Serum Uric Acid: A Risk Factor and a Target for Treatment?

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Serum uric acid was first noted to be associated with increased BP by Frederick Mohamed in the 1870s. Although the link was rediscovered periodically over the years, it generally was dismissed as a surrogate marker for decreased renal function that led to increased uric acid and increased risk for hypertension and cardiovascular (CV) disease. Recently, however, several lines of evidence suggest that increased serum uric acid may be a significant modifiable risk factor. Increased serum uric acid is associated with increased risk for future hypertension in several large longitudinal clinical trials as well as an independent risk factor for poor CV prognosis. Animal model experiments demonstrate that increased serum uric acid causes increased BP that initially is reversible but becomes irreversible, salt sensitive, and uric acid independent over time. The mechanisms include the direct action of uric acid on smooth muscle and vascular endothelial cells. Finally, in adolescents with new-onset essential hypertension, the prevalence of elevated serum uric acid is >90%, and preliminary clinical trial evidence suggests that agents that lower serum uric acid may lower BP in this select population. Although the investigations are still preliminary, serum uric acid represents a possible new and intriguing target for the reduction of morbidity and mortality associated with hypertension and CV disease.

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History of Uric Acid and Hypertension

The concept that uric acid may be involved in hypertension is not a new one. In fact, in the paper published in 1879 that originally described essential hypertension, Frederick Akbar Mohamed noted that many of his subjects came from gouty families. He hypothesized that uric acid might be integral to the development of essential hypertension (1). Ten years later, this hypothesis reemerged when Haig (2) proposed low-purine diets as a means to prevent hypertension and vascular disease. In 1909, the French academician Henri Huchard noted that renal arteriolosclerosis (the histologic lesion of hypertension) was observed in three groups: Those with gout, those with lead poisoning, and those who have a diet enriched with fatty meat. All of these groups are associated with hyperuricemia (3).

The association between elevated serum uric acid and hypertension was observed and reported repeatedly in the 1950s to 1980s but received relatively little sustained attention because of the lack of a mechanistic explanation (4–6). Twenty-five to 40% of adult patients with untreated hypertension have hyperuricemia (>6.5 mg/dl), and this number increases dramatically when serum uric acid in the high-normal range is included (7,8). In certain special cases of hypertension, such as cyclosporine-associated hypertension and pre-eclampsia, the correlation between elevated serum uric acid and hypertension is >70% (9). Despite these observations, the lack of a causal mechanism led to mild elevations of serum uric acid being largely ignored in medical practice. Uric acid was removed from routine laboratory panels, such as the serum metabolism and chemistries-20 (SMAC-20), in the early 1980s and is not considered a risk factor for hypertension by either the American Heart Association (10) or the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (11).

Mild Hyperuricemia in the Rat, an Animal Model for Essential Hypertension

The study of mild hyperuricemia required an animal model before the lack of any mechanistic detail that had plagued the hypothesis over 100 yr could be addressed. The biggest challenge comes from the presence of the enzyme urate oxidase in all mammals except humans and the great apes. Consequently, normal serum uric acid levels in potential mammalian systems are in the 0.5- to 1.5-mg/dl range (humans typically have 3.5 to 7.0 mg/dl), and additional uric acid administered in the diet or intravenously is metabolized rapidly to allantoin without altering serum levels. The obvious solution would be a uricase knockout animal; however, such mice develop uric acid nephropathy and die of renal failure before 3 mo of age, limiting their utility for the study of chronic elevations of uric acid.

In the late 1990s, Johnson and colleagues (12) developed a model using a pharmacologic inhibitor of urate oxidase, oxonic acid, that allows the study of sustained mild hyperuricemia. When fed 2% oxonic acid in their standard diet, Sprague-

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Dawley rats have an increase of mean serum uric acid concentrations from 0.5 to 1.4 g/dl to 1.7 to 3.0 mg/dl (12). During a 7-wk treatment period, systolic BP increases an average of 22 mmHg. The increase in BP can be prevented entirely 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 BP. In fact, the increase in BP is linearly related to the rise in uric acid ($r = 0.77$). It is important to note that the change in BP 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 7 wk on a low-salt diet and oxonic acid, if the oxonic acid is removed, then the serum uric acid falls to normal as does the BP over 3 wk; however, if formally hyperuricemic rats then are switched to a high-salt diet, then they become hypertensive (13). In short, mild hyperuricemia leads to an irreversible salt-sensitive hypertension over time.

