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Uric Acid and Cardiovascular Risk

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An association of gout with hypertension, diabetes, kidney disease, and cardiovascular disease has been observed since the late 19th century. Early investigators, such as Frederick Mahomed, Alexander Haig, and Nathan Smith Davis, hypothesized that uric acid might be a cause of hypertension or renal disease. In 1897, in his presidential address to the American Medical Association, Dr. Davis wrote, “High arterial tension in gout is due in part to uric acid or other toxic substances in the blood which increase the tonus of the [renal] arterioles.”¹ Since agents that lower uric acid levels were not available earlier in Davis’s career, however, there were no studies indicating that uric acid had a causal role in these conditions.

The association between uric acid and cardiovascular disease was largely ignored until the mid-1950s and early 1960s, when it was rediscovered.^{2,3} Since then, a number of epidemiologic studies have reported a relation between serum uric acid levels and a wide variety of cardiovascular conditions, including hypertension,² metabolic syndrome,⁴ coronary artery disease,⁵ cerebrovascular disease,⁶ vascular dementia,⁷ preeclampsia,⁸ and kidney disease.^{9,10} The relation between uric acid and cardiovascular disease is observed not only with frank hyperuricemia (defined as more than 6 mg per deciliter [360 μ mol per liter] in women and more than 7 mg per deciliter [420 μ mol per liter] in men) but also with uric acid levels considered to be in the normal to high range (>5.2 to 5.5 mg per deciliter [310 to 330 μ mol per liter]).^{11–13}

The relative importance of these associations remains controversial. Some experts, such as the Framingham Heart Study group, have argued that uric acid is not a risk factor for cardiovascular disease and that clinicians should rely only on classic risk factors in patient assessment.¹⁴ Nor have serum uric acid levels been considered a cardiovascular risk factor by major professional societies.^{15,16}

This review summarizes relevant studies concerning uric acid and possible links to hypertension, renal disease, and cardiovascular disease. Although such evidence is mounting, it does not yet support the general treatment of asymptomatic hyperuricemia to reduce cardiovascular risk. However, there would seem to be sufficient evidence to warrant clinical trials to determine whether lowering uric acid levels would be of clinical benefit in the prevention or treatment of cardiovascular and renal diseases.

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Dr. Johnson reports being listed as an inventor on several patent applications related to the role of uric acid in hypertension and the metabolic syndrome and being an author of *The Sugar Fix*, a book for the lay public on fructose and uric acid published by Rodale in 2008. No other potential conflict of interest relevant to this article was reported.

URIC ACID AND CARDIORENAL DISEASE — CAUSE OR CONSEQUENCE?

One difficulty in determining whether uric acid per se should be considered a cardiovascular risk factor is that elevated uric acid levels are often associated with established cardiovascular risk factors (Table 1). For example, uric acid levels are higher in many groups at increased cardiovascular risk, such as postmenopausal women, blacks, and people with hypertension, the metabolic syndrome, or renal disease. The increased risk of cardiovascular disease observed with Westernization of native peoples, immigration to Western countries, and movement from rural to urban communities also correlates with increased uric acid levels.¹⁷ Furthermore, the sharp rise in hypertension, obesity, diabetes, and kidney disease in the United States over the past 100 years has also been associated with a progressive rise in serum uric acid levels.¹⁷ Mean uric acid levels in men increased gradually from less than 3.5 mg per deciliter (210 μmol per liter) in the 1920s to 6.0 to 6.5 mg per deciliter (360 to 390 μmol per liter) in the 1970s.^{18–21} Women tend to have lower levels (by 0.5 to 1.0 mg per deciliter [30 to 60 μmol per liter]) than men, probably because of the uricosuric effect of estrogens.²²

