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The Role of Uric Acid in Pediatric Hypertension

Daniel I. Feig, MD, PhD, MS, FAAP
Chief of Pediatric Hypertension Clinics, Renal Section, Department of Pediatrics, Baylor College of Medicine

Richard J. Johnson, MD
Robert Cade Professor of Medicine, Chief, Division of Nephrology, Hypertension and Transplantation, University of Florida School of Medicine

Abstract

Over the past few years increasing evidence has supported the possible role of uric acid as a mediator of high blood pressure. Both animal model data and tissue culture experiments suggest that uric acid might cause increased blood pressure by a two phase process. A first phase dominated by a uric acid mediated vasoconstriction followed by induction of renal afferent arteriolosclerosis and altered pressure natriuresis leading to a sodium dependent hypertension. We have assessed children with newly diagnosed essential hypertension and through cross-sectional studies and clinical trials. Elevated uric acid is closely associated with new onset essential hypertension in children and preliminary data suggests that lowering uric acid can lower blood pressure in some patients. Future studies will be needed to determine if the mechanisms shown in animal models can be extrapolated to children.

Keywords

Hypertension; Children; Uric Acid; Obesity; Clinical Research

The History of Uric Acid and Hypertension

The concept that uric acid may be involved in hypertension is not a new one. As early as the 1870's, Frederick Akbar Mohamed noted that many of his hypertensive patients came from gouty families and hypothesized that uric acid might be integral to the development of essential hypertension [1]. Ten years later Haig [2] proposed low purine diets as a means to prevent hypertension and vascular disease. In 1909, Henri Huchard, noted that renal arteriolosclerosis (the histological lesion of hypertension) was observed in 3 groups; those with gout, lead poisoning, or have a diet consisting mainly of fatty meats, all of which are associated with hyperuricemia[3]. The association between elevated serum uric acid and hypertension was repeatedly observed and reported in the 1950s–80s [4–6] but the lack of a causal mechanism led to mild elevations of serum uric acid being largely ignored in medical practice.

Recent epidemiological studies have supported a link between uric acid and the onset of hypertension. Three longitudinal Japanese studies in the last 6 years have shown an association between serum uric acid and incident hypertension. Nakanishi et al. and demonstrated a 1.6

Corresponding Author: Daniel I. Feig, MD, PhD, MS, Department of Pediatrics, Renal Section, Baylor College of Medicine, 1102 Bates Avenue, MC3-2482, Houston, TX 77030, dfeig@bcm.tmc.edu.

fold increased risk of new hypertension over 6 years in young adult office works with serum uric acid in the highest tertile[7]. Tanaguichi et al. demonstrated a 2-fold increased risk of new hypertension over 10 years associated with elevated uric acid in the Osaka Health Study[8]. Masuo et al. evaluate the linear association of serum uric acid and systolic blood pressure, finding an average increase of 23mm Hg per 1mg/dl increase in serum uric acid among non-obese young men[9]. In an ethnically diverse population within the Bogalusa Heart Study, higher childhood and young adult serum uric acid levels associated with incident hypertension progressive increase in blood pressure within the normal range[10]. A recent re-evaluation of the Framingham Heart Study data also suggests that higher serum uric acid levels is associated with increased risk of progression from normal blood pressure (bp) to hypertension[11]. Studies specifically of older and elderly patients have had much more variable results with regard to a link between these factors[12–15] suggesting that if uric acid leads to hypertension, there may be a preferential effect in the young.

Animal Models, Insights into Mechanism

In the late 1990s Johnson and colleagues developed a model using a pharmacologic inhibitor of urate oxidase, oxonic acid, that allows the study of sustain mild hyperuricemia[16]. When fed a diet of 2% oxonic acid in their standard chow, Sprague-Dawley rats have an increase of mean serum uric acid concentrations from 0.5–1.4gm/dl to 1.7–3.0mg/dl[16]. Over a 7-week treatment period, systolic blood pressures increase an average of 22mm Hg. The increase in blood pressure can be entirely prevented by the co-administration of the xanthine oxidase inhibitor allopurinol, or by the uricosuric agent benziodarone, indicating that the rise in uric acid is the cause of the increased blood pressure. In fact, the increase in blood pressure is linearly related to the rise in uric acid (r=0.77). It is important to note that the change blood pressure is seen maximally when the rats are maintained on a low salt diet and that there are no changes in renal function or measurable health parameters of the rats. After seven weeks on a low salt diet and oxonic acid, if the oxonic acid is removed, the serum uric acid falls to normal as does the blood pressure over 3 weeks; however, if formally hyperuricemic rats are then fed a high salt diet, they become hypertensive[17]. These studies show that, in rats, mild hyperuricemia leads to a reversible uric acid mediated hypertension in the short term but an irreversible salt sensitive hypertension over time.

The two-phase development of hypertension in the rat model provides a potential explanation for greater correlation between uric acid and hypertension in younger and pre-hypertensive populations. If humans also develop a sodium sensitive hypertension after sufficient duration of hyperuricemia, older, and especially elderly patients would not necessarily have the same uric acid responsiveness. Consequently, definitive determination of whether uric acid causes hypertension and to what extent hyperuricemia ought to be managed must be studied in the young.

