Uric Acid Excretion Predicts Increased Blood Pressure Among American Adolescents of African Descent

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ABSTRACT

Background: Hyperuricemia predicts the incidence of hypertension in adults and its treatment has blood pressure (BP)-lowering effects in adolescents. To date, no studies have examined the predictive usage of hyperuricemia or urinary uric acid excretion on BP changes in adolescents. Mechanistic models suggest that uric acid impairs both endothelial function and vascular compliance, which would potentially exacerbate a myriad of hypertensive mechanisms, yet little is known about interaction of uric acid and other hypertension risk factors.

Materials and Methods: The primary study was aimed at the effects of stress on BP in adolescents. A community sample of 84 low-income, urban adolescents (50% male, 95% African American, mean age = 13.36 ± 1 years) was recruited from public schools. Youth completed a 12-hour (overnight) urine collection at home and their BP was measured during rest and in response to acute psychosocial stress. Seventy-six of the adolescents participated in a follow-up visit at 1.5 years when their resting BP was reassessed. In this substudy, we assessed the relationship of renal urate excretion and BP reactivity.

Results: After adjusting for resting BP levels at baseline and other covariates, higher levels of uric acid excretion predicted greater BP reactivity to acute psychosocial stress and higher resting BP at 18 months.

Conclusions: Urinary excretion of uric acid can serve as an alternative, noninvasive measure of serum uric acid levels that are predictive of BP changes. As hyperuricemia-associated hypertension is treatable, urban adolescents may benefit from routine screening for hyperuricemia or high uric acid excretion.

Key Indexing Terms: Uric acid; Blood pressure; Pediatric; African American. **[Am J Med Sci 2017;353(4):336–341.]**

BACKGROUND

Uric acid, the end product of purine metabolism in humans, has long been implicated in the development of hypertension and cardiovascular disease risk.[1] After adjustments for other risk factors (e.g., body mass index [BMI], metabolic syndrome and renal function), serum urate levels emerge as an independent risk factor for the incidence of hypertension over 4 to 21-year periods in multiple ethnic populations of adults.[2-5] Among children and adolescents, serum urate levels have been linked with elevated systolic and diastolic blood pressure (BP) in cross-sectional studies,[6-8] but no investigations have examined the longitudinal effects of uric acid on BP in children and adolescents.

Animal and tissue culture models suggest that uric acid increases BP through a 2-step process. The initial steps are activation of the renin-angiotensin system and downregulation of endothelial nitric oxide elaboration, resulting in acute vasoconstriction that creates reversible hypertension. The second step is irreversible arteriolosclerosis that causes irreversible, sodium-sensitive hypertension that is no longer responsive to urate-lowering therapy.[9] Initial data from randomized clinical trials demonstrate that urate-lowering therapy, whether xanthine oxidase inhibition or uricosuric agents, results in BP reduction in adolescents with newly diagnosed essential hypertension or prehypertension.[10,11] In a similar small randomized controlled trial, urate-lowering therapy had no effects on BP in adults older than 40 years.[12] Taken together, these data support the 2-step uric acid–mediated hypertension hypothesis and underscore the need to better understand the role of uric acid in pediatric hypertension, as early intervention may prevent irreversible vascular changes and mitigate long-term cardiovascular risk. In addition to increasing resting BP, uric acid may also increase BP reactivity to acute stress through excessive vasoconstriction. Indeed, higher levels of serum uric acid were related to greater increase in systolic BP (SBP) during laryngoscopy and tracheal intubation among adult patients.[13] However, no studies have examined the role of uric acid in response to acute psychosocial stress that reliably elevates cardiovascular responses.[14]

All previous studies examining links between uric acid and BP have used serum or plasma levels of uric acid. Clinically, 24-hour urinary excretion levels of uric acid are important for differentiating causes of hyperuricemia and selecting urate-lowering therapy. High urate clearance may result from impaired uric acid reabsorption in rare conditions such as Fanconi syndrome and familial

juvenile hypouricemic nephropathy, or be the physiological response to hyperuricemia. Thus, it is of interest whether urinary excretion of uric acid relates to BP changes in a similar manner as serum levels. Uric acid excretion and serum uric acid are modestly positively correlated ($r = 0.19$) in healthy individuals[15] and may produce similar relationships to other variables, particularly among individuals without medical conditions that impair the clearance of uric acid, such as insulin resistance[16] and kidney disease.[17]

