly according to serum uric acid level. In all baseline serum uric

acid quartiles, the participants receiving active treatment were less likely to experience cardiovascular events than those receiving placebo. This effect was significant in all but the lowest quartile (not shown).

After adjustment for age, gender, race, body mass index, history of heart attack, stroke and diabetes, serum creatinine, glucose, cholesterol, triglycerides and high-density lipoprotein cholesterol, the HRs of cardiovascular events increased with higher serum uric acid quartiles (P for trend = 0.009) (model B; Table 2). The same model with serum uric acid as a continuous variable showed a HR of 1.07 (95% CI = 1.01–1.15) for a 0.06 mmol/l serum uric acid increase. The risk of coronary heart disease increased significantly with higher serum uric acid quartiles (P for trend = 0.048), but did not reach significance when performing the same analysis with serum uric acid as a continuous variable (HR = 1.09, 95% CI = 0.99–1.21). Serum uric acid was not significantly associated with stroke and all-cause mortality.

After 1 year of treatment, 49% of the participants in the active treatment group experienced an increase in serum uric acid ≥ 0.06 mmol/l, compared with 16% in the placebo group. In the active treatment group, after adjustment for baseline serum uric acid and all confounders used in baseline adjusted model B, the participants with an increase of serum uric acid

≥ 0.06 mmol/l and those with an increase < 0.06 mmol/l had a similar relative risk of any cardiovascular event, stroke, and all-cause mortality (Table 3). For the outcomes of any cardiovascular event and stroke, active treatment was always better than placebo. But, for coronary heart disease, the benefit of active treatment versus placebo was offset in participants who experienced an increase in serum uric acid ≥ 0.06 mmol/l. Those with an increase in serum uric acid ≥ 0.06 mmol/l had a similar coronary heart disease risk as the placebo group (HR = 0.96, 95% CI = 0.67–1.39), while those who had a lower increase had a significantly lower relative risk compared with the placebo group (HR = 0.56, 95% CI = 0.37–0.85). Direct comparison within the active treatment group revealed that participants who did not experience an increase in serum uric acid ≥ 0.06 mmol/l had a significantly lower risk of coronary heart disease (HR = 0.58, 95% CI = 0.37–0.92) compared with those who did. Such a difference in risk of coronary heart disease was not explained by effects on blood pressure. After 1 year, the mean systolic and diastolic blood pressures in the active treatment group with an increase ≥ 0.06 mmol/l were 141 ± 15 and 69 ± 10 mmHg, versus 144 ± 17 and 70 ± 10 mmHg in the active treatment group with an increase < 0.06 mmol/l ($P < 0.001$ and $P = 0.05$). The increase of serum uric acid in the placebo group was not significantly associated with cardiovascular events (Table 3).

Table 2 Relations of baseline serum uric acid quartile to any cardiovascular event, coronary heart disease, stroke and all-cause mortality

Serum uric acid quartile	Events (n)	Rate per 1000 person-years	Adjusted model A [HR (95% CI)]	Adjusted model B [HR (95% CI)]
Any cardiovascular event				
I	155	32.7	1	1
II	147	34.5	1.05 (0.84–1.31)	1.04 (0.82–1.31)
III	168	38.1	1.22 (0.98–1.52)	1.28 (1.01–1.61)
IV	168	41.1	1.32 (1.06–1.64)	1.32 (1.03–1.69)
<i>P</i> for trend		0.02	0.006	0.009
Coronary heart disease				
I	64	13.0	1	1
II	72	16.3	1.23 (0.88–1.73)	1.28 (0.91–1.82)
III	79	17.1	1.40 (1.00–1.94)	1.44 (1.01–2.05)
IV	75	17.5	1.41 (1.01–1.97)	1.43 (0.98–2.08)
<i>P</i> for trend		0.07	0.031	0.048
Stroke				
I	71	14.5	1	1
II	54	12.2	0.84 (0.59–1.20)	0.80 (0.55–1.16)
III	62	13.5	0.96 (0.68–1.36)	0.99 (0.69–1.42)
IV	56	13.0	0.92 (0.65–1.31)	0.85 (0.57–1.28)
<i>P</i> for trend		0.67	0.81	0.91
All-cause mortality				
I	105	20.9	1	1
II	114	25.1	1.21 (0.93–1.58)	1.26 (0.96–1.66)
III	92	19.5	1.00 (0.75–1.32)	1.01 (0.75–1.37)
IV	92	20.9	1.05 (0.79–1.40)	1.05 (0.77–1.44)
<i>P</i> for trend		0.61	0.96	0.67

Model A, Adjusted for age, gender and race; model B, adjusted for age, gender, race, active treatment, body mass index, history of heart attack, stroke and diabetes, serum creatinine, glucose, total cholesterol, high-density lipoprotein cholesterol and triglycerides. HR, Hazard ratio; CI, confidence interval.