To investigate the role of uric acid in disease, epidemiologists have often used multivariate analyses to assess whether an elevated uric acid level is an independent cardiovascular risk factor. Using this approach, a number of studies have suggested that uric acid is not independent of other established risk factors, especially hypertension, for the development of cardiovascular disease.^{14,23–25} Consequently, some expert groups have argued that studies indicating uric acid is an independent risk factor did not sufficiently control for other known risk factors. Furthermore, if uric acid were a risk factor, then a mechanism by which uric acid could cause cardiovascular disease should be apparent. Others have posited that one of the main functions of uric acid is its role as an antioxidant, which, if anything, would make it beneficial to people with cardiovascular disease.^{26,27} Finally, the elevation of uric acid levels in patients with cardiovascular disease could simply be a result of the common presence of factors such as reduced glomerular filtration rate, hyperinsulinemia, renal vasoconstriction, or diuretic use (all of which reduce net renal excretion of uric acid) or of alcohol use, tissue ischemia, or oxidative stress (which may increase uric acid generation).^{28–30}

A similar argument has been made for the association of elevated uric acid levels with chronic kidney disease. Before drugs that lower uric acid level became available, more than 50% of patients with gout had some renal insufficiency and nearly 100% had renal disease at autopsy.^{31,32} The kidney lesions in patients with gout are characterized by advanced arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis, often with the presence of urate crystals in the outer medulla.³² The presence of such urate deposits gave rise to the name “gouty nephropathy” for this condition. However, the hypothesis that renal injury was caused by the deposition of urate crystals seemed flawed or incomplete, considering that the crystal deposition was focal and thus unlikely to explain the diffuse nature of the disease and that crystals could also be found in normal kidneys in the absence of inflammation. Furthermore, the most characteristic findings, which are advanced arteriolosclerosis and glomerulosclerosis, are indistinguishable from those observed with longstanding hypertension or age-related glomerulosclerosis and may simply reflect the fact that most patients with gout have hypertension and are older.³³ Consequently, for the past 30 years there has been a widespread belief that uric acid is unlikely to be a risk factor for renal disease.³⁴

URIC ACID AND CARDIOVASCULAR DISEASE — A REAPPRAISAL

Several events have led to the ongoing reappraisal of the role of uric acid in cardiovascular disease. Some studies that have controlled for multiple risk factors suggest that uric acid may be an independent risk factor for both cardiovascular disease^{13,35–37} and kidney disease.^{38–40} Other studies have noted that an elevated level of uric acid predicts the development of

hypertension,^{41–56} obesity,⁴⁸ kidney disease,^{38–40} and diabetes.^{51,57} Studies using animal models and cell cultures have identified mechanisms by which uric acid might induce cardiovascular and renal disease,^{58–60} and there have been reports of cardiovascular and renal benefits from lowering uric acid levels in recent preliminary clinical trials.^{9,10,61,62}

Should we accept the assumption that to be defined as “causal,” a factor must be independent of other risk factors? In effect, this assumption has already been challenged by reports that elevated uric acid levels must be both a direct and an indirect cause of renal disease and cardiovascular disease. For example, Yu and colleagues reported that renal disease developed in 40% of patients with gout, but they argued that uric acid was probably not the cause of the disease since hypertension — a much more likely cause of renal disease — also developed in most of these patients.³³ The Framingham Heart Study reported that uric acid was not a causal risk factor for cardiovascular events because uric acid was not independent of hypertension.¹⁴ However, if uric acid caused hypertension, and hypertension caused kidney disease and heart disease, then uric acid might not be independent of hypertension when evaluated as a risk factor for kidney or heart disease.

HYPERURICEMIC HYPERTENSION

Recent experimental and clinical evidence supports the possibility that an elevated uric acid level may lead to hypertension (Table 2). Numerous studies have reported that hyperuricemia carries an increased relative risk for hypertension developing within 5 years, independent of other risk factors (Table 3).^{41–56} Studies of uric acid levels and the development of hypertension have generally been consistent, continuous, and of similar magnitude. Hyperuricemia is also common among adults with prehypertension,⁶³ especially when microalbuminuria is present.⁶⁴ The observation that hyperuricemia precedes the development of hypertension indicates that it is not simply a result of hypertension per se. Only one study showed that uric acid did not predict the development of hypertension, and it involved subjects in whom hypertension had developed after the age of 60 years.⁴³

