# Uric Acid and Hypertension: An Update With Recommendations

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The association between increased serum urate and hypertension has been a subject of intense controversy. Extracellular uric acid drives uric acid deposition in gout, kidney stones, and possibly vascular calcification. Mendelian randomization studies, however, indicate that serum urate is likely not the causal factor in hypertension although it does increase the risk for sudden cardiac death and diabetic vascular disease. Nevertheless, experimental evidence strongly suggests that an increase in *intracellular* urate is a key factor in the pathogenesis of primary hypertension. Pilot clinical trials show beneficial effect of lowering serum urate in hyperuricemic individuals who are young, hypertensive, and have preserved kidney function. Some evidence suggest that activation of the renin–angiotensin system (RAS) occurs in hyperuricemia and blocking the RAS may mimic the effects of xanthine oxidase inhibitors. A reduction in intracellular urate may be achieved by lowering serum urate concentration or by suppressing intracellular urate production with dietary measures that include reducing sugar, fructose, and salt intake. We suggest that these elements in the western diet may play a major role in the pathogenesis of primary hypertension. Studies are necessary to better define the interrelation between uric acid concentrations inside and outside the cell. In addition, large-scale clinical trials are needed to determine if extracellular and intracellular urate reduction can provide benefit hypertension and cardiometabolic disease.

*Keywords:* blood pressure, fructose, hypertension, renin–angiotensin system, uric acid, xanthine oxidase.

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In the 1870s, a young medical student by the name of Frederick Akbar Mahomed took on a research project at Guy's Hospital with the goal of measuring blood pressure. The sphygmograph had been recently invented by the French physiologist, Etienne-Jules Marey, but it was wieldy and not quantitative, so Mahomed constructed a lighter weight model that provided actual measurements. Using the machine, he confirmed the association of kidney disease (as noted by proteinuria) with high blood pressure, but he also noted that subjects could have high blood pressure in the absence of kidney disease, which turned out to be the first description of primary hypertension. He then noted that this latter condition was frequently associated with elevated serum urate, and he postulated that uric acid might have a causal role in the condition.[1]

Since Mahomed's initial discovery, there have been thousands of articles that have evaluated the relationship of uric acid and hypertension with no clear consensus of the role of uric acid in this condition.[2,3] In this review, we will summarize the current evidence for a causal role for the association of uric acid with hypertension, and discuss the major controversies in the literature.

## URIC ACID BIOLOGY

Uric acid is an end product of purine metabolism (Figure 1). Uric acid can be generated from amino acid precursors or from purines provided in the diet. Indeed, one source of foods that stimulates uric acid production are those that solicit the umami taste,[4] which include glutamate-rich foods (i.e., glutamate is metabolized to uric acid in the liver) and purine-rich foods, especially those that contain inosine monophosphate (IMP), adenosine monophosphate (AMP), or uric acid itself. Uric acid can also be generated

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from the breakdown of DNA and RNA (such as occurs with tumor lysis syndrome) or from the breakdown of ATP (such as occurs with fructose metabolism or alcohol). We have recently shown that high salt diets and high glycemic diets can induce the expression of aldose reductase that leads to increased fructose generation and metabolism in the liver, resulting in an increase in intracellular uric acid production.[5,6] Ischemia can also activate the transcription factor HIF1 alpha and NFAT5 that can induce aldose reductase and xanthine oxidase with the production of both endogenous fructose and uric acid generation.[7] Similarly, heat stress and dehydration act through similar pathways to generate uric acid.[8]

Uric acid is both metabolized and excreted. In the remote past, our human ancestors metabolized most of the uric acid we produced with the enzyme uricase (also known as urate oxidase), generating 5-hydroxyisourate and eventually allantoin. However, uricase was fully mutated, resulting in it being nonfunctional in humans today.[9] Nevertheless, uric acid can still be metabolized as it can react with oxidants, lipid radicals, with peroxynitrite to generate triuret, and with nitric oxide to make 6-aminouracil.[10,11] These products are normally minimally generated but are overproduced in those people who smoke, have preeclampsia, or who have chronic kidney disease (CKD) or diabetes.[10,12,13]

Uric acid is excreted by the kidneys (two-thirds) and the gut (one-third). For the kidney, the normal fractional excretion is about 10% but it can increase as eGFR falls and this may increase the risk for crystallization in the setting of low urine pH. The primary drivers of urate reabsorption are the transporters URAT1 and Glut9, while ABCG2 pumps uric acid into the urine. However, in the gut, SLC2A9 and ABCG2 are important in secreting uric acid into the gut lumen where it is degraded by bacteria.

