Childhood Uric Acid Predicts Adult Blood Pressure

The Bogalusa Heart Study

Arnold B. Alper Jr, Wei Chen, Lillian Yau, Sathanur R. Srinivasan, Gerald S. Berenson, L. Lee Hamm

Abstract—Uric acid has been proposed as an important risk factor in the development of primary hypertension in humans. However, limited information is available linking childhood uric acid levels and blood pressure levels in adulthood. This study examined 334 whites and 243 blacks enrolled in the Bogalusa Heart Study as children aged 5 to 17 years and as adults aged 18 to 35 years. The average follow-up period was 12 years. Childhood uric acid was significantly correlated with childhood and adult blood pressure, both systolic and diastolic. In a multivariate regression analysis, adjusting for age, sex, race, childhood body mass index, childhood uric acid levels, and change in levels of uric acid were significant predictors of adult diastolic blood pressure, whereas change in uric acid was a significant predictor of adult systolic blood pressures. In conclusion, elevated childhood serum uric acid levels are associated with increased blood pressure beginning in childhood and higher blood pressure levels that persist into adulthood, in males and females, whites and blacks, suggesting that early elevations in serum uric acid levels may play a key role in the development of human hypertension. (Hypertension. 2005;45:34-38.)

Key Words: uric acid • blood pressure • children

Essential hypertension affects up to 25% of adults and significantly increases the risk of myocardial infarction, stroke, congestive heart failure, and renal failure.1,2 There are significant race and gender differences in the incidence of hypertension, and the disease process has been clearly shown to begin in childhood.3

During the past several years, several clinical and laboratory studies have suggested that uric acid might be an important factor in the development of primary hypertension in humans. Hyperuricemia has been demonstrated to predict and be an independent risk factor for hypertension in adults.4,5 Also, 25% to 40% of adult patients with untreated hypertension have hyperuricemia (>386.6 μmol/L [6.5 mg/dL]).6,7 Earlier studies in children and young adults showed uric acid levels were higher in white subjects and were associated with higher diastolic blood pressure (DBP) and lean body mass.8,9 Recently, Feig and Johnson10 demonstrated a significant correlation between elevated uric acid levels (>327 μmol/L [5.5 mg/dL]) and blood pressure (BP) in children and adolescents. However, to date, there is a paucity of information on the relationship between childhood uric acid levels and adult BP. Using the longitudinal data from the Bogalusa Heart Study, a community-based study of the cardiovascular risk factors beginning in childhood, we examined the predictability of BP in adults from childhood uric acid levels,11 understanding the early stages of this relationship will help in the early identification and prevention of hypertension.

Materials and Methods

Study Population

The Bogalusa Heart Study consists of multiple cross-sectional surveys of all children, aged 5 to 17 years, and multiple surveys of young adults, aged ≥18 years, in a biracial (black–white) population, 65% white and 35% black. Of the young adults aged 18 to 35 years who were examined in the 1988 to 1991 and 1995 to 1996 surveys, 577 also participated in the 1973 to 1974 and 1976 to 1977 surveys as children and had serum uric acid levels measured as children and adults. The cohort of 577 subjects included 243 blacks and 333 females, with an average follow-up period of 11.4 years between surveys, with a range of 7.4 to 15.0 years. A total of 23 subjects who were hypertensive as adults or on antihypertensive medication were included in the analysis. The institutional review board approved consent forms used for these surveys, and informed consent was obtained from study participants or parents (in the case of children).

General Examinations

Examiners used identical protocols across all surveys, and these have been unchanged since 1973.12 All subjects were instructed to fast for 12 to 24 hours before venipuncture, and compliance was determined by interview on the date of the examination. Height and weight were recorded in triplicate to the nearest 0.1 cm and 0.1 kg, respectively, and mean values were used. As a measure of obesity, body mass index ([BMI] weight in kilograms divided by the square of the height in meters) was calculated. Replicate BPs were obtained from the

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right arm of the subjects in a relaxed, sitting position. Arm measurements were done to ensure proper cuff size. Systolic BP (SBP) and DBP were recorded at the first, fourth, and fifth Korotkoff phases using mercury sphygmomanometers. BP levels were reported as the mean of 6 replicate readings, taken by each of 2 randomly assigned and trained observers. For these analyses fourth phase was assigned and trained observers. For these analyses fourth phase was more reliably measured in childhood and more predictive of adult hypertension.13

Laboratory Analysis
Serum uric acid levels were determined as part of multiple chemistry profile (SMA20) by the multichannel Olympus Au-5000 analyzer (Olympus) with the uricase method.14 The measurement error, estimated from the coefficient of variation of 373 pairs of blind duplicate determinations in the survey of children, was 3.7%. The intraclass correlation, a measure of reproducibility, was 0.99.

