Hyperuricemia and Hypertension

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Over the past century, uric acid has been considered a possible risk factor for hypertension and cardiovascular disease. However, only in the past decade, animal models and clinical trials have supported a more mechanistic link. Results from animal models suggest a 2-phase mechanism for the development of hyperuricemic hypertension in which uric acid induces acute vasoconstriction by activation of renin–angiotensin system, followed by uric acid uptake into vascular smooth muscle cells leading to cellular proliferation and secondary arteriolosclerosis that impairs pressure natriuresis. This acute hypertension remains uric acid dependent and sodium independent, whereas the chronic hypertension becomes uric acid independent and sodium dependent. Small clinical trials, performed in adolescents with newly diagnosed essential hypertension, demonstrate that reduction of serum uric acid can reduce blood pressure. Although more research is clearly necessary, the available data suggest that uric acid is likely causative in some cases of early onset hypertension.

Key Words: Hypertension, Uric acid, Animal models, Clinical trials

The History of Uric Acid and Hypertension

The possibility that uric acid may be a cause of hypertension has been considered for more than a century. Frederick Mahomed, in the 1870s, postulated that hypertension resulted from a circulating toxin that caused an increase in blood pressure and subsequently damaged the vasculature of the heart and kidneys.[1] Although he suggested several candidate molecules, he proposed uric acid is an important mediator and published the first sphymograph tracings showing a subject with gout with increased systemic blood pressure.[1] A few years later, Alexander Haig also linked uric acid with elevated blood pressure and went so far as to write a textbook that suggested a diet to lower uric acid and control blood pressure in the general population.[2] In 1897, Nathan Davis, in an address to the American Medical Association, proposed that gout was a major cause of hypertension that manifested as arteriolar disease, interstitial renal injury, and myocardial hypertrophy.[3] In 1909, Henri Huchard hypothesized that the vascular lesions associated with hypertension had 3 causes: uric acid, lead, and intake of fatty meats; the latter also yields increased uric acid.[4] In 1913, Desgrez reported the first animal model evidence supporting the link between uric acid and hypertension, noting that uric acid infusions increased blood pressure in a rabbit model.[5] In 1915, Urodonal, a drug consisting of theobromine and methenamine, was introduced in France as a treatment to lower uric acid and control blood pressure; however, it was eventually proven to be ineffective. Nevertheless, at the end of the 19th century and the first 2 decades of the 20th century, uric acid was already linked with hypertension and cardiovascular (CV) diseases.

Interest in the possible link between hypertension and uric acid waxed and waned during much of the 20th century. Although some of the CV risk trials measured uric acid and suggested an association between uric acid and hypertension, or CV disease (Table 1), 2 factors led most investigators to conclude that uric acid was an associated surrogate marker for more important risk factors such as obesity, diabetes, and CKD.[53] The first was a lack of a plausible physiological mechanism, and the second was that despite consistent correlation, the link between serum uric acid and CV disease was not always statistically independent of other factors such as hypertension, renal disease, and diabetes. In the 1980s, uric acid was removed from some of the common laboratory panels, markedly reducing the available epidemiologic data on uric acid in otherwise healthy patients and those suffering from CV disease. The move was made because of the majority of serious side effects from the urate-lowering drug, allopurinol, observed in patients with asymptomatic hyperuricemia,[57] and intended to reduce the risk of unnecessary medication side effects associated with the treatment of asymptomatic hyperuricemia.

Animal Models of Hyperuricemic Hypertension

Although significant epidemiological evidence supported the hypothesis that uric acid may be associated with hypertension, it was not until the experiments of Johnson and colleagues in 2001, established a plausible mechanism. Using a rat model of pharmacologically induced hyperuricemia, they showed that increased serum uric acid level results in hypertension within 2 weeks. The increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) are proportional to