Hyperuricemia is also more common in primary hypertension than in secondary hypertension, at least in adolescents.¹¹ In one study an elevated uric acid level (>5.5 mg per deciliter [330 μ mol per liter]) was observed in nearly 90% of adolescents with essential hypertension, whereas uric acid levels were significantly lower in controls and teens with either white-coat or secondary hypertension.¹¹ The observation that uric acid levels were not elevated in secondary hypertension also reduces the likelihood that the hyperuricemia results from hypertension. Interestingly, the relationship of uric acid levels to hypertension in people with established hypertension varies. In some studies hyperuricemia is present in 40 to 60% of subjects with untreated hypertension,^{2,65,66} whereas other studies reported lower frequencies.^{2,67} Some of the variability might be due to the inclusion of patients with secondary hypertension in various reports. Furthermore, the strength of the relationship between uric acid level and hypertension decreases with increasing patient age and duration of hypertension,⁶⁸ suggesting that uric acid may be most important in younger subjects with early-onset hypertension.

The development of a model of mild hyperuricemia in animals provided the first direct evidence that uric acid elevation may lead to blood-pressure elevation. In this regard, it is worth noting that humans and apes have higher uric acid levels than most other mammals, since they lack the hepatic enzyme uricase, which degrades uric acid to allantoin. To render rats hyperuricemic (which is necessary in order to use them as an animal model), they are treated with a uricase inhibitor. In this model, several weeks after the uric acid level is increased, hypertension develops. In such animals, blood pressure correlated directly with serum levels of uric acid and decreased when uric acid was reduced with either a xanthine oxidase inhibitor or a uricosuric agent.⁵⁹ In this model, the hypertension was shown to be due to uric acid–mediated renal

vasoconstriction resulting from a reduction in endothelial levels of nitric oxide, with activation of the renin–angiotensin system.^{69–71} Consistent with these observations, elevated uric acid levels in humans also correlate with endothelial dysfunction and increases in plasma renin activity.^{72–75}

Over time, microvascular renal disease — with histology that is similar to arteriosclerosis, the classic lesion of essential hypertension — develops in rats with hyperuricemia.^{70,76} The observation that the microvascular changes still developed, even when blood pressure was controlled by a diuretic, coupled with the demonstration of direct effects of uric acid on endothelial cells and vascular smooth-muscle cells, suggests that uric acid may cause microvascular disease independently of hypertension.^{77,78} For example, in experiments with cultured vascular smooth-muscle cells, uric acid induces cellular proliferation, inflammation, oxidative stress, and activation of the local renin–angiotensin system.^{59,69,77,79,80}

The development of renal microvascular lesions may provide an additional mechanism by which uric acid can cause hypertension. For example, similar microvascular lesions can be induced in rats with normal serum levels of uric acid through the infusion of angiotensin II or blockage of nitric oxide synthesis. Once these lesions are induced, a salt-sensitive hypertension develops and persists even when infusion of angiotensin II is stopped or the blockade of nitric oxide synthesis is reversed.^{81,82} In another study of rats with hyperuricemia, when the uricase inhibitor was stopped after renal microvascular disease and interstitial inflammation had become pronounced, blood pressure would improve only if the rats remained on a low-salt diet.⁷⁶ Both the experimental and human studies provide a possible explanation for how uric acid might cause hypertension in humans (Fig. 1). Furthermore, the experimental studies provide a rationale as to why uric acid would be linked with newly diagnosed or early-onset hypertension, since subjects with longstanding hypertension might already have renal microvascular disease that could be primarily responsible for their current hypertensive condition.

Preliminary clinical trial data also support a role for uric acid in early-onset primary hypertension. After an open-label pilot study in 5 adolescent patients with hypertension, which indicated that allopurinol lowered blood pressure,⁷⁹ a double-blind, placebo-controlled crossover trial was performed in 30 adolescents with hyperuricemia and hypertension.⁶² In this trial, treatment with allopurinol was associated with a significant reduction in both casual (measured at the physician's office) and ambulatory blood pressure, and the reduction was similar in magnitude to that achieved with most antihypertensive agents (-6.9 ± 4.4 mm Hg and -5.1 ± 2.4 mm Hg as compared with -2.0 ± 0.4 and -2.4 ± 0.7 for placebo for casual systolic and diastolic blood pressure, respectively [$P = 0.007$ and $P = 0.03$]).⁶² For patients in whom uric acid levels decreased to less than 5 mg per deciliter ($300 \mu\text{mol}$ per liter) during allopurinol therapy, blood pressure became normal in 86% (19 of 22 patients), as compared with 3% (1 of 30) during the placebo phase of the study.⁶²