Histologic evaluation of the renal tissue of the hyperuricemic, hypertensive rats reveals an expansion of the vascular smooth muscle and narrowing of the lumina of the afferent arterioles. This lesion, arteriolosclerosis, is the pathognomonic lesion associated with essential hypertension in humans. It is interesting that the development of arteriolosclerosis can be prevented using allopurinol to control uric acid levels; however, hydrochlorothiazide, which normalizes BP without lowering serum uric acid, does not prevent the development of arteriolosclerosis, indicating that uric acid, not hypertension, is the causative stimulus (14,15).

Several studies have elucidated the mechanisms by which increased serum uric acid leads to hypertension in the rat model. Direct staining of renal tissue for renin reveals that hyperuricemia causes an average of 62% of juxtaglomerular apparatuses to stain positive for renin, in comparison with <40% of controls ($P < 0.05$) (14). Histologic evaluation also reveals a dramatic increase in renal parenchymal infiltration with macrophage, suggesting that hyperuricemia confers a proinflammatory state on the kidneys of effected rats. Analysis of the serum of treated and control rats also reveals a 50% fall in total plasma nitrates during mild hyperuricemia (16,17). Taken together, these experimental results indicate that mild hyperuricemia induces renal inflammation, activation of the renin-angiotensin system, and downregulation of nitric oxide production, all of which are potentially important pathways that lead to uric acid–mediated hypertension.

Recent *in vitro* studies also have elucidated the possible mechanism of uric acid–mediated arteriolosclerosis. Primary human vascular smooth muscle cells (HVSMC) are induced to proliferate by addition of uric acid to the growth medium in a dose-dependent manner (18). The human smooth muscle cells express the urate-transport channel URAT1 as evidenced by both Northern and Western analyses. Consistent with this observation, cultured HVSMC rapidly take up ^{14}C-urate, and blockade of this uptake by probenecid attenuates the uric acid–mediated induction of proliferation in a dose-dependent manner (19). Signaling studies have revealed further the possible mechanism by which urate uptake leads to HVSMC proliferation (13,18,20). This pathway is summarized in Figure 1.

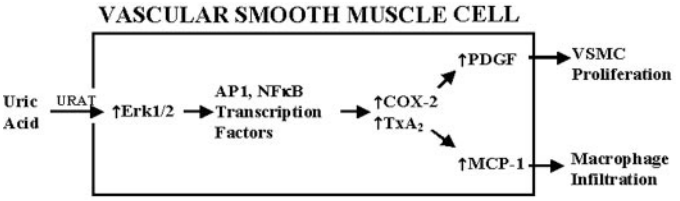

Figure 1. The effect of uric acid on vascular smooth muscle cells (VSMC). Uric acid is taken up through the probenecid-sensitive urate-transport channel URAT1. This leads mitogen-activated protein kinase activation and extracellular signal–regulated kinase 1 and 2 (Erk 1/2) phosphorylation. In turn, transcription factors NF-κB and AP1 are activated leading to increased cyclooxygenase-2 (COX-2) expression and activity. The COX-2 product Thromboxane A_2 mediates increased expression and elaboration of platelet derived growth factor (PDGF) and monocyte chemoattractant protein-1 (MCP-1), which induce VSMC proliferation and macrophage infiltration, respectively (13,18–20).

The Rat Revisited: Uric Acid and Progressive Renal Injury

Uric acid–mediated arteriolopathy and interstitial inflammation suggest mechanisms that would exacerbate or potentiate progressive renal functional decline after injury, also known as renal progression. Our collaborative groups have investigated the effect of uric acid on multiple mechanisms of progressive renal injury. Two representative systems are the remnant kidney model and the model of cyclosporine nephropathy. In the remnant kidney model, rats undergo unilateral nephrectomy and ligation of two of the three main branch renal arteries on the contralateral side. Hyperuricemic remnant kidney rats (caused by addition of 2% oxonic acid to their diets) had higher BP, greater proteinuria, and higher serum creatinine. Their histology revealed a 50% increase in glomerulosclerosis and a 30% increase in interstitial fibrosis compared with rats with remnant kidneys alone (21,22). Similar results were seen in the rat model of cyclosporine nephropathy. Addition of oxonic acid to cyclosporine treatment led to higher uric acid levels, more severe arteriolar hyalinosis, macrophage infiltration, and tubulointerstitial damage compared with rats that were treated with cyclosporine alone (23). Furthermore, treatment of cyclosporine-exposed rats with allopurinol improves GFR (23), and in human liver transplant patients who were receiving cyclosporine, treatment with allopurinol resulted in improved renal function (24).

