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BRIEF REPORT

Effects of serum uric acid on blood-pressure lowering treatment

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ABSTRACT

If hyperuricemia is an independent risk factor in blood-pressure control, urate-lowering therapy should be used to reduce cardiovascular risk. It may also act as a prognostic marker of other abnormalities. This review presents current evidence on the relationship between hyperuricemia and hypertension.

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KEYWORDS
Serum uric acid; gout; blood hypertension; urate lowering therapy

Introduction

Serum uric acid (SUA) level has been shown to be associated with an increased risk of cardiovascular morbidity and mortality[1], and it was found to be correlated with hypertension in children and adults[2,3]. The role of uric acid in blood-pressure (BP) control has been investigated to understand whether hyperuricemia is an independent risk factor, so that a urate lowering therapy should be used to reduce cardiovascular risk, or whether it represents a marker of other prognostic abnormalities. It has also been observed that urate lowering drugs may have an antihypertensive effect[1]. This article will briefly review the evidence of the link between hypertension and SUA and will discuss the impact of uric acid on BP lowering therapy.

Hyperuricemia in hypertensive patients

Uric acid has been shown to play a role in the early stages of vascular damage and contribute to the development of hypertension[4]. Elevated SUA levels are frequently seen in adults with hypertension, and this phenomenon was initially thought to reflect renal damage accompanying established hypertension. Nevertheless, SUA could have a pathophysiologic role and represent a predictor of hypertension.

SUA level in children was found to be correlated with 24 hour ambulatory BP[2], and with increased risk for development of hypertension in adults[5–7] (Figure 1).

Hyperuricemia in hypertensive patients seems to be closely related to undesired BP patterns and markers of high cardiovascular risk[8]. In 81 patients with metabolic syndrome and new diagnosis of hypertension, hyperuricemia was a risk factor for non-dipping pattern ($p < .0001$, odds ratio [OR] = 8.1, 95% confidence interval [CI] = 1.9–33.7). Patients in the highest quadrant for uric acid levels had higher morning BP surge incidence ($p = .003$), and higher night diastolic BP compared with lowest quadrant patients ($p = .013$). Uric acid levels were also positively correlated with night ambulatory BP ($r = .268$, $p = .05$), and night diastolic BP ($r = .3$, $p = .05$)[8].

SUA level was associated with increasing values of morning BP surge and development of new cardiovascular events[9]. In a total of 921 patients who underwent 24 hour ambulatory BP monitoring and were followed for a median of 40 months there was a significant relationship between increasing quartiles of serum uric acid level and increasing values of morning BP surge ($p < .0001$). Patients in the highest quartile stratified by elevated pressure surge and serum uric acid level had a 3.55 odds of major cardiovascular event compared with patients in the lowest quartile[9].

Prognostic effect of uric acid

Several studies have addressed the question of whether elevated SUA is a bystander of hypertension, linked to other metabolic cardiovascular risk factors, or a predictive and independent risk factor.

In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, 3200 subjects were randomly recruited from a general population of northern Italy, and the 2045 who responded underwent a thorough assessment of cardiovascular risk profile including home, office and 24 hour ambulatory BP, SUA, metabolic, renal, and anthropometric variables, and left-ventricular mass index. Measurements were repeated after 10 years, and cardiovascular and all-cause mortality were assessed over a 16 year follow-up[10].

Mean baseline value of SUA was 4.9 ± 1.3 (SD) mg/dl, with a near-normal distribution. It was positively and significantly related not only to metabolic variables and serum creatinine