Statistical Analysis
Data analysis was performed using SAS version 8.0.15 Significances of race and sex differences in mean values of study variables and covariates were tested using t tests (Table 1). Correlations between childhood uric acid and adulthood BP were assessed by partial Pearson correlation coefficients (r value), adjusting for age at baseline, by the 2 sex groups and the 4 race-by-sex groups (Table 2). Multivariate regression models were used to examine the significance of childhood uric acid in predicting adulthood BP adjusting for covariates (Table 3). These covariates included race, sex, age at baseline, change in age from baseline to follow-up, childhood BMI, childhood SBP, childhood uric acid, and the rate of change in uric acid. The annual change in uric acid level was measured for all subjects and is defined as the change in uric acid levels between measurements divided by the number of follow-up years. Separate analysis of the hypertensives (n = 23) and nonhypertensives was performed. There were no significant changes to the correlation values or P values when the hypertensives were excluded from analysis. Both groups had very similar correlation values, so all subjects were included in the final analysis. Because of strong correlation between SBP and DBP, separate regression models were used.

Results
Childhood and adulthood characteristics are given by ethnicity and sex in Table 1. Race and sex differences for SBP,
DBP, and serum uric acid values are adjusted for age and BMI. During childhood, there was a significant \((P<0.05)\) sex difference (female > male) for DBP, especially among whites. Blacks had a significantly lower serum uric acid than whites \((P<0.0001)\) and within each ethnicity; females had a significantly lower serum uric acid than males \((P<0.0001)\). During adulthood, SBP and DBP showed significant \((P<0.0001)\) sex (male > female) differences. Although uric acid continued to demonstrate a significant \((P<0.0001)\) sex difference, there was no significant ethnic difference noted in the adult cohort. The 23 subjects who developed hypertension as adults had a higher mean childhood serum uric acid level than the 554 subjects who remained normotensive \((5.12 \text{ versus } 4.30; \ P=0.007)\).

### Correlation Between Childhood Serum Uric Acid and SBP and DBP

To test our hypothesis of a causal link between uric acid and BP, we evaluated the correlation between BP, both systolic and diastolic, childhood and adult, and serum uric acid. The correlations for uric acid and BP are shown in Table 2. For the entire cohort, childhood serum uric acid is strongly associated with childhood SBP \((r=0.31; \ P=<0.0001)\) and DBP \((r=0.20; \ P=<0.0001)\) as well as adult SBP \((r=0.29; \ P=<0.0001)\) and DBP \((r=0.28; \ P=<0.0001)\). However, this correlation varies significantly with race and sex. Females showed a significant correlation between serum uric acid and BP in childhood and adulthood in blacks and whites. Males had a significant or marginal correlation between uric acid and adult SBP and DBP; however, this correlation was only seen in white males. Any correlation between uric acid and BP in black males in either childhood or adulthood was not statistically significant.

### Independent Predictors of Adult BP

Table 3 shows the independent predictors of adult BP levels. For adult SBP and DBP, BMI, sex, change in age, and change in uric acid were significant \((P \text{ value } <0.05)\) predictors. For adult DBP, childhood serum uric acid was also a significant predictor, whereas for adult SBP, race was also a significant predictor (Table 3).

### Discussion

Longitudinal observations in a community-based study demonstrate that childhood serum uric acid levels and their rates of change from childhood to adulthood are strongly related to BP levels in the entire cohort; this statistical correlation was consistent in young adult females and white males but not black males. These data were derived from apparently healthy young adults, all but 23 of whom had BP levels within normal limits. As predicted, those subjects who developed hypertension had a higher mean childhood serum uric acid level, but the correlation between childhood uric acid and adult BP remained significant even in the normotensive subjects who had a lower mean childhood uric acid. This study also confirms the findings of several other small studies that show a correlation between childhood uric acid and childhood BP. The present data did not find any statistically significant differences in childhood BP levels for race or sex. However, despite similar BMIs in adulthood, males had significantly higher BP levels compared with females and blacks compared with whites. Correlation between uric acid in childhood and BP was found in all race and sex groups except black males; whether this represents a real difference or a lack of statistical power in this smaller group is undetermined.