Genetics also play a role in uric acid metabolism, and recent GWAS studies have identified over 180 genes that influence serum uric acid levels, accounting for nearly 8% of the variance in serum urate levels.[14] Genetic polymorphisms in SLC2A9 account for the majority of this variance.[14] Most evidence supports diet and/or obesity as having the primary role in the rise in serum urate over the last century,[15] but genetics may be playing a dominant role in the mild differences observed in those subjects on a stable western diet.[16]

## URIC ACID AND HYPERTENSION: EXPERIMENTAL STUDIES

Since rats and mice, unlike humans, produce urate oxidase, the development of a hyperuricemic model has generally involved inhibiting or knocking down mouse or rat uricase. The mouse knockout model develops exuberant hyperuricemia and kidney disease, but studies have shown that they also develop modest metabolic abnormalities in insulin secretion (in male mice) with the development of hypertension and lipid abnormalities (in female mice).[17] The more common model of hyperuricemia is performed by inhibiting rat uricase with oxonic acid as these rats develop modest hypertension that is prevented by a variety of agents that lower serum urate, as well as by inhibitors of the renin–angiotensin system (RAS), agents that block oxidative stress, or compounds that increase endothelial nitric oxide production.[18–21] While initially the hypertension is fully reversible by uric acid lowering agents, as kidney disease develops (as noted by the development of an arteriolopathy and interstitial inflammation), the hypertension becomes salt-sensitive and uric acid-independent.[22] These observations are consistent with recent studies that suggest hypertension may

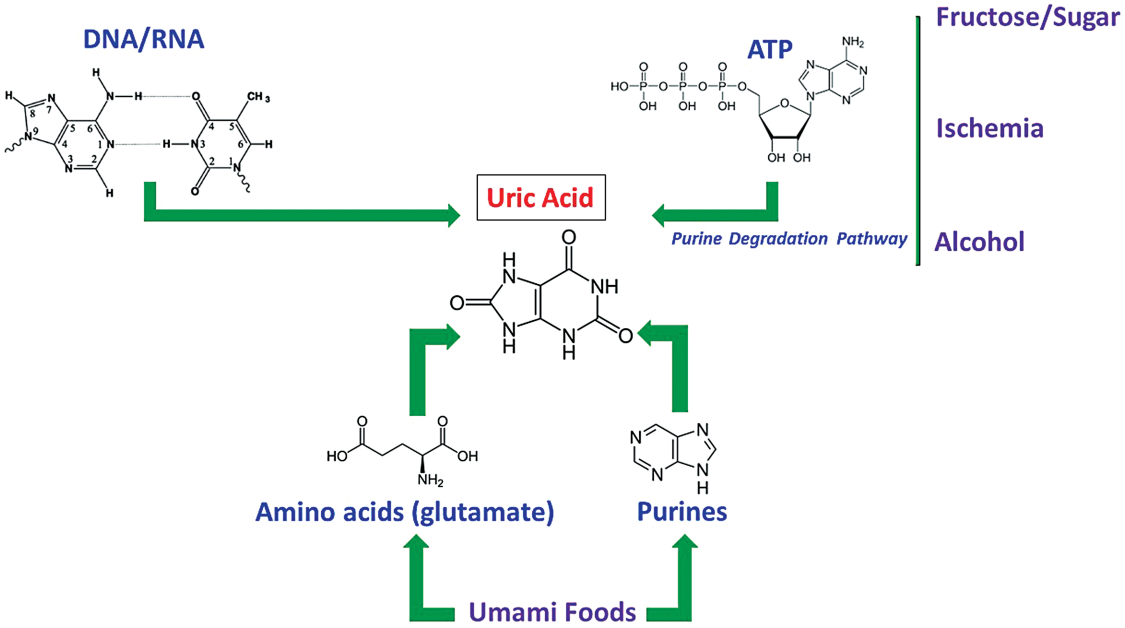


**Figure 1.** Generation of uric acid, a purine endproduct. Uric acid can be generated from precursors, primarily umami-based foods, as well as from ATP degradation, such as occurs with fructose-based sugars, ischemia, and alcohol, or from cell turnover and injury with release of RNA and DNA. The endogenous production of fructose can occur from high glycemic and high salt diets that activate aldose reductase.

initially result from the generation of kidney vasoconstriction, ischemia, and oxidative stress which are followed by the activation of immune mechanisms cause a persistent inflammation in target organs that drive the increase in blood pressure (BP).[23,24] A pathway showing the proposed mechanism of uric acid-induced hypertension is shown in Figure 2.