There has been a major increase in the prevalence of hypertension worldwide, and there is evidence that uric acid levels are rising as well.^{18–21} Might these two observations be linked?⁸² It is widely believed that the increased prevalence of obesity has contributed to the increased prevalence of hypertension.⁸³ Over the past 200 years there has been a large increase in fructose intake in the developed world, an increase that correlates temporally with increases in hypertension and obesity.^{84,85} Fructose is unique among sugars in that it rapidly causes depletion of ATP and increases both the generation and the release of uric acid.⁸⁶ Experimental data support a link between fructose intake, hyperuricemia, and increases in blood pressure. For example, the development of hyperuricemia, hypertension, and a metabolic-like syndrome with renal hemodynamic and histologic changes very similar to those observed with hyperuricemia has been reported in rats fed with fructose. Treating these rats with xanthine

oxidase inhibitors, including allopurinol or febuxostat, lowered uric acid levels and partially prevented these changes.^{60,87} Epidemiologic studies have also linked fructose intake with increased risk of hyperuricemia^{88,89} and the metabolic syndrome.^{90,91} Furthermore, although some controversy exists as to whether fructose can induce hypertension in rats, the administration of high-fructose diets to humans can induce many features of the metabolic syndrome, including an acute rise in blood pressure.^{92,93} Thus, one might speculate that fructose-induced hyperuricemia could have a role in the increased prevalence of hypertension worldwide.^{60,85} The ingestion of other foods (such as purine-rich fatty meats) or drinks (such as beer) or exposure to toxins (such as lead, in amounts adequate to cause low-level lead poisoning) that alter uric acid levels may also contribute to elevated uric acid levels and a “hyperuricemic” form of hypertension.

In addition to diet, there is evidence that low birth weight increases the risk of hypertension and obesity later in life.⁹⁴ Among the mechanisms by which low birth weight might lead to an increased risk of hypertension is a congenital reduction in nephron number.⁹⁵ Although there is little direct evidence for this hypothesized mechanism in humans, in one report Keller et al. observed that 10 white subjects with essential hypertension who died in traffic accidents had fewer nephrons than 10 age-matched controls who died similarly.⁹⁶ It is known that mothers who give birth to infants with a low birth weight or infants who are small for gestational age frequently have conditions associated with hyperuricemia, such as preeclampsia, essential hypertension, and obesity.⁷⁸ Uric acid transfers freely from maternal to fetal circulation, and high levels of maternal and fetal uric acid correlate with lower birth weight among infants.^{8, 97} Given the antiangiogenic effects of elevations in uric acid,⁷⁷ it is possible to speculate that such elevations could contribute to low birth weight and reduced nephron number, which might predispose a child to the development of hypertension later in life.⁷⁸

If a child’s parent is obese or has hypertension, it is more likely that similar conditions will develop in the child because of genetic or environmental (dietary) traits. In one study, Franco et al. reported that children between 8 and 13 years of age who had been low-birth-weight infants had relatively high uric acid levels and evidence of endothelial dysfunction, though none had hypertension.⁹⁸ Another study reported that children whose parents have a history of hypertension have higher uric acid levels, a higher body-mass index (BMI), and higher levels of triglycerides independent of hypertension.⁹⁹ Both lean and obese children of parents with hypertension have been observed to have a low fractional excretion of uric acid and evidence of higher plasma renin activity and increased proximal sodium reabsorption.¹⁰⁰ We previously reported that adolescents with essential hypertension had relatively high uric acid levels that correlated inversely with their birth weights.¹¹