Among U.S. adults, Americans of African descent (AA) have the highest rates of hypertension compared to other ethnic groups (>40% versus <30%).[18] These racial differences in hypertension emerge in childhood[19] and become more pronounced in adolescence,[20] underscoring the importance of studying modifiable risk factors that contribute to hypertension among AA youth. Therefore, we focused our study on a population of low-income urban adolescents of mostly African descent who are at a greater risk for hypertension and hyperuricemia than other demographic groups.[20,21] These youth also resided in a geographic area with one of the highest incidence of hypertension in the United States.[22]

Given the lack of prospective, longitudinal studies on the effect of uric acid in BP in pediatric populations and unknown usage of urinary excretion of uric acid, we examined 12-hour urinary excretion of uric acid as a predictor of BP changes over a 1.5-year period in a community sample of adolescents. A 12-hour overnight urine collection was conducted instead of the standard 24-hour collection due to its substantially greater feasibility in community-dwelling youth and high correspondence with 24-hour collection values (e.g., intraclass correlation coefficient = 0.96 for creatinine clearance).[23] Given the lack of research on the role of uric acid in BP reactivity to acute stress, we also examined BP response to a standardized psychosocial stressor.

METHODS

Study Design and Patient Population

The project described here has been conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. All study procedures were approved by the Institutional Review Board of the University of Alabama at Birmingham and all participants provided written informed consent. This prospective study was designed as a pilot study to examine the effects of stress on health in low-income, urban adolescents. The primary analyses focused on the effects of violence exposure on physical and mental health. Secondary analyses included the roles of urinary and salivary biomarkers in health outcomes. The sample size was determined by power analyses for the primary aims in the context of available resources. The sample included 84 adolescents recruited from 4 middle schools serving grades 6-9 (age group: 12-15) in low-income urban areas in Birmingham, Alabama. The schools were randomly selected from local schools serving low-income populations. Across the 4 schools, 83-87% of students were eligible for free or reduced price lunch. All students in regular education classrooms were eligible to participate. Students received an envelope that contained a description of the study, contact information form and informed consent and assent forms. Families interested in participating were instructed to return a completed contact information form to the school. These families were contacted by study staff and scheduled for a visit at a university laboratory.

From approximately 240 invited students, 129 (54%) provided their contact information and 84 of those (65%) completed the visit (recruitment was curtailed by limited resources). Trained research assistants conducted individual interviews with the adolescent and parent. The parent interview included a question on family annual income. The adolescent interview included BP measurements before and during a standardized social stress task (discussed later) as well as collection of anthropometric measurements (height and weight). At the end of the interview, the collection of 12-hour overnight urine from the adolescent was explained and scheduled during the following week. Approximately 1.5 years after the baseline assessments, families were re-contacted and scheduled for a follow-up interview. The adolescent follow-up interview included measurement of resting BP.

BP Measurements and Stress Testing

All BP measurements were obtained on the non-dominant arm using an automated oscillometric device (Dinamap, Tampa, FL). The baseline BP measurement was obtained after approximately 30 minutes of non-stressful interview, when the adolescent has been sitting quietly and resting for 5 minutes. Next, the Trier Social Stress Task-Child version (TSST-C)[24] was introduced to the adolescent and he or she was given 5 minutes to prepare an ending of a story. Then, 2 adult judges in white coats entered the room, sat behind a desk and asked the adolescent to tell them for 5 minutes how the story ends (speech task). Then, they asked the adolescent to do a serial subtraction task for another 5 minutes (math task). The judges followed a standardized protocol and provided no positive feedback (e.g., smiling or nodding) during the stress task. The adolescent remained seated and 3 BP measurements were taken 3 minutes apart during the speech and math tasks; they were averaged to indicate BP during stress ($r > 0.70$ for SBP and 0.51 for DBP, $P < 0.001$). BP stress response was computed by subtracting baseline resting BP from BP during stress. At the follow-up interview 1.5 years later, only resting BP was assessed after the adolescent was interviewed for approximately 30 minutes and has been sitting quietly and resting for 5 minutes. Two