The cellular mechanisms driving the hypertensive response involve either intracellular production of uric acid (*via* xanthine oxidase) or uptake of urate into the target cell, followed by the induction of mitogen activated protein kinases (such as p38) and a burst of oxidative stress mediated by NADPH oxidase. This is associated with oxidative stress in the mitochondria, resulting in the inhibition of aconitase and enoyl CoA hydratase, as well as activation of stress pathways involved in inflammation and immune activation (NFKB, chemokines, inflammasomes, heat shock proteins), cell proliferation (PDGF), and vasoconstriction pro(renin) and intracellular angiotensin system, endothelin, thromboxanes.[25–34] While the response varies, inflammatory effects of soluble uric acid have been demonstrated in many cell types, including monocytes, vascular endothelial and smooth muscle cells, kidney tubular cells, hepatocytes, adipocytes, and pancreatic islet cells. Cellular pathways of inflammation are shown in Figure 3.

## URIC ACID AND HYPERTENSION: EPIDEMIOLOGICAL STUDIES

Hyperuricemia is common in people who present with primary hypertension, and tends to be especially common in those with accelerated (or malignant) hypertension.[35] Some of the hyperuricemia might represent coexistent CKD or the use of thiazide diuretics that increase serum uric acid levels. However, hyperuricemia can be present in individuals in the absence of these findings. In children, the cutoff for an elevated serum urate is in the 5.2 to 5.5 mg/dl range, and children and adolescents presenting with new onset hypertension often have serum urate levels above this cutoff.[36–38] Similarly, in pregnancy, serum urate usually falls to less than 4 mg/dl, but many patients presenting with hypertension or preeclampsia tend to have serum urate levels >4 mg/dl.[39] In hypertensive individuals who have hyperuricemia, there is also an increased frequency to be hypertensive during sleep (nondipping type)[40,41] and serum urate tends to correlated better with central BP than pulsatile pressure.[42] People with hyperuricemia and hypertension also tend to have elevated plasma renin activity.[43,44] Another aspect of uric acid and BP is that the relationship tends to be linear between the 3 and 10 mg/dl range.[45,46] Sugary beverages containing fructose also increase serum urate and are associated with hypertension.[47] Indeed intake of fructose-containing sweetened beverages is dose-dependently associated with incident hypertension, although this association was not found when other food sources containing fructose were analyzed.[48] The discrepancy may relate to the fact that fructose contained in fluids is absorbed more rapidly in the gut, resulting in greater concentrations in the portal circulation and liver, in comparison with solid foods in which fructose is absorbed more slowly due to presence of fiber and other foods.[49]

Hyperuricemia is also a potent independent predictor of hypertension, with an approximately two-fold increased risk within 5–10 years.[50–52] The risk is less evident in the elderly or who have pre-existent kidney disease.

Hyperuricemia also is a potent independent predictor of incident CKD, of metabolic syndrome and its various components, and of nonalcoholic fatty liver disease.[53–55] Thus, these studies support the hypothesis that hyperuricemia might predict the development of hypertension.

## URIC ACID AND HYPERTENSION: MENDELIAN RANDOMIZATION STUDIES

Genome wide association studies (GWAS) have been used to identify genetic polymorphisms that control serum urate levels, allowing the development of a genetic scoring system to evaluate the risk for hypertension in large population studies. In an approach called Mendelian randomization, the genetic risk scores for hyperuricemia have been found to predict the risk for gout, but failed to predict the development of hypertension, CKD, and cardiometabolic diseases.[56–58] Results in studies that have linked genetic scores for hyperuricemia with hypertension and metabolic diseases are thought to be due to pleiotropy, in which the genetic polymorphisms influence both serum urate and cardiometabolic disease through common pathways.[14,59,60] However, this interpretation is linked with similar assumptions as multivariable analysis that assume variables are independent and not causally linked *via* bidirectional or multidirectional pathways.[61] Only two Mendelian Randomization studies found the genetic score to be associated with cardiovascular disease (sudden cardiac death)[62] and diabetic vascular disease.[63] However,

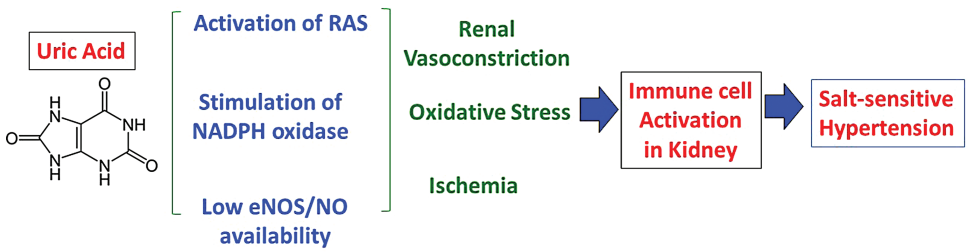


**Figure 2.** Potential mechanism of uric acid induced hypertension. Uric acid induces oxidative stress, a decrease in endothelial nitric oxide availability, and activation of both plasma renin activity and intrakidney angiotensin activity, leading to kidney vasoconstriction, ischemia, and oxidative stress in the kidney. This triggers activation of the immune system that causes persistent kidney vasoconstriction and salt-sensitive hypertension.