It is also possible that genetic polymorphisms of transporters or enzymes involved in uric acid metabolism affect blood pressure, especially in younger subjects. For example, hypertension has been associated with polymorphisms of xanthine oxidoreductase.¹⁰¹ Solute carrier family 2, member 9 (SLC2A9) is a newly identified fructose and uric acid transporter in which several genetic polymorphisms have been identified that are associated with an increased risk of gout.^{102,103} Nevertheless, these polymorphisms were not observed to be associated with hypertension.¹⁰² This result may indicate that uric acid is not a direct causal risk factor for hypertension, or it might reflect the fact that polymorphisms in *SLC2A9* account for only a small fraction of the variance in serum uric acid, meaning that it may be difficult to detect an effect.^{102,103}

URIC ACID, THE METABOLIC SYNDROME, AND DIABETES

Increasing evidence suggests that uric acid may play a role in the metabolic syndrome. Historically, the elevated level of uric acid observed in the metabolic syndrome has been

attributed to hyperinsulinemia, since insulin reduces renal excretion of uric acid.³⁰ Hyperuricemia, however, often precedes the development of hyperinsulinemia,^{12,104} obesity,⁴⁸ and diabetes.^{51,57,105} Hyperuricemia may also be present in the metabolic syndrome in people who are not overweight or obese. In one study only 5.9% of subjects with a normal BMI and a uric acid level of less than 6.0 mg per deciliter (360 μ mol per liter) had the metabolic syndrome; in contrast, 59% of subjects with a normal BMI and a uric acid level of more than 10 mg per deciliter (60 μ mol per liter) had evidence of the metabolic syndrome.¹⁰⁶

The strongest evidence of a role for uric acid in the development of the metabolic syndrome has been from studies in animal models showing that decreasing uric acid levels can prevent or reverse features of the metabolic syndrome.^{60,87,107} Two mechanisms have been suggested to explain how hyperuricemia might induce the metabolic syndrome. The first mechanism is related to the fact that glucose uptake in skeletal muscle depends in part on increases in blood flow mediated by the insulin-stimulated release of nitric oxide from endothelial cells. Features of the metabolic syndrome develop in mice lacking endothelial nitric oxide synthase.¹⁰⁸ The observations that hyperuricemia can induce endothelial dysfunction in rats⁶⁹ and that treatment with allopurinol can improve endothelial function in patients with hyperuricemia⁷⁴ would support this mechanism. The second mechanism concerns the inflammatory and oxidative changes uric acid induces in adipocytes,¹⁰⁹ a process that is key in causing the metabolic syndrome in obese mice.¹¹⁰ In addition, xanthine oxidoreductase (the enzyme that generates uric acid from xanthine) is expressed in adipocytes and is critical to the process of adipogenesis; indeed, xanthine oxidoreductase knockout mice have only half the adipocyte mass of their control littermates.¹¹¹

URIC ACID AND CHRONIC KIDNEY DISEASE

Both experimental and clinical studies suggest the possibility that an elevated level of uric acid itself can lead to kidney disease without the deposition of uric acid crystals.^{58,59} Experimental studies in rats have shown that raising uric acid levels can cause de novo kidney disease as well as accelerate existing kidney disease.^{58,59} The principal lesions from increased uric acid in the rat are glomerulosclerosis, interstitial fibrosis, and arteriolar disease, conditions similar to those observed in “gouty” nephropathy, except for the absence of intrarenal urate crystals.^{58,59} The mechanism of injury appears to be related to the development of preglomerular arteriolar disease that impairs the renal autoregulatory response and thereby causes glomerular hypertension.¹¹² Similar histologic findings are also present in the hereditary human disease familial juvenile hyperuricemic nephropathy.