Recent Epidemiology: A Change in Perspective

In the same period during which reports of animal models of mild hyperuricemia have been published, five new studies that reported that serum uric acid predicts the development of hypertension appeared in the literature. This is a significant departure from previous decades, in which there was considerable skepticism over a potential association between uric acid in high BP. Before 1990, only Khan *et al.* (25) had reported that an increased serum uric acid is an independent risk factor for hypertension; however, it had been noted that 25 to 40% of

adults with hypertension have serum uric acid >6.5 mg/dl and >60% have a serum uric acid >5.5 mg/dl (7,8) and that there was a linear relationship between serum uric acid and systolic BP in both white and black patients (26). Three reports that indicated that serum uric acid is an independent risk factor for hypertension were published in the 1990s (27–29), and five more were published in the past 4 yr (30–34), including two in the first month of 2005 (Table 1). The recent evaluation of a subset of the Framingham Heart Study found that serum uric acid level was an independent predictor of hypertension and BP progression over as little as 4 yr.

Uric Acid and Essential Hypertension in Children

In adolescents, the association between elevated serum uric acid and the onset of essential hypertension is even more striking. The Moscow Children's Hypertension Study found hyperuricemia (>8.0 mg/dl) in 9.5% of children with normal BP, 49% of children with borderline hypertension, and 73% of children with moderate and severe hypertension (35). The Hungarian Children's Health Study followed all 17,624 children who were born in Budapest in 1964 for 13 yr and found that significant risk factors for the development of hypertension were elevated heart rate, early sexual maturity, and hyperuricemia (36). These two studies do not separate the hypertensive children by underlying diagnosis, so the relationship between serum uric acid and hypertension may be skewed by ascertainment bias. In a small study, Gruskin (37) compared adolescents (13 to 18 yr of age) who had essential hypertension with age-matched healthy control subjects who had normal BP. The hypertensive children had both elevated serum uric acid (mean >6.5 mg/dl) and higher peripheral renin activity. In a racially mixed population of patients who were referred for the evaluation of hypertension, Feig and Johnson observed that the mean serum uric acid level (± SD) in control subjects and children with white coat hypertension were nearly identical (3.6 ± 0.8 and 3.6 ± 0.7 mg/dl, respectively; $P = 0.80$) but slightly higher in secondary hypertension (4.3 ± 1.4 mg/dl; $P = 0.008$) and significantly elevated in children with primary hypertension (6.7 ± 1.3 mg/dl; $P = 0.000004$) (38). There was a tight, linear correlation between the serum uric acid levels and the systolic and diastolic BP in patients who were referred for evaluation of hypertension ($r = 0.8$ for systolic BP and $r = 0.6$ for diastolic BP) (38). Among patients who were referred for evaluation of hypertension, a serum uric acid >5.5 mg/dl had an 89% positive predictive value for essential hypertension, whereas a serum uric acid level <5.0 had a negative predictive value for essential hypertension of 96% (38).

Results from a very small, unblinded pilot study in children suggested that uric acid may contribute directly to the onset of hypertension in some humans. Five children, aged 14 to 17 yr of age, with newly diagnosed and as yet untreated essential hypertension were treated for 1 mo with allopurinol as a solitary pharmacologic agent. All five children had a decrease in BP by both casual and ambulatory monitoring, and four of the five were normotensive at the end of 1 mo. All five also had a rebound in their BP after discontinuation of the therapy (39). Because this study was very small and not blinded, a great deal of care should be taken in interpreting or generalizing the results; however, they are intriguing. A blinded, randomized, placebo-controlled, crossover trial is under way and nearing completion and should shed greater light on the utility of uric acid–lowering regimens in the management of new-onset hypertension in children.