Pediatric Observational Data

In adolescents there is a close association between elevated serum uric acid and the onset of essential hypertension. The Moscow Children's Hypertension Study found hyperuricemia (>8.0mg/dl) in 9.5% of children with normal blood pressure, 49% of children with borderline hypertension and 73% of children with moderate and severe hypertension [18]. The Hungarian Children's Health Study followed all 17,624 children born in Budapest in 1964 for 13 years and found that significant risk factors for the development of hypertension were elevated heart rate, early sexual maturity, and hyperuricemia [19]. These two studies do not separate the hypertensive children by underlying diagnosis so the relationship between serum uric and hypertension may be skewed by ascertainment bias. In a small study, Gruskin [20] compared adolescents (13–18 years of age) with essential hypertension to age-matched, healthy controls

with normal blood pressures. The hypertensive children had both elevated serum uric acid (mean >6.5mg/dl) and higher peripheral renin activity. In a racially diverse population referred for the evaluation of hypertension, Feig and Johnson observed that the mean serum uric acid level children with white coat hypertension was 3.6±0.7mg/dl, slightly higher in secondary hypertension (4.3±1.4mg/dl, *p=0.008*) and significantly elevated in children with primary hypertension (6.7±1.3mg/dl, *p=0.001*) [21]. There was a tight, linear correlation between the serum uric acid levels and the systolic and diastolic blood pressures in the population referred for evaluation of hypertension (r=0.8 for SBP and r=0.6 for DBP). Each 1mg/dl increase in serum uric acid was associated with an average increase of 14mm Hg in systolic blood pressure and 7mm Hg in diastolic blood pressure [21]. Among patients referred for evaluation of hypertension, a serum uric acid >5.5mg/dl had an 89% positive predictive value for essential hypertension while a serum uric acid <5.0 had a negative predictive value for essential hypertension of 96% [21]. The correlation also extends to children with pre-hypertension. Three-hundred consecutive children with pre-hypertension or confirmed hypertension, whose evaluation whose evaluation did not reveal a clear cause of secondary hypertension, were evaluated for serum uric acid (Figure 1). The correlation is strong, $r = 0.45$, $p<0.001$, albeit not as close as seen in established hypertension.

The evaluation of a large referral population of children with essential hypertension and elevated uric acid reveal several observations that are consistent with the mechanisms of uric acid mediated hypertension seen in the animal model. Among 513 children consecutively evaluated for hypertension, children with essential hypertension (N=206) had higher blood hemoglobin (14.6±1.3g/dl) compared to those with secondary hypertension (N=176, hemoglobin 12.8±1.6) or white coat hypertension (N=135, hemoglobin 12.5±1.2g/dl). In children with serum uric acid >6mg/dl, the average hemoglobin is 15.4±1.4g/dl. While the mechanism is not yet established, one possibility is that uric acid mediated vasoconstriction and arteriolosclerosis, seen in the rat model, leads to decreased microvascular perfusion and increased serum erythropoetin. Polycythemia and hypertension have been previously described in patients with hyperuricemia and gout, however, it has been assumed that the elevation in uric acid was secondary to the hematopoietic disorder[22,23]. In obese patients with pre-hypertension and serum uric acid >5mg/dl, systemic vascular resistance (measured by non-invasive bioimpedence) is elevated relative obese children with normal uric acid and similar blood pressure (2482±306 vs. 1843±291 dynesec/cm^5/m^2). While these physiologic observations do not prove that the effects of increased serum uric acid are the same in humans as in rats, they are consistent with a vasoconstrictive effect due to the uric acid.

Intervention Trials

Results from a small, unblinded pilot study in children suggest that uric acid may directly contribute to the onset of hypertension in some humans. Five children, age 14–17 years of age, with newly diagnosed and as yet untreated essential hypertension were treated for 1 month with allopurinol as a solitary pharmacological agent. All five children had a decrease in blood pressure by both casual and ambulatory monitoring and 4 of the 5 were normotensive at the end of one month. All 5 also had a rebound in their blood pressures following discontinuation of the therapy[24]. Because this study was very small and not blinded, care should be taken in interpreting the results. Definitive, randomized, blinded clinic trials of the efficacy and safety of lowering uric acid as an anti-hypertensive measure are underway and are expected to be completed by late 2006.

The Reason for Hyperuricemia

The causes of mild to moderate hyperuricemia in the young are not well established. In the elderly a variety of mechanisms, including decreased renal function, may increase uric acid.

There are numerous medications that impair renal clearance of uric acid including loop and thiazide diuretics[25] and genetic polymorphisms in anion transporters such as Uric Acid Anion Transporter 1 (URAT-1) may lead to hyperuricemia[26]. Approximately 15% of uric acid clearance is through the GI tract, consequently small bowel disease or altered phenotype can also contribute[27]. Diets rich in fatty meats, seafood and alcohol increase serum uric acid [28,29] and obesity confers a three-fold increased risk of hyperuricemia[30]. Finally, as uric acid is the endpoint of the purine disposal pathway, impairment of the efficiency of purine recycling metabolism or overwhelming the recycling pathway with excessive cell death or cell turnover will increase serum uric acid[31].