More recent epidemiologic studies also suggest that uric acid may have a role in causing renal disease. For example, an elevated uric acid level is an independent predictor of the development of both microalbuminuria⁶⁴ and renal dysfunction in subjects with normal renal function^{38–40} and is associated with an impaired glomerular filtration rate in patients with type 1 diabetes who do not have proteinuria.¹¹³ In contrast, the uric acid level does not predict the renal progression of established chronic kidney disease,¹¹⁴ suggesting that in established disease structural (and nonreversible) microvascular and glomerular lesions have already developed and are driving disease progression independently of uric acid levels.^{71,76}

Recent studies suggest that lowering levels of uric acid may slow progression of renal disease, especially in patients with hyperuricemia. Siu et al. reported that the treatment of asymptomatic hyperuricemia in patients with mild renal disease (chronic kidney disease at stage 3) resulted in delayed disease progression.⁹ Likewise, Kanbay et al. recently reported that treatment of asymptomatic hyperuricemia improved renal function.⁶¹ Talaat et al. used a different approach in which they withdrew allopurinol from a group of patients with chronic kidney disease who were in stable condition. This withdrawal resulted in worsening of hypertension and

acceleration of kidney dysfunction in the patients who were not taking angiotensin-converting-enzyme inhibitors.¹⁰

OTHER CARDIOVASCULAR DISEASES ASSOCIATED WITH HYPERURICEMIA

Hyperuricemia is strongly associated with peripheral, carotid, and coronary vascular disease, with the development of stroke, with preeclampsia, and with vascular dementia.^{7,14,23–25,115} The relationship of uric acid with cardiovascular events is particularly strong, especially in patients at high risk for heart disease and in women.¹¹⁶ Some of the cardiovascular benefits of losartan reported in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study¹¹⁷ and for atorvastatin reported in the Greek Atorvastatin and Coronary-Heart-Disease Evaluation (GREACE) study¹¹⁸ have also been attributed to the ability of these drugs to lower uric acid levels. Whether uric acid has a causal relationship in these conditions remains to be determined.

CAVEATS AND FUTURE DIRECTIONS

There are several important limitations and caveats related to the recent studies we have cited in considering a causal role for uric acid in cardiovascular disease. First, most of the clinical trials we referenced are small and examined highly defined populations. For example, it is not known whether lowering uric acid levels with allopurinol will be effective in people with more severe or longstanding hypertension as compared with those in the preliminary studies cited. Nor do we know whether the beneficial effect of allopurinol observed in completed and preliminary human studies is due to the reduction of uric acid or to a reduction in xanthine oxidase-associated oxidants. Although the experimental studies suggest that the benefit results from lowering uric acid,^{70,77,79,80,119,120} the improvement of endothelial function observed in patients with hyperuricemia and heart failure or diabetes occurred among patients who received allopurinol but not among those receiving other drugs designed to lower uric acid levels.^{121,122} One possible explanation for this result is that xanthine oxidase inhibitors are more effective than other agents in lowering intracellular levels of uric acid, and consequently had a greater influence on intracellular regulation of endothelial vascular activity.⁷⁷ Alternatively, uric acid may be more of a marker, and the benefit of allopurinol may be the result of its ability to block xanthine oxidase-associated oxidants.

We also need a better understanding of the biologic functions of uric acid as they may relate to cardiovascular disease. Although uric acid may have proinflammatory effects on vascular cells and adipocytes, it can also function as an antioxidant.^{26,123,124} It has been suggested that the antioxidant effects of uric acid are protective in several neurologic diseases, including multiple sclerosis and Parkinson's disease. Conversely, uric acid can also function as a pro-oxidant, either by generating radicals during its degradation or by stimulating NADPH oxidase.^{109,125} Uric acid can also stimulate innate immunity through the effects of microcrystalline uric acid on the function of dendritic cells and T cells.^{126,127} Studies by our group and others also suggest a role for T cells in the pathogenesis of salt-sensitive hypertension.^{128,129} Thus, it remains possible that uric acid may have a variety of as yet incompletely defined actions in cardiovascular disease.

Right now there are not sufficient data to recommend the treatment of asymptomatic hyperuricemia. Allopurinol is not a benign drug, and may occasionally precipitate a hypersensitivity syndrome that can be fatal. The data reviewed in this article are the basis for a hypothesis that still needs to be tested.