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those of uric acid. This can be ameliorated by uric acid-lowering drugs (allopurinol or benziodarone). Early hypertension is completely reversible with urate reduction, but prolonged hyperuricemia results in irreversible sodium-sensitive hypertension that becomes uric acid independent.[58,59] The early hypertension is mediated by increased renal renin activity and reduction of circulating plasma nitrates[58,60-62] leading to a phenotype of excessive vasoconstriction that can be reversed by reduction of uric acid or renin–angiotensin system blockade. The later irreversible hypertension is secondary to altered intrarenal vascular architecture. Uric acid enters vascular smooth muscle cells via uric acid anion transporter-1 channel, resulting in activation of kinases, nuclear transcription factors, cyclooxygenase-2 generation, and the platelet derived growth factors (PDGF) and inflammatory proteins (C reactive protein, monocyte chemoattractant protein-1) resulting in the VSCM proliferation, shifted pressure natriuresis, and sodium-sensitive hypertension.[63-67] If recapitulated in humans, this model suggests that there may be a period of reversible hypertension early in the developmental course (Fig 1).

These mechanistic studies, as well as the recent epidemiologic data described later in the text, have led to a dramatic increase in the number of research publications addressing the link between uric acid and hypertension. The number had remained relatively constant from 1970 to 2000 but has been consistently rising since (Fig 2).

CLINICAL SUMMARY

- At least in adolescents, uric acid contributes, mechanistically, to the development of elevated blood pressure.
- Patients with elevated uric acid may be more responsive to uric acid-lowering therapy early in the course of their disease.
- Allopurinol and probenecid have side effect profiles that are inferior to conventional antihypertensive medication so are not optimal alternatives for preventive therapy.
- Reduction in dietary sweetener intake may be a useful approach to uric acid reduction in elect patients.

Epidemiology

Numerous longitudinal CV risk trials have evaluated the possible relationship between serum uric acid, hypertension, CV disease, and CKD (Table 1). As early as 1972, the Israeli Heart Trial, an evaluation of the medical data of young adults inducted into the armed services, demonstrated that the tertile with highest uric acid level was associated with double the risk of incident hypertension within 5 years.[6] The association is robust across racial groups, with similar findings in African Americans noted in the Coronary Artery Risk Development In Young Adults trial[16] and several trials demonstrating the same association in Asians and Asian Americans.[17,18,20-22] Several studies in children and adolescents, particularly the Hungarian Children's Study,[11] the Moscow Children's,[9] and the National Health and Nutrition Examination Survey (NHANES),[14] in the 1980s and early 1990s, demonstrated a particularly strong association between uric acid and hypertension. Studies specifically of older and elderly patients have had more variable results.[53,68-70] In particular, some of the studies found that the association between uric acid and CV risk did not retain significance in certain multiple regression models, particularly if the risk conferred by hypertension is controlled in the model.[53-56] One explanation may be that the CV risk caused by uric acid functions through the development of hypertension; alternatively, there may be a preferential effect in the young.

In the past decade, new epidemiological studies have rekindled an interest in the link between uric acid and hypertension. Three longitudinal studies in Japanese subjects showed an association between serum uric acid and incident hypertension. Nakanishi and colleagues demonstrated a 1.6-fold increased risk of new hypertension over 6 years in young adult office workers with serum uric acid in the highest tertile.[21] Tanaguichi and colleagues demonstrated a 2-fold increased risk of new hypertension over 10 years associated with elevated uric acid level in the Osaka Health Study.[17] Masuo and colleagues evaluated the linear association of serum uric acid and SBP, finding an average increase of 27 mm Hg per 1-mg/dL increase in serum uric acid among non-obese young men.[20] In an ethnically diverse population within the Bogalusa Heart Study, higher serum uric acid levels during childhood and young adulthood were associated with incident hypertension and progressive increase in blood pressure even within the normal range.[23] A post hoc analysis from the Framingham Heart Study also suggested that a higher serum uric acid level is associated with increased risk of rising blood pressure.[24] Taken together, the preponderance of evidence supports a close epidemiologic link between uric acid and hypertension that is robust across ethnic, racial, and anthropomorphic categories but may be attenuated in the elderly population.