Table 3 Hazard ratio (HR) of cardiovascular events, coronary heart disease, stroke and all-cause mortality according to 1 year change in serum uric acid (SUA) in the active treatment group^a

Treatment group	Any cardiovascular event [HR (95% CI)]	Coronary heart disease [HR (95% CI)]	Stroke [HR (95% CI)]	All-cause mortality [HR (95% CI)]
Placebo, SUA increase < 0.06 mmol/l after 1 year (<i>n</i> = 1543)	1	1	1	1
Placebo, SUA increase ≥ 0.06 mmol/l after 1 year (<i>n</i> = 296)	1.02 (0.71–1.46)	1.08 (0.63–1.83)	0.92 (0.52–1.61)	1.09 (0.69–1.71)
Active treatment, SUA increase < 0.06 mmol/l after 1 year (<i>n</i> = 985)	0.60 (0.46–0.79)	0.56 (0.37–0.85)*	0.56 (0.37–0.84)	1.06 (0.79–1.42)
Active treatment, SUA increase ≥ 0.06 mmol/l after 1 year (<i>n</i> = 942)	0.70 (0.54–0.91)	0.96 (0.67–1.39)	0.58 (0.38–0.88)	0.98 (0.71–1.34)

^a Adjusted for age, gender, race, baseline serum uric acid, body mass index, history of heart attack, stroke and diabetes, serum creatinine, glucose, total cholesterol, high-density lipoprotein cholesterol and triglycerides. HR, Hazard ratio; CI, confidence interval. * HR = 0.58 (0.37–0.92) versus active treatment and SUA increase ≥ 0.06 mmol/l after 1 year.

Discussion

In the SHEP, higher baseline serum uric acid levels significantly predicted ‘any cardiovascular event’ and coronary heart disease, but not stroke and all-cause mortality. This association was not explained by differences in other cardiovascular risk factors. The benefit of diuretic treatment on cardiovascular events was similar among participants with low and high baseline serum uric acid, but the benefit of active treatment on coronary events was offset in participants who experienced an increase in serum uric acid ≥ 0.06 mmol/l after randomization.

In several studies, serum uric acid independently predicted cardiovascular events [1,8,9], coronary heart disease [9,10], stroke [5] or all-cause mortality [2,9,10], while in others the correlation of serum uric acid with other cardiovascular risk factors largely explained some of the associations [3,4,7,21]. Differences in comorbidity, age distribution and lack of power may account for inconsistencies among the studies.

Our findings in the SHEP confirm and extend the results of Alderman *et al.* [1]. In a cohort of 7978 treated hypertensive patients, cardiovascular disease incidence was significantly associated with serum uric acid (HR = 1.22, 95% CI = 1.11–1.35), controlling for other known cardiovascular risk factors. This research group also found that the cardioprotective effect of diuretics increased from 31 to 38% after adjustment for serum uric acid [22], suggesting that the diuretic-related increase in serum uric acid may partially offset the treatment benefits.

To our knowledge, this study in the SHEP is the first study that looked at an increase in serum uric acid determined by randomized diuretic as a risk factor for cardiovascular events. It is reasonable that participants who took higher doses of chlorthalidone had (by definition) ‘more difficult to treat hypertension’, and would therefore have higher future cardiovascular risk (con-

founding by indication) [23]. However, the increased risk of coronary events among those in the active treatment group who experienced a serum uric acid increase ≥ 0.06 mmol/l compared with those with an increase < 0.06 mmol/l was not explained by differences in blood pressure. The 1-year systolic and diastolic blood pressures were slightly but significantly lower in the active treatment group with an increase ≥ 0.06 mmol/l than in the group with an increase < 0.06 mmol/l. Furthermore, we performed our analyses adjusted for reported history of myocardial infarction, stroke and diabetes, and levels of serum creatinine, lipids and glucose after 1 year of treatment, and were thus able to investigate the independent effect of serum uric acid changes on cardiovascular events.

The fact that we did not find different blood pressures in those who did and did not experience a serum uric acid increase ≥ 0.06 mmol/l may explain why increased serum uric acid did not predict the risk of stroke in the SHEP, and suggests that mechanisms other than effects on blood pressure control may account for the increased risk of cardiovascular events in those who have increased levels of serum uric acid. Recent evidence that inflammatory cytokines play an important role in atherosclerosis [24], and that urate promotes the production of cytokines supports the view that uric acid may causally affect the atherosclerotic process [12]. A prothrombotic effect through platelet activation is another possible mechanism by which uric acid may directly promote cardiovascular events. Uric acid has also antioxidant properties [25,26]. Beevers and Lip recently speculated that, because the coronary prevention by thiazide diuretics in the SHEP was greater than expected, a small rise in serum uric acid might even have been beneficial [27]. However, this hypothesis is not supported by the present analyses.

Because they are secondary in nature, the present data ought to be interpreted with caution. As the SHEP

excluded participants with major morbidity, the results of this study cannot be generalized to patients with severe renal failure, congestive heart failure, unstable angina or with recent stroke or myocardial infarction. Furthermore, the treatment goal of SBP < 160 mmHg is not up to date anymore, as the sixth report of the Joint National Committee on Hypertension recommends treatment of SBP above 140 mmHg [28]. However, it is unlikely that this may have biased the association of serum uric acid and cardiovascular disease. In addition, reserpine, used in the SHEP as a substitution drug if atenolol was not tolerated, is currently less frequently used than other agents for the treatment of hypertension.

If confirmed by other workers, the present findings may have important implications for the treatment of hypertension. Serum uric acid independently predicts cardiovascular events in older persons with isolated systolic hypertension, and further studies are needed to assess whether pharmacological reduction of serum uric acid decreases their cardiovascular risk. Persons with high baseline serum uric acid levels experienced the same benefit from diuretic-based treatment as those with low baseline serum uric acid levels. Monitoring serum uric acid change during diuretic treatment may help to identify patients who will most benefit from treatment.

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