Uric Acid as a Potential Target of Therapy

The results from both animal and human studies strongly implicate uric acid as a factor in the onset of essential hypertension in some individuals and as a potential contributor to the progression of renal injury. The animal model data also present a mechanism by which uric acid leads to the renal pathologic changes, afferent arteriolosclerosis, of essential hypertension. If the arteriolosclerosis is irreversible and later hypertension becomes uric acid independent, then this would both explain why xanthine oxidase inhibitors and uricosurics have not previously been noted to be useful antihypertensive

Table 1. Epidemiological studies that suggested that serum uric acid predicts hypertension

Author	Year Published	Study Size	Duration of Follow-Up (yr)	Increased Risk
Kahn *et al.* (25)	1972	10,000 men	5	2-fold
Selby *et al.* (29)	1990	2062 adults	6	3-fold
Hunt *et al.* (28)	1991	1482 adults	7	2-fold
Jossa *et al.* (27)	1994	619 men	12	1.2-fold
Taniguchi *et al.* (30)	2001	6356 men	10	2-fold
Masuo *et al.* (31)	2003	433 men	5	+27 mmHg in systolic BP per each 1-mg/dl change in uric acid
Nakanishi *et al.* (32)	2003	2310 men	6	1.6-fold
Nagahama *et al.* (40)	2004	4489 adults	23	1.5-fold in men 1.9-fold in women
Alper *et al.* (33)	2005	577 children	11	Predicts diastolic hypertension
Sundstrom *et al.* (34)	2005	3119 adults	4	1.5-fold

agents and suggest their potential utility as first-line drugs for primary prevention of essential hypertension in selected populations. It is important, however, to interpret the results judiciously. We do not as yet have conclusive human clinical trial data to prove the utility of uric acid–lowering regimens as antihypertensive agents, hypertension prevention agents, or agents to attenuate progressive renal injury. Until and unless clinical trial data demonstrate these actions, the use of allopurinol or uricosuric agents for all asymptomatic hyperuricemic patients is not yet warranted. As the clinical trials are under way, the recommendations regarding the use clinical use of uric acid–lowering regimens may be modified in the near future.

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References

1. Mohamed FA: On chronic Bright's disease, and its essential symptoms. *Lancet* 1: 399–401, 1879
2. Haig A: On uric acid and arterial tension. *BMJ* 1: 288–291, 1889
3. Huchard H: Arteriolosclerosis: Including its cardiac form. *JAMA* 53: 1129–1132, 1909
4. Gertler MM, Garn SM, Levine SA: Serum uric acid in relation to age and physique in health and in coronary heart disease. *Ann Intern Med* 34: 1421–1431, 1951
5. Breckenridge A: Hypertension and hyperuricaemia. *Lancet* 1: 15–18, 1966
6. Brand FN, McGee DL, Kannel WB, Stokes J 3rd, Castelli WP: Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. *Am J Epidemiol* 121: 11–18, 1985
7. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH: Hyperuricemia in primary and renal hypertension. *N Engl J Med* 275: 457–464, 1966
8. Kinsey D, Walther R, Sise HS, Whitelaw G, Smithwick R: Incidence of hyperuricemia in 400 hypertensive subjects. *Circulation* 24: 972–973, 1961
9. Curtis JJ, Luke RG, Jones P, Diethelm AG: Hypertension in cyclosporine-treated renal transplant recipients is sodium dependent. *Am J Med* 85: 134–138, 1988
10. Pearson T, Blair S, Daniels S, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco RL, Sallis JF Jr, Smith SC Jr, Stone NJ, Taubert KA: AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 106: 388–391, 2002
11. Chobanian A, Bakris G, Black H, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *JAMA* 289: 2560–2572, 2003
12. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 38: 1101–1106, 2001
13. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, Mazzali M, Johnson RJ: Uric acid hominoid evolution and the pathogenesis of salt-sensitivity. *Hypertension* 40: 355–360, 2002
14. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ: Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 282: F991–F997, 2002
15. Johnson RJ, Rodriguez-Iturbe B, Schreiner GF, Herrera-Acosta J: Hypertension: A microvascular and tubulointerstitial disease. *J Hypertens* 20[Suppl 3]: S1–S7, 2002
16. Kang DH, Nakagawa T, Feng L, Johnson RJ: Nitric oxide modulates vascular disease in the remnant kidney model. *Am J Pathol* 161: 239–248, 2002
17. Finch J, Mu W, Parra G, Nakagawa T, Johnson RJ: Hyperuricemia induces endothelial dysfunction in rats [Abstract]. *J Am Soc Nephrol* 14: 143A, 2003
18. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ: A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 13: 2888–2897, 2002
19. Price K, Mu W, Raines E, Nakagawa T, Johnson RJ: Expression of a urate transporter in human vascular smooth muscle cells [Abstract]. *J Am Soc Nephrol* 14: 145A, 2003
20. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L, Johnson RJ: Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 41: 1287–1293, 2003
21. Kang DH, Joly AH, Oh SW, Hugo C, Kerjaschki D, Gordon KL, Mazzali M, Jefferson JA, Hughes J, Madsen KM, Schreiner GF, Johnson RJ: Impaired angiogenesis in the remnant kidney model: I. Potential role of vascular endothelial growth factor and thrombospondin-1. *J Am Soc Nephrol* 12: 1434–1447, 2001
22. Kang DH, Hughes J, Mazzali M, Schreiner GF, Johnson RJ: Impaired angiogenesis in the remnant kidney model: II. Vascular endothelial growth factor administration reduces renal fibrosis and stabilizes renal function. *J Am Soc Nephrol* 12: 1448–1457, 2001
23. Kang DH, Kim YG, Andoh TF, Gordon KL, Suga S, Mazzali M, Jefferson JA, Hughes J, Bennett W, Schreiner GF, Johnson RJ: Post-cyclosporine-mediated hypertension and nephropathy: Amelioration by vascular endothelial growth factor. *Am J Physiol Renal Physiol* 280: F727–F736, 2001
24. Neal D, Tom B, Gimson A, Gibbs P, Alexander GJ: Hyperuricemia, gout and renal function after liver transplantation. *Transplantation* 72: 1689–1691, 2001
25. Kahn HA, Medalie JH, Neufeld HN, Riss E, Goldbourt U: The incidence of hypertension and associated factors: The Israel ischemic heart study. *Am Heart J* 84: 171–182, 1972
26. Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tyroler HA: Serum uric acid. Its relationship to coronary