Uric Acid Metabolism

The causes of hyperuricemia in the young are not well established; however, many possibilities exist and probably coexist. Increased uric acid can result from decreased renal function, and in general, children with CKD and ESRD have higher serum uric acid.[35] Genetic

Table 1. Epidemiology of Uric Acid and Hypertension and Cardiovascular Disease

Study	Population	Risk of Hypertension	Reference
Israeli Heart (1972)	Ten thousand Israeli men, aged 17-25 years, enrolled at military induction	Two-fold risk at 5 years	6
Fessel and colleagues (1973)	Two hundred twenty-four white males in the western United States, aged >35 years	Greater increase in SBP at 4 years	7
Gruskin (1985)	Fifty-five adolescents, racially mixed U.S. population	Higher uric acid level, higher BP	8
Moscow Children's Study (1985)	One hundred forty-five Caucasian children in Moscow, aged 8-17 years	Uric acid level >8 mg/dL predicts severe hypertension	9
Brand and colleagues (1985)	Four thousand two hundred eighty-six men and women aged 35-50 years in the Framingham cohort	A linear relation between uric acid and SBP rise	10
Hungarian Children's (1990)	Seventeen thousand six hundred forty-three Hungarian children, aged 6-19 years	Uric acid predicts adolescent hypertension	11
Kaiser Permanente (1990)	Two thousand sixty-two adult men and women in the Kaiser Permanente Multiphasic Health Checkup cohort in northern California	Two-fold risk at 6 years	12
University of Utah (1991)	One thousand four hundred eighty-two adult men and women in 98 Utah pedigrees	Two-fold risk at 7 years	13
NHANES (1993)	Six thousand seven hundred sixty-eight healthy children aged 6-17 years	Uric acid predicts adolescent hypertension	14
Olivetti Heart Study (1994)	Six hundred nineteen adult males from southern Italy	Two-fold risk at 12 years	15
Coronary Artery Risk Development In young Adults study (1999)	Five thousand one hundred fifteen black men and women aged 18-30 years	Increased risk at 10 years	16
Osaka Health Survey (2001)	Six thousand three hundred fifty-six Japanese men aged 35-60 years	Two-fold risk at 10 years	17
Hawaii-LA-Hiroshima Study (2001)	One hundred forty Japanese American males aged 40-69 years	3.5-fold risk at 15 years	18
Feig and Johnson (2003)	One hundred seventy-five racially diverse children aged 6-18 years in Texas	Uric acid level >5.5 mg/dL predicts hypertension	19
Osaka Factory Study (2003)	Four hundred thirty-three non-obese Japanese men aged 18-40 years	Per 1.0 mg/dL ↑ in uric acid level 27 mm Hg ↑ in SBP at 5 years	20
Osaka Health Survey (2003)	Two thousand three hundred ten male office workers in Japan aged 35-59 years	1.6-fold risk at 6 years	21
Okinawa (2004)	Four thousand four hundred eighty-nine Japanese men and women aged >30 years	1.7-fold risk at 13 years	22
Bogalusa Heart (2005)	Five hundred seventy-seven black (58%) and white (42%) children were enrolled and followed into adulthood, age 18-35 years	↑ risk for diastolic HTN at 11 years	23
Framingham (2005)	Three thousand three hundred twenty-nine men and women in the Framingham cohort	1.6-fold risk at 4 years	24
Normative Aging Study (2006)	Two thousand sixty-two healthy men aged 40-60 years at enrollment	1.5-fold risk at 21 years	25
ARIC (2006)	Nine thousand one hundred four mixed race (black and white) men and women, aged 45-64 years at enrollment	1.5-fold risk at 9 years	26
Beaver Dam Survey (2006)	Two thousand five hundred twenty white men (44%) and women (56%) aged 43-84 years in Wisconsin	1.65-fold risk at 10 years	27

(*Continued*)

Table 1. Epidemiology of Uric Acid and Hypertension and Cardiovascular Disease (*Continued*)