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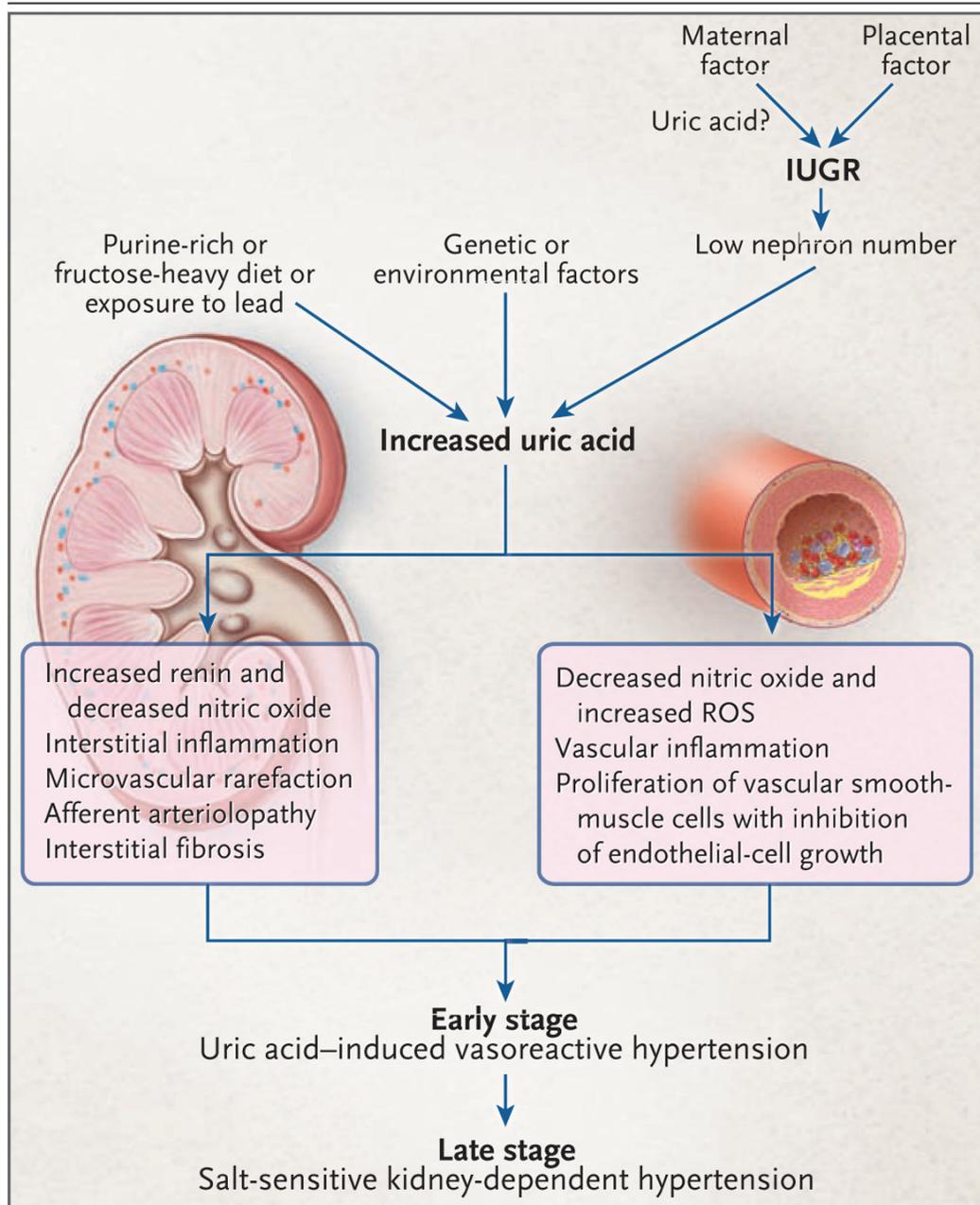


Figure 1. Proposed Mechanism for Uric Acid–Mediated Hypertension

Excessive intake of fructose or purine-rich meats or exposure to low doses of lead may result in chronic hyperuricemia. Mothers with high uric acid levels that are the result of diet or conditions such as preexisting hypertension, obesity, or preeclampsia may transfer uric acid into the fetal circulation through the placenta, which may ultimately contribute to intrauterine growth retardation (IUGR) and a reduction in nephron number. Among babies born with a low nephron number, hyperuricemia may develop in childhood because of genetic or environmental factors. Chronic hyperuricemia would stimulate the renin–angiotensin system and inhibit release of endothelial nitric oxide, contributing to renal vasoconstriction and possibly increasing blood pressure. Persistent renal vasoconstriction may contribute to arteriosclerosis

and the development of salt-sensitive hypertension, even if the hyperuricemia is corrected. ROS denotes reactive oxygen species.