heart disease risk factors and cardiovascular disease, Evans County, Georgia. *Arch Intern Med* 132: 401–410, 1973
27. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, Mancini M, Trevisan M: Serum uric acid and hypertension: The Olivetti heart study. *J Hum Hypertens* 8: 677–681, 1994
28. Hunt SC, Stephenson SH, Hopkins PN, Williams RR: Predictors of an increased risk of future hypertension in Utah. A screening analysis. *Hypertension* 17: 969–976, 1991
29. Selby JV, Friedman GD, Quesenberry CP Jr: Precursors of essential hypertension: Pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol* 131: 1017–1027, 1990
30. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K: Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men. The Osaka Health Survey. *J Hypertens* 19: 1209–1215, 2001
31. Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML: Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension* 42: 474–480, 2003
32. Nakanishi N, Okamato M, Yoshida H, Matsuo Y, Suzuki K, Tatara K: Serum uric acid and the risk for development of hypertension and impaired fasting glucose or type II diabetes in Japanese male office workers. *Eur J Epidemiol* 18: 523–530, 2003
33. Alper A, Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL: Childhood uric acid predicts adult blood pressure. *Hypertension* 45: 34–38, 2005
34. Sundstrom J, Sullivan L, D'Agostino R, *Levy D, Kannel WB, Vasan RS*: Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence in the Framingham Heart Study. *Hypertension* 45: 28–33, 2005
35. Rovda Iu I, Kazakova LM, Plaksina EA: [Parameters of uric acid metabolism in healthy children and in patients with arterial hypertension]. *Pediatriia* 19–22, 1990
36. Torok E, Gyarfas I, Csukas M: Factors associated with stable high blood pressure in adolescents. *J Hypertens Suppl* 3: S389–S390, 1985
37. Gruskin AB: The adolescent with essential hypertension. *Am J Kidney Dis* 6: 86–90, 1985
38. Feig DI, Johnson RJ: Hyperuricemia in childhood primary hypertension. *Hypertension* 42: 247–252, 2003
39. Feig DI, Nakagawa T, Karumanchi SA, Oliver WJ, Kang DH, Finch J, Johnson RJ: Hypothesis: Uric acid, nephron number and the pathogenesis of essential hypertension. *Kidney Int* 66: 281–287, 2004
40. Nagahama K, Inoue T, Iseki K, Touma T, Kinjo K, Ohya Y, Takashito S: Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan. *Hypertens Res* 27: 835–841, 2004