Study	Population	Risk of Hypertension	Reference
Health Professional Followup (2006)	Seven hundred fifty mostly white men in Massechussetts	1.08-fold risk at 8 years	28
MRFIT (2007)	Three thousand seventy-three men aged 35-57 years	1.8-fold risk at 6 years	29
Nurses Health (2009)	One thousand four hundred ninety-six women, racially diverse, aged 32-52 years	1.9-fold risk at 6 years	30
Qingdao Port Health (2009)	Seven thousand two hundred twenty men (74%) and women (26%) in Quingdoa China mean age 37 years	1.39-fold risk for men and 1.85-fold risk for women at 4 years	31
Jones and colleagues. (2009)	One hundred forty-one children, aged 7-18 years, 64% male, 71% black	2.1-fold risk in adolescence by ABPM	32
Leite and colleagues. (2010)	One thousand four hundred ten men and women in Milan, Italy, young cohort aged 42-59 years, older cohort aged 60-74 years	Increased risk in middle age, not elderly subjects	33
Grayson and colleagues. (2010)	Fifty-five thousand six hundred seven adults, meta-analysis of 18 prospective studies	1.41-fold risk, each 1 mg/dL uric acid	34
Silverstein and colleagues. (2011)	One hundred eight racially diverse children, aged 6-18 years in Texas and Washington, DC	Linear association between SBP and uric acid level in children on renal replacement therapy	35
GOCADAN (2012)	One thousand seventy-eight Alaskan native Americans with CKD II-III	1.2-fold age-adjusted risk	36
Fadrowski (2012)	Six thousand thirty-six adolescents, aged 11-17 years evaluated in NHANES	Uric acid level >5.5 mg/dL, 2.03-fold risk	37
Study	**Population**	**CV Risk**	**Reference**
Lehto and colleagues (1998)	One thousand seventeen patients with diabetes, mean age 58 years, followed for 7 years	OR: 1.91, independent on MR	38
Liese and colleagues (1999)	One thousand forty-four healthy adults, 50-60 years old, followed for 8 years	OR: 1.7-2.8, independent on MR	39
Alderman and colleagues (1999)	Seven thousand nine hundred seventy-eight hypertensive adults, mean age 53 years, followed for 6 years	OR: 1.5, independent on MR	40
Fang and Alderman (2000)	Five thousand nine hundred twenty-six healthy adults, mean age 48 years, followed for 16 years	OR: 3.0, independent on MR	41
Franse and colleagues (2000)	Four thousand three hundred twenty-seven elderly adults, mean age 71 years, followed for 5 years	OR: 1.5, independent on MR	42
Verdecchia and colleagues (2000)	One thousand seven hundred twenty adults with hypertension, mean age 51 years, followed for 4 years	OR: 1.9, independent on MR	43
Mazza and colleagues (2001)	Three thousand two hundred eighty-two healthy adults, mean age 74 years, followed for 14 years	OR: 1.6, independent on MR	44
Wang and colleagues (2001)	One thousand eight hundred seventy-three Chinese adults, mean age 66 years, followed for 3 years	OR: 1.34, independent on MR	45
Bickel and colleagues (2002)	One thousand seventeen with coronary artery disease, mean age 62 years, followed for 2.2 years	OR: 2.7, independent on MR	46
Weir and colleagues (2003)	Two thousand four hundred eighty-two stroke patients, mean age 72 years, follow-up 2 years	OR: 1.3, independent on MR	47

(*Continued*)

Table 1. Epidemiology of Uric Acid and Hypertension and Cardiovascular Disease (*Continued*)