Conclusions and Recommendations

While the evidence for a role of uric acid in the onset of a subset of individuals is mounting, it is still premature to consider uric acid lowering drugs for the treatment of hypertension outside of a clinical trial context. Numerous safe and effective treatments have been tested and are available for the management of hypertension in young and older patients. The currently available hypo-uricemic agents have side effect profiles that do not compare very favorable to the available anti-hypertensive agents. The greatest theoretical benefit of treating hyperuricemia in this context is the possibility, predicated on the results of animal models and not yet proven in humans, that elevated uric acid may lead to irreversible microvascular changes. This possibility of preventing or significantly delaying, permanent sodium sensitive hypertension needs considerably more scientific support before uric acid lowering agents should be added to routine clinical practice.

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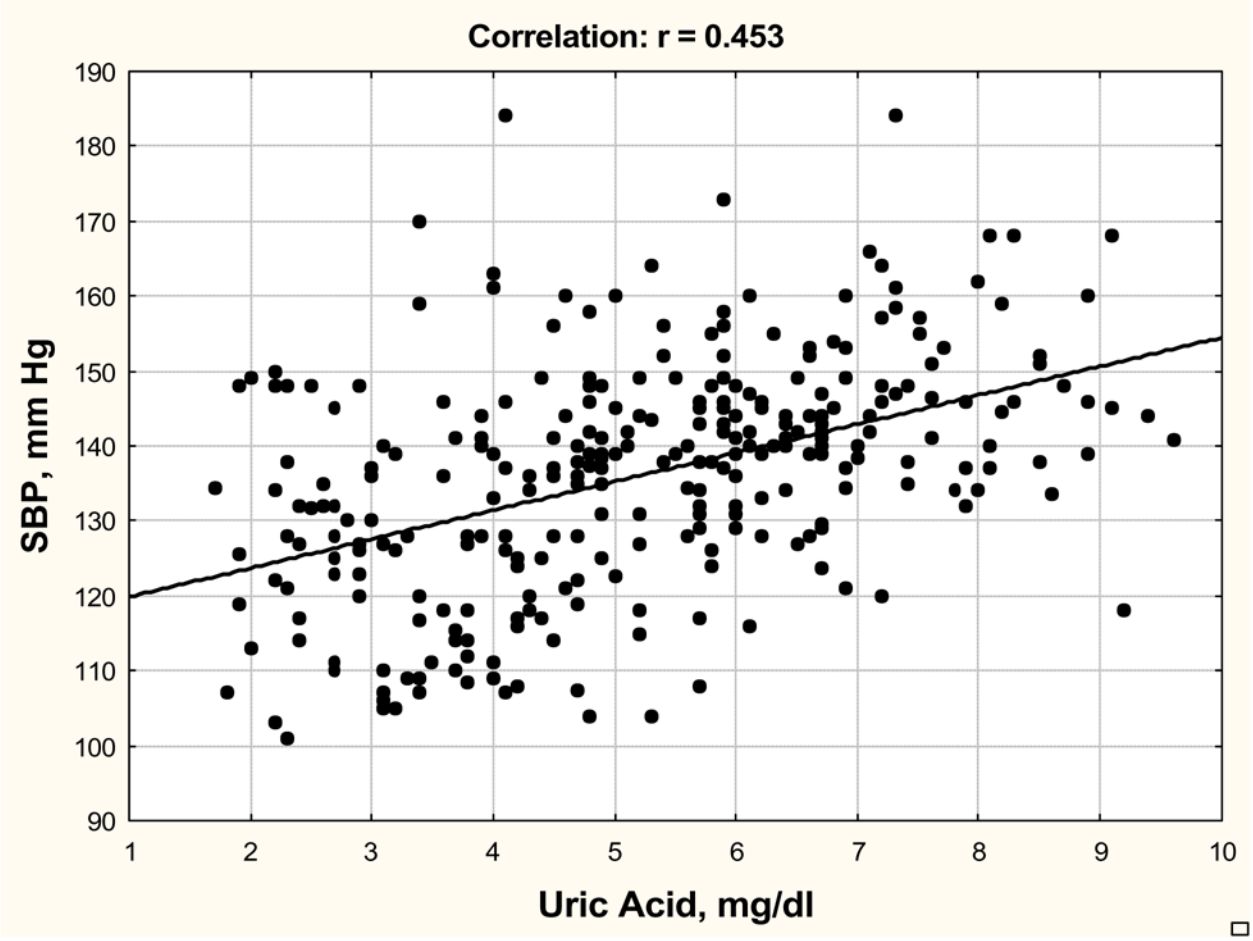

Figure 1.
Correlation between systolic blood pressure and serum uric acid of 300 children consecutively evaluated in the Hypertension Clinic at Texas Children's Hospital who did not have evident renal, cardiac or endocrine disease at the time of initial evaluation.