The reason for differential effect of serum uric acid on BP between the sexes is unknown but may be at least partially explained by the gender-specific differences in salt sensitivity. Some literature demonstrates that females, particularly young females, are more likely to show BP reductions in response to sodium depletion than males. The INTERSALT study, one of the largest interpopulation studies on sodium excretion and BP, showed a stronger positive association between sodium excretion and SBP in women than in men. Also, studies by Wilson et al on black adolescents and Sinaiko et al on sixth- to eighth-graders showed that only females had a BP reduction in response to a low sodium diet. Thus, if the mechanism by which higher uric acid levels cause an elevated BP is thought to be attributable to salt sensitivity, it might be expected that the effect would be greater in adolescent females. Obviously, differential mechanisms between genders for hypertension are complex and vary across studies.

An increase in childhood BP will likely track into adulthood, and this is a possible mechanism by which increased childhood uric acid levels cause increased adult BP. However, childhood BP/baseline BP is included as a covariate in the model for SBP and DBP. Despite this, uric acid and change in uric acid are significant independent predictors of adult BP.

Significant positive correlations have been reported previously between adult uric acid and BP and are predictive.
of the relationship between childhood uric acid levels and adult BP. However, this is the first study to examine the relationship between childhood uric acid levels and adult BP.

In this study, we hypothesized that childhood serum uric acid levels are correlated with adult BP levels based on strong epidemiologic data that showed serum uric acid correlated with hypertension in adults.\textsuperscript{5–7,20} Epidemiologic studies show a continuous relationship of serum uric acid with BP that is stronger for younger subjects than older subjects.\textsuperscript{21,22} This is consistent with experimental studies that demonstrate that once elevated uric acid levels cause sufficient renal injury, animals develop salt-sensitive hypertension regardless of the level of uric acid.\textsuperscript{23} Thus, it appears that maintaining a lower uric acid would be more effective at prevention rather than lowering uric acid in the treatment of hypertension because once intrarenal vascular disease develops, hypertension is then driven by renal disease.

Decreased renal blood flow, characteristically found in many individuals with hypertension, may result in increased urate reabsorption and a subsequent elevation in serum uric acid.\textsuperscript{24} Thus, elevated uric acid levels could simply reflect the level of BP and may not contribute to it pathogenetically. However, none of the subjects in this study were initially hypertensive so that a subtle relationship of uric acid and BP were investigated. Several lines of evidence suggest that uric acid is a causal factor in human hypertension. Elevated adult uric acid is known to be an independent predictor of the development of hypertension and thus can precede hypertension.\textsuperscript{4,5,16} Also, Feig and Johnson demonstrated recently that serum uric acid is strongly correlated with BP in childhood primary hypertension but not secondary hypertension or white-coat hypertension.\textsuperscript{10} If uric acid were just a marker of hypertension, a similar degree of hyperuricemia would be expected in children with secondary hypertension.

Although the mechanisms of the association between childhood uric acid levels and adult BP are not known, plausible physiological mechanisms by which higher levels of uric acid might cause hypertension have been suggested by recent experimental studies. Uric acid can enter vascular smooth muscle cells and stimulate a number of factors, including platelet-derived growth factor and mitogen-activated protein kinase. These factors induce vascular smooth muscle proliferation and preglomerular arteriopathy.\textsuperscript{25–26} Once a vascular lesion is established, salt sensitivity can persist despite correction of serum uric acid levels.\textsuperscript{24} The mechanism of the persistent salt sensitivity is thought to be attributable to renal ischemia that leads to activation of the renal renin-angiotensin system, renal vasoconstriction, and increased sodium reabsorption.\textsuperscript{27,28} Finally, increased uric acid levels can cause an increase in juxtaglomerular renin production and a decrease in macula densa NO synthase expression, both of which directly lead to increased BP.\textsuperscript{29}

Perspectives
Higher childhood serum uric acid, even within a normal range, is strongly associated with adult BP, for SBP and DBP. This evidence supports a role for uric acid in the development of hypertension and possibly renal disease. The mechanisms and implications of this association are uncertain at present but deserve further investigation based on the present study in conjunction with several other studies, animal and clinical, that support an association.

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