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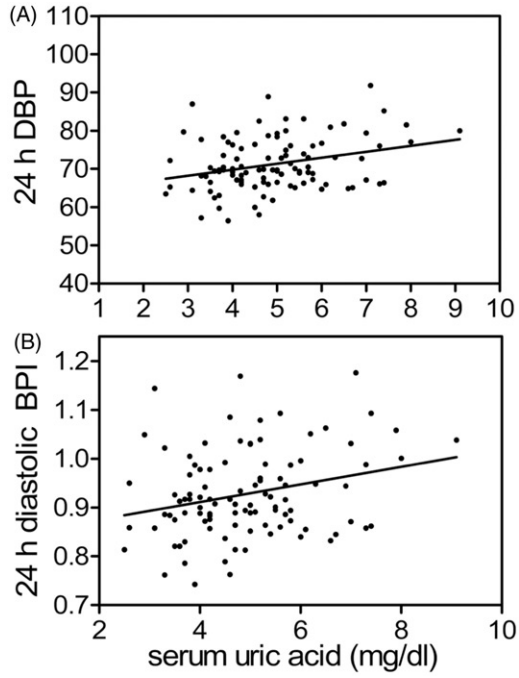

Figure 1. Serum uric acid (SUA) plotted against mean 24 hour diastolic BP (A) and 24 h DBP index (B). Pearson correlation coefficient for mean 24 h DBP = 0.29, $p = .0033$, and for 24 hour DBPI = 0.26, $p = .0094$. Reprinted by permission from Macmillan Publishers Ltd: Pediatr Res 64:556-61 copyright 2008[2].

level but also to office, home and ambulatory BP values (24 hour daytime and night-time), as well as to left ventricular mass index. The relationships remained significant after adjustment for age and sex. Higher SUA was found in patients who developed new onset hypertension by the second measurement. A 1 mg/dl increase in the baseline SUA was associated with a significant increase in the risk of developing new-onset office, home and ambulatory hypertension. The association persisted also after partial adjustment (age and sex) and, with the exception of new-onset office hypertension, after full adjustment, for potential confounders (Figure 2). An increase in SUA of 1 mg/dl also independently predicted cardiovascular and all-cause mortality, the fully adjusted increase in risk being 22% ($p = .03$) and 12% ($p = .04$), respectively (Figure 3)[10].

The study confirmed that an increase in SUA reflected the presence of metabolic risk factors, and showed that SUA was linked to the presence of cardiac damage as well as of an elevation of both in and out-of-office BP. The authors concluded that SUA may exert an adverse prognostic effect not only via other cardiovascular risk factors, but also directly[10].

The correlation of SUA with incident hypertension had also been previously observed in a community-based sample (3329 Framingham Study participants (mean age 48.7 years; 55.6% women) free of: hypertension; myocardial infarction; heart failure; renal failure; or gout)[11]. SUA level was an independent predictor of incident hypertension and BP progression at short-term follow-up. Age- and sex-adjusted rates of hypertension incidence increased progressively from 9.8% for the lowest quartile to 15.6% for the top quartile of SUA; BP progression rates increased from 32.8% (lowest quartile) to 39.6% (top quartile)[11].

SUA was also found to predict new-onset hypertension in a Japanese general population[12], and a recent meta-analysis had found similar data[13].

Serum uric acid and blood-pressure variability

BP variability is associated with cardiovascular events and mortality in hypertensive patients. In recent decades, it has been shown that increased BP variability (BPV) obtained by 24 hour ambulatory BP monitoring was associated with end-organ damage, cardiovascular events, and mortality[14]. Although the underlying mechanism is still undetermined, it has been proposed that BPV is associated with pro-inflammatory markers (e.g. high-sensitivity C-reactive protein, soluble E-selectin, interleukin 6), independent of BP. Inflammation may be a mediator for the link between BPV and hypertension target organ damage. SUA is also implicated with pro-oxidant effects, endothelial dysfunction, and renal microvascular changes driven by direct proliferative, pro-atherogenic, and pro-inflammatory effects on smooth muscle and vascular endothelial cells[14].

Increased SUA was independently associated with short-term BPV in untreated essential hypertension patients[14]. The association of SUA with BPV was investigated in 300 untreated essential hypertension patients (mean age 57.3 ± 13.6 years). BPV was quantified as the standard deviation (SD) of the 24 hour, daytime, and night-time mean values obtained by using ambulatory BP monitoring. SUA values were found to be positively correlated with 24 hour systolic BPV and night-time systolic and diastolic BPV (Pearson coefficients of .246, .280, and .353, respectively; $p < .001$ for all). It was also found that log SUA had an independent association with 24 hour systolic BPV and night-time systolic and diastolic BPV[14].