Table 1
Cardiovascular Conditions and Risk Factors Associated with Elevated Uric Acid.

Hypertension and prehypertension
Renal disease (including reduced glomerular filtration rate and microalbuminuria)
Metabolic syndrome (including abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein cholesterol, insulin resistance, impaired glucose tolerance, elevated leptin level)
Obstructive sleep apnea
Vascular disease (carotid, peripheral, coronary artery)
Stroke and vascular dementia
Preeclampsia
Inflammation markers (C-reactive protein, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule type 1)
Endothelial dysfunction
Oxidative stress
Sex and race (postmenopausal women, blacks)
Demographic (movement from rural to urban communities, Westernization, immigration to Western cultures)

Table 2
Evidence Linking Uric Acid and Hypertension.

An elevated uric acid level consistently predicts the development of hypertension.

An elevated uric acid level is observed in 25–60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.

Raising the uric acid level in rodents results in hypertension with the clinical, hemodynamic, and histologic characteristics of hypertension.

Reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset.

Table 3
Hyperuricemia and the Development of Hypertension.*

Study	No. of Patients	Relative Risk of Hypertension	95% CI
Kaiser Permanente, 1990 ⁵³	2062 adults	2.1 times greater at 6 yr (high vs. low quintile)	1.20–3.98
University of Utah, 1991 ⁴⁴	1482 adults	1.44 times greater per SD increment at 7 yr	1.03–2.01
Olivetti Heart, 1994 ⁴⁶	619 men	1.23 times greater per 1 mg/dl increase at 12 yr	1.07–1.39
CARDIA, 1999 ⁴²	5115 men	1.21 times greater per SD increment at 10 yr	1.03–1.41
Osaka Health Survey, 2001 ⁵⁶	6356 men	2 times greater at 10 yr (high vs. low quintile)	1.56–2.60
Hawaii–Los Angeles–Hiroshima, 2001 ⁴⁵	140 men	2.0 times greater at 15 yr (high vs. low quartile)	1.02–3.9
Osaka Factory, 2003 ⁴⁸	433 men	1.0 mg/dl, increased 27 mm Hg SBP at 5 yr	Not calculated
Osaka Health Survey, 2003 ⁵¹	2310 men	1.13 times greater per SD increment at 6 yr	1.06–1.21
Okinawa, 2004 ⁵⁰	4489 adults	1.46 times greater for men (uric acid ≥ 7 mg/dl) and 1.94 for women (uric acid ≥ 6 mg/dl) at 13yr	1.09–2.03 1.05–3.57
Bogalusa Heart, 2005 ⁴¹	679 children	Increased risk for diastolic hypertension at 11 yr	Not calculated
Framingham Heart, 2005 ⁵⁵	3329 adults	1.17 times greater per SD increment at 4 yr	1.02–1.33
Normative Aging, 2006 ⁵²	2062 men	125 times greater at 21 yr (uric acid >6.5 mg/dl)	1.08–1.34
ARIC, 2006 ⁴⁹	9104 adults	1.1 times greater per SD increment at 9 yr	1.02–1.14
Beaver Dam Health Survey, 2006 ⁵⁴	2520 adults	1.65 times greater at 10 yr (high vs. low quintile)	1.41–1.93
Health Professionals' Follow-up, 2006 ⁴³	750 men	1.02 times greater per SD increment at 8 yr	0.92–1.13
MRFIT, 2007 ⁴⁷	3073 men	1.1 times greater per SD increment at 6 yr	1.02–1.19

* To convert the values for uric acid to micromoles per liter, multiply by 59.48. ARIC denotes Atherosclerosis Risk in Communities, CARDIA Coronary Artery Risk Development in (Young) Adults, MRFIT Multiple Risk Factors Intervention Trial, and SBP systolic blood pressure.