Study	Population	Risk of Hypertension	Reference
Niskanen and colleagues (2004)	One thousand four hundred twenty-three healthy Finnish adults, mean age 53 years, followed for 12 years	OR: 4.8, independent on MR	48
Athyros and colleagues (2004)	One thousand six hundred adults with hypertension and congestive heart failure, mean age 59 years, followed for 3 years	OR: 3.0, independent on MR	49
Hakoda and colleagues (2005)	Ten thousand six hundred fifteen atomic bomb survivors, mean age 49 years followed for 25 years	OR: 1.8, independent on MR	50
Suliman and colleagues (2006)	Two hundred ninety-four adults with ESRD, mean age 53 years, followed for 3 years	OR: 1.3, independent on MR	51
Bos and colleagues (2006)	Four thousand three hundred eighty-five adults in Rotterdam Study, aged >55 years, followed for 8.5 years	OR: 1.7, independent on MR	52
Culleton and colleagues (1999)	Six thousand seven hundred sixty-three adult men, mean age 47 years, followed for 4 years, Framingham cohort	OR: 4.1, not independent on MR	53
Moriarity and colleagues (2000)	Thirteen thousand five hundred four healthy adults, mean age 50 years, followed for 8 years	OR: 3.0, not independent on MR	54
Sakata and colleagues (2001)	Eight thousand one hundred seventy-two healthy adults, mean age 49 years, followed for 14 years	OR: 2.3, not independent on MR	55
Simon (2006)	Two thousand seven hundred sixty-three women, mean age 66 years, followed for 4 years	OR: 1.1, not independent on MR	56

Abbreviations: ABPM, ambulatory blood pressure monitoring; MR, multiple regression; BP, blood pressure; HTN, hypertension; NHANES, the National Health and Nutrition Examination Survey; SBP, systolic blood pressure.

polymorphisms in anion transporters such as uric acid anion transporter-1[71] and the SLC2A9 that encodes for glucose transporter 9 gene, an anion transporter with affinity for uric acid,[72,73] can lead to hyperuricemia by altering proximal tubular urate clearance. Approximately 15% of uric acid clearance is through the gastrointestinal tract; consequently, small bowel disease can also contribute to increased serum uric acid.[74] Diets rich in fatty meats, seafood, and alcohol increase serum uric acid,[75,76] and obesity confers a 3-fold increased risk of hyperuricemia.[77] There are also numerous medications that alter renal clearance of uric acid, even in the presence of normal glomerular filtration rate, including loop and thiazide diuretics,[78] and these may represent an uncommon cause of hyperuricemia. 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.[79]

Serum uric acid levels also correlate with sweetener consumption.[80] Sweetener consumption in the United States has dramatically increased since the introduction of high-fructose corn syrup in the early 1970s.[81] Fructose raises uric acid levels rapidly via activation of the fructokinase pathway in hepatocytes.[82] Fructokinase consumes adenosine triphosphate leading to an increased load of intracellular purines requiring metabolism and disposal through xanthine oxidase-mediated metabolism ending in uric acid.[82] The administration of large quantities of fructose to rats, 60% of their caloric intake, results in hyperuricema, elevated blood pressure, and the development of preglomerular arteriolopathy.[83] Furthermore, lowering uric acid level prevents these changes despite ongoing fructose consumption.[81] The requirement for prodigious fructose intake in rats to raise uric acid levels may be because rats have uricase, an enzyme that metabolizes uric acid to allantoin. Humans, genetically deficient in uricase, may require less fructose consumption to result in hyperuricemia.

Human studies show that fructose loading leads to increased serum uric acid levels acutely, and that chronic increase in fructose consumption leads to chronically increased serum uric acid level and increases in blood pressure.[84] With the nearly universal exposure to sweetened foods and beverages in the pediatric population, it is likely that much of the hyperuricemia, especially that associated with obesity, is dietary rather than genetic in origin.[85] Consistent with this hypothesis, epidemiological studies have shown a relationship of fructose with serum uric acid in most, but not all, studies.[86] One reason some