Impact of serum uric acid on blood-pressure lowering therapy

Once it is assumed that SUA is an independent risk factor for hypertension, the question arises whether SUA has a role in blood-pressure control. This issue is relevant to understanding whether elevated SUA levels may impair the efficacy of blood-pressure lowering therapy, and/or urate lowering therapy should be associated with antihypertensive drugs.

The analysis of data from the PAMELA study showed that several metabolic factors, such as blood glucose and total cholesterol, might interact with blood-pressure control, suggesting that additional metabolic factors should be evaluated[15].

The possible role of SUA was studied in a cohort of 2191 subjects enrolled in a survey (Brisighella Heart Study), among whom 146 new cases of arterial hypertension and 394 treated but uncontrolled hypertensive patients with different levels of SUA were identified[16]. Their hemodynamic characteristics were compared with those of age- and sex-matched normotensive ($N = 324$) and controlled hypertensive ($N = 470$) subjects. SUA levels were significantly higher in untreated hypertensive and uncontrolled hypertensive patients when

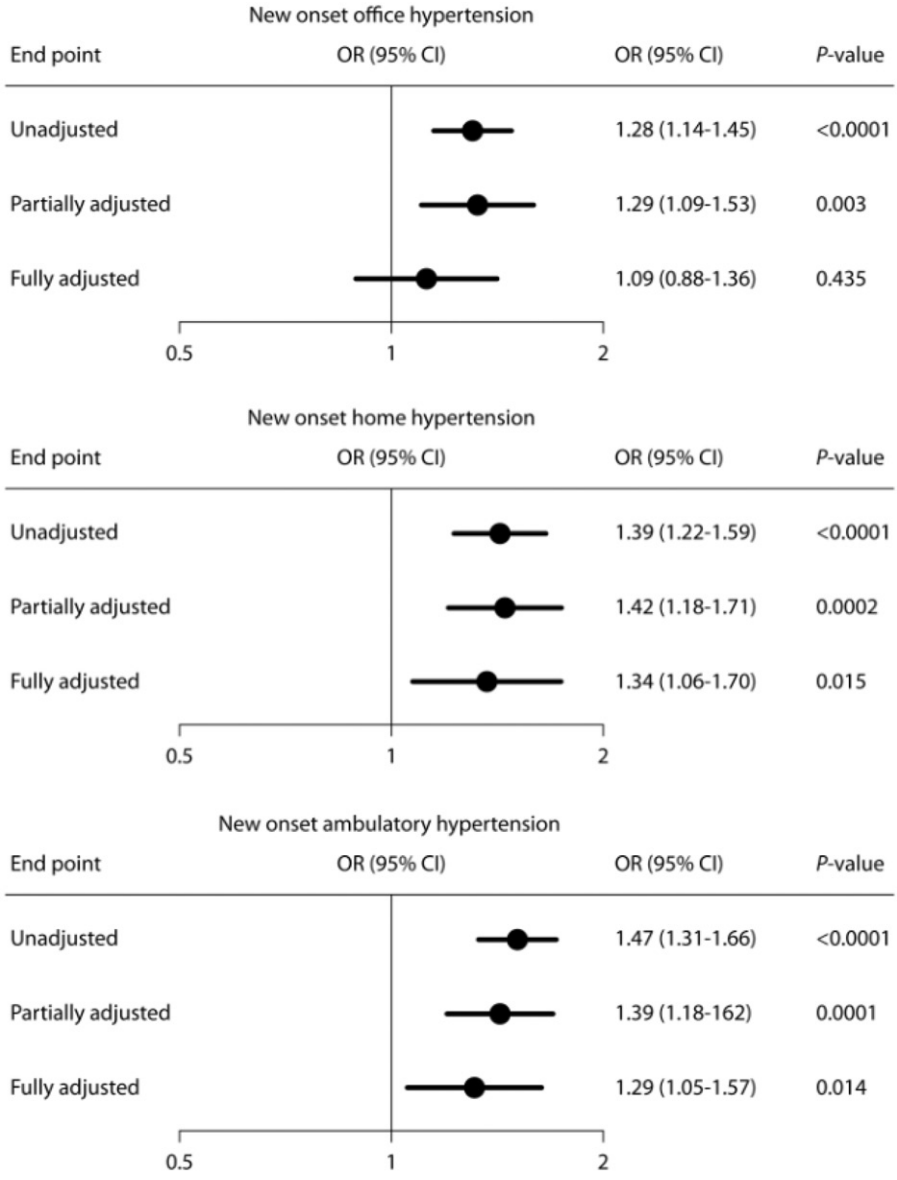

Figure 2. Odds ratio (OR) and 95% confidence interval (95% CI) of developing office, home and ambulatory hypertension, associated with a 1 mg/dl increase of serum uric acid. Data shown unadjusted, partially adjusted (age and sex), and fully adjusted (age, sex, the ratio between serum total and HDL-cholesterol, serum triglycerides, smoking, serum glucose, BMI, serum creatinine, LVMI, baseline office, home or ambulatory SBP) confounders. Abbreviations. HDL, high-density lipoprotein; LVMI, left ventricular mass index. Reproduced with permission[10].