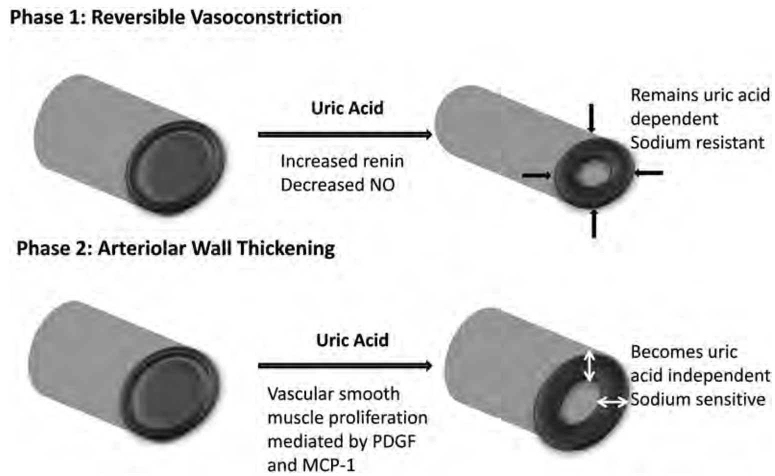

Figure 1. Animal model data suggest that hyperuricemia leads to hypertension in a stepwise fashion. The effects of uric acid on the blood vessel are shown. The first phase is direct, uric acid-dependent activation of the renin–angiotensin system and downregulation of the nitric oxide production, leading to vasoconstriction. At this stage, uric acid reduction results in vascular relaxation and improved blood pressure. The second phase, which develops over time, is uric acid-mediated arteriolosclerosis. Uric acid uptake into vascular smooth muscle cells causing the activation and elaboration of production of growth factors and monocyte chemotattractant protein-1. This results in the autocrine stimulation of vascular smooth muscle cell proliferation, vascular wall thickening, loss of vascular compliance, and a shift in pressure natriuresis. This process is not reversed by the late reduction of uric acid and causes permanent sodium-sensitive hypertension.

studies may be negative could reflect the action of fructose, as it tends to increase uric acid mostly in the postprandial setting and since most studies use fasting uric acid levels, it is possible that an elevation in mean 24-hour uric acid level would be missed.

Jalal and colleagues used the NHANES (2000-2003), which was a survey of healthy adults in the United States, in which direct blood pressure measurement was available, as well as dietary intake of fructose as determined by dietary questionnaire. The major finding was that there was a strong independent relationship of fructose intake with elevated SBP.[86] Interestingly, the relationship was independent of fasting serum uric acid level. In a different study, Nguyen and colleagues also found an independent relationship of sugary soft drinks with hypertension in adolescents.[85] Perez-Pozo and colleagues administered 200 g of fructose per day to healthy overweight males with or without allopurinol for a 2-week period.[87] In this study, an increase in serum uric acid level was observed in association with a significant increase in daytime SBP and both 24-hour and daytime DBP. Allopurinol reduced the serum uric acid and blocked the blood pressure rise. Although the dose of fructose was very high, 25% of the NHANES cohort consumed similar quantities.[86]

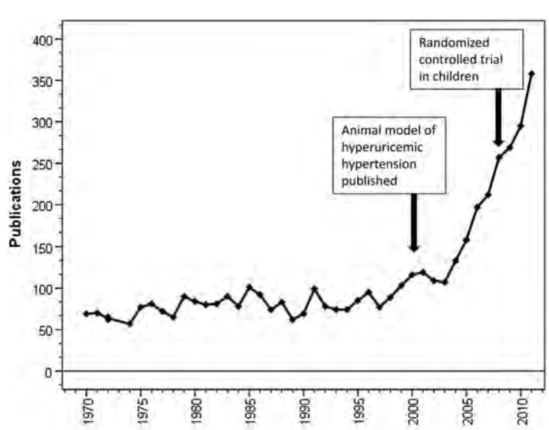

Figure 2. Number of research articles published per year, 1970 to 2011, on the topic of the role of uric acid in hypertension. Articles were identified on PubMed using search terms uric acid, urate, hypertension, cardiovascular disease, fructose, sweetened beverages, xanthine oxidase inhibitors, allopurinol, uricosurics, and probenecid. Reviews were excluded, and abstracts were reviewed for relevance.