compared to normotensive subjects and controlled hypertensive patients. Pulse wave velocity (PWV) was significantly higher ($p < .001$) in undiagnosed and uncontrolled hypertensive patients, while controlled hypertensive patients had PWV values comparable to normotensive controls. Worse BP control was associated with SUA levels (OR 1277, 95% CI 1134–1600 mg/dl), and PWV (OR 1201, 95% CI 1089–1423 m/s), but not with age, body mass index, nor estimated glomerular filtration rate. These findings showed that high SUA level could be associated with inadequate BP control in subjects treated with antihypertensive drugs, and subjects with both uncontrolled BP and relatively high SUA levels also had increased arterial stiffness. Arterial stiffness could be a factor impairing BP control during treatment[16].

Cho *et al.* evaluated the effect of hyperuricemia on BP control in hypertensive patients, and investigated whether hyperuricemia predicted uncontrolled hypertension through a large-scale prospective cohort study with hypertensive patients treated with fimasartan (the Kanarb–Metabolic Syndrome study); 10,601 hypertensive patients were recruited, 7725 completed the follow-up, and 6506 were included in the analysis[17]. Hyperuricemia increased the risk of uncontrolled hypertension after 3 months of fimasartan medication (OR 1.247; 95% CI 1.063–1.462). Data proved that hyperuricemia could also increase the risk of uncontrolled BP in hypertensive patients without metabolic syndrome[17].

Systolic blood pressure (SBP) is the most important marker of cardiovascular complications in the elderly. Several studies have suggested that the treatment of isolated systolic hypertension in the elderly was associated with a reduction in overall cardiovascular mortality of 22%, in coronary heart disease mortality of 26%, and in stroke mortality of 33%. However, control of systolic pressure is attained by only 34% of treated patients[18]. SUA was found to be an independent