Pediatric Clinical Trials

In adolescents, there is a close association between elevated serum uric acid level and the onset of essential hypertension. The Moscow Children's Hypertension Study found hyperuricemia (>8.0 mg/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.[88] 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.[11] These 2 studies do not separate the hypertensive children by underlying diagnosis, essential hypertension versus that caused by renal, cardiac, or endocrinologic causes independent of uric acid, so the relationship between serum uric and hypertension may be attenuated somewhat. In a small study, Gruskin[8] compared adolescents (13-18 years of age) with essential hypertension with age-matched healthy control subjects with normal blood pressures. The hypertensive children had both elevated serum uric acid level (mean, >6.5 mg/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 in children with white coat hypertension was 3.6 ± 0.7 mg/dL, slightly higher in secondary hypertension (4.3 ± 1.4 mg/dL, $P = .008$), and significantly elevated in children with primary hypertension (6.7 ± 1.3 mg/dL, $P = .000004$).[19] There was a tight linear correlation between the serum uric acid levels and the SBPs and DBPs in the population referred for evaluation of hypertension ($r = 0.8$ for SBP and $r = 0.6$ for DBP). Each 1-mg/dL increase in serum uric acid was associated with an average increase of 14 mm Hg in SBP and 7 mm Hg in DBP.[19] Among patients referred for evaluation of hypertension, a serum uric acid level >5.5 mg/dL had an 89% positive predictive value for essential hypertension, whereas a serum uric acid level <5.0 mg/dL had a 96% negative predictive value for essential hypertension.[19]

Results from small pilot studies in children suggest that uric acid may directly contribute to the onset of hypertension in some humans. Five children, aged 14 to 17 years, with newly diagnosed and as yet untreated essential hypertension were treated for 1 month with allopurinol as a solitary pharmacological agent. All 5 children had a decrease in blood pressure by both casual and ambulatory monitoring, and 4 of the 5 were normotensive at the end of 1 month.[89] In a separate study, 30 adolescents with newly diagnosed essential hypertension were treated in a randomized, double-blinded, crossover trial with allopurinol verus placebo. Sixty-seven percent of children while on allopurinol, and 91% of children who have serum uric acid <5.5mg/dL on treatment, had normal blood pressure, compared with 3% of children who were on placebo.[90] Although these observations need to be confirmed in larger and more general population, if serum uric acid is indeed directly causing renal arteriolopathy, altered regulation of natriuresis, and persistent systemic hypertension, it is a modifiable risk factor for CKD in the absence of other mechanisms.

Conclusions

The combination of epidemiological, animal model, and clinical trial supports a causative role for uric acid in some patients with elevated blood pressure. The controversy over its role stems from the lack of a plausible causative mechanism before 2001 and its overlap with other more conventional risk factors such as renal disease, diabetes, and obesity. However, more recent mechanistic studies support uric acid-mediated activation of the renin–angiotensin system, a process with rapid onset that can also be rapidly controlled, followed by a more gradual alteration of renovascular geometry and sodium handling that results in chronic salt-sensitive hypertension. The implications of this paired mechanism are 2-fold. First, it would explain the greater magnitude of effect seen in younger patients, or at least the attenuation of affect in the elderly patients. Second, it may represent a unique opportunity in newly diagnosed hyperuricemic hypertension, in which metabolic control may delay or prevent irreversible vasculopathy and permanent future hypertension.

The best approach to mild to moderate hyperuricemia remains an open question. The currently available medications, especially allopurinol, are associated with significant, even life-threatening, side effects that preclude its safe use in populations as large as those at risk for future hypertension. Furthermore, as there are many classes of readily available antihypertensive medications with more optimal safety profiles, direct management of hypertension is reasonable. The caveat to such an approach is the poor actual control rates in both adult and pediatric hypertension with current conventional approaches that bespeaks the need for novel therapeutics. The link between fructose intake and serum uric acid may also hold important promise; however, although fructose loading clearly leads to increased serum uric acid levels and increased blood pressure in clinical trials, the efficacy of fructose reduction has not been proven. A post-hoc evaluation of the PRIMIER trial, a large trial of the efficacy of non-pharmacologic therapy for hypertension and CV risk mitigation, demonstrated that those subjects with the greatest reduction in sweetener consumption also had the greatest reduction in blood pressure[91]; however, additional research is needed to confirm its efficacy.

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