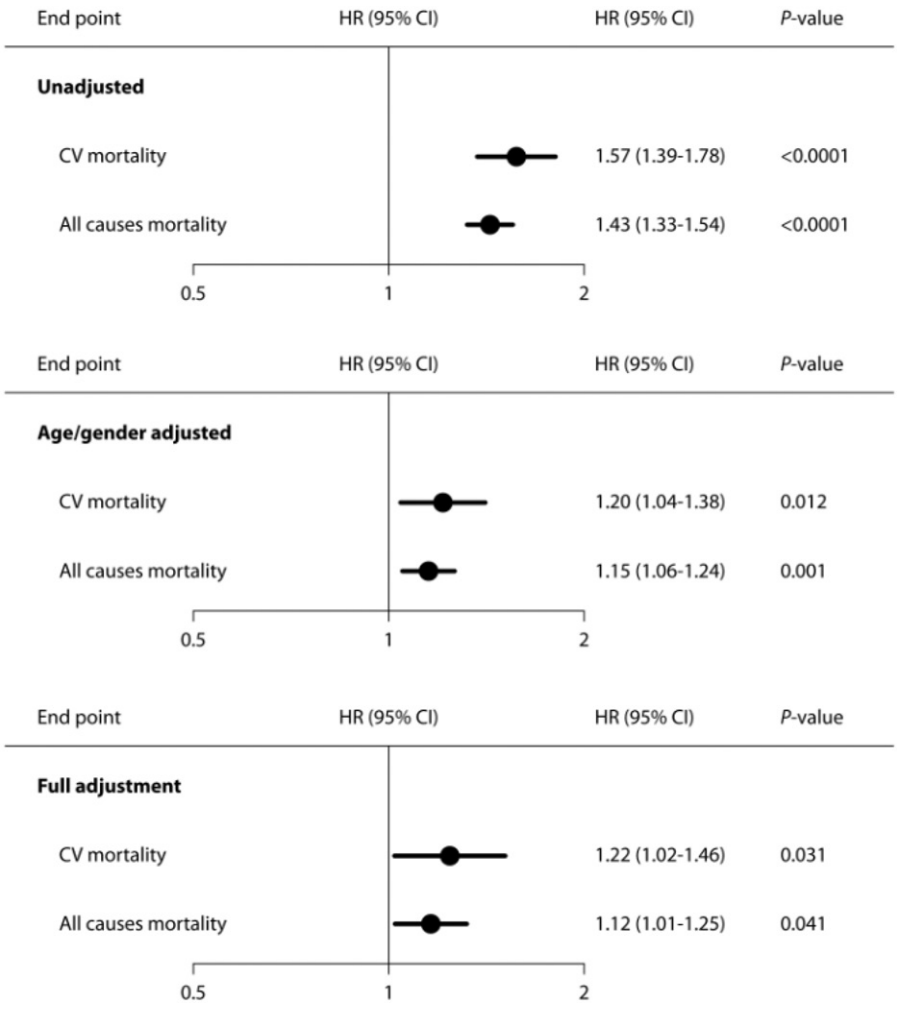

Figure 3. Hazard ratio (HR) and 95% confidence interval (95% CI) of CV and all-cause mortality associated with a 1 mg/dl increase of serum uric acid. Data shown unadjusted, partially adjusted (age and sex), and fully adjusted (age, sex, smoking, BMI, baseline ambulatory SBP, left-ventricular mass index, serum glucose, the ratio between total and HDL cholesterol, triglycerides, serum creatinine, previous CV event and diuretic therapy). Abbreviations. CV, cardiovascular; HDL, high-density lipoprotein. Reproduced with permission[10].

predictor of poor response to monotherapy of systolic hypertension in a longitudinal study, together with initial SBP level, time since diagnosis, and diabetes mellitus[18,19].

Mechanisms linking serum uric acid with blood-pressure control

Observational studies suggest that SUA has a role in the pathophysiology of hypertension, and some underlying mechanisms are being found, although this relationship is not fully understood. Yang *et al.* found that genetic variations in xanthine dehydrogenase partly contribute to hypertension and its complications, including atherosclerosis and chronic kidney disease[20].

In a prospective, population-based cohort in the Netherland, it was found that a higher sodium intake over time was associated with greater increases in SUA[21]. In addition, a higher sodium intake was associated with an increased risk of developing hypertension, principally in those individuals who had higher levels of SUA. These results suggest that a high-sodium diet over the long term may lead to endothelial dysfunction and vascular damage[21].

Finally, SUA independently predicted blunted renal vascular responsiveness to angiotensin (Ang) II in humans, consistent with the activation of the intrarenal renin–angiotensin system (RAS) that is found in experimental hyperuricemia[22].

Conclusions

Relevant evidence has gathered proving the relationship of SUA with hypertension, and several underlying mechanisms have been demonstrated. This link may be clinically important in identifying hyperuricemia as an independent risk factor predicting the development of hypertension and increased cardiovascular risk. In addition, data suggests that SUA may impact on the response to antihypertensive treatment, so that further studies are required to elucidate the possible role of a urate lowering therapy in the treatment of the hypertensive patient.

Transparency

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Declaration of financial/other relationships

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