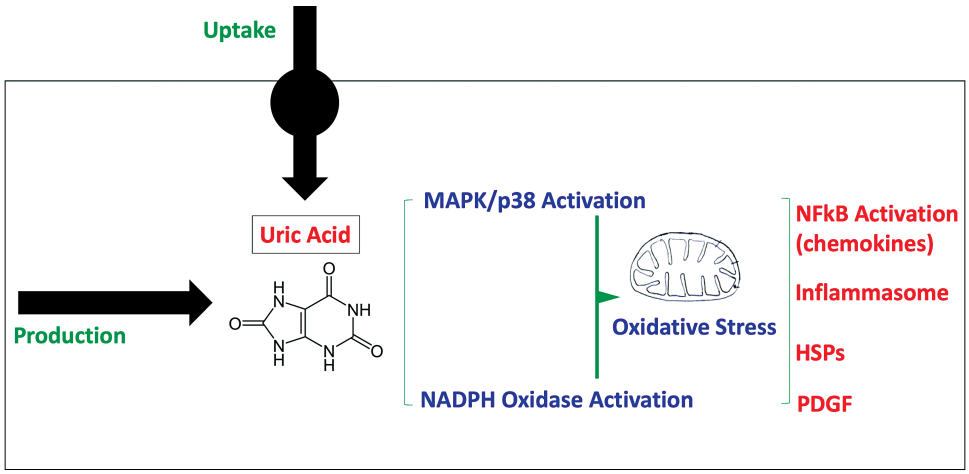


**Figure 3.** Intracellular mechanisms of uric acid induced inflammation. Uric acid can be produced inside the cell by activation of xanthine oxidoreductase or by uptake *via* specific urate transporters. Once uric acid levels increase, there is activation of both mitogen activated protein kinases (MAPK) as well as stimulation of NADPH oxidase that triggers mitochondrial and cytoplasmic oxidative stress. This is associated with activation of inflammatory pathways (including NFκB activation, inflammasome activation, release of growth factors and heat shock proteins) as well as a down regulation of energy production by the mitochondria with a shift toward glycolysis.

smaller studies have linked polymorphisms with increased risk for obesity, hypertension, and CKD.[64–67]

Mendelian randomization studies provide strong evidence that serum urate is not causal in cardiometabolic disease, but one must remember that it is the intracellular uric acid that has the biological effects while extracellular uric acid is thought to be involved primarily as a risk factor for gout. Indeed, most of the genetic score is based on polymorphisms that affect urate transport as opposed to uric acid generation, but it is not known how these transporters regulate intracellular urate. It is known that the polymorphisms in the major transporter (SLC2A9) affecting the genetic score have widely different effects depending on where it is knocked out, with it causing hyperuricemia without hypertension in the liver specific knockout, hyperuricemia with hypertension in the intestinal knockout, and hypouricemia if it is the systemic knockout.[68–70] Likewise, our group has found that high salt diets induce intracellular fructose metabolism and intracellular hepatic urate generation with a rise in BP and development of metabolic syndrome but without the development of hyperuricemia,[6] thus showing how even diet can have opposing effects on intracellular vs. serum urate. It is therefore of interest that polymorphisms in xanthine oxidase that drives urate production have been reported to predict the development of hypertension.[71–74]

## CLINICAL TRIALS OF LOWERING URIC ACID IN HYPERTENSION

To date there have been only a few studies with small numbers of subjects that have investigated whether uric acid lowering therapy can reduce BP in hypertension associated with hyperuricemia (Table 1).

### Hypertension in children and adolescents

The strongest data have been observed in hyperuricemic children with primary hypertension. In an 8-week, double blind, placebo-controlled crossover study, allopurinol was found to reduce both clinic and ambulatory BP in adolescents with newly diagnosed hypertension compared with controls, and this was associated with a significant reduction in systemic vascular resistance with a fall in plasma renin activity.[43] In those subjects who achieved serum urate levels at the goal of <5.0 mg/dl, allopurinol normalized the BP of 19 of 22 subjects while placebo treatment resulted in normal BP in only one of 30 subjects. In a second parallel study in obese prehypertensive subjects, both allopurinol and probenecid also showed a significant fall in systemic BP in prohypertensive obese adolescents. An added benefit was that the lowering of uric acid was associated with a decrease in weight (1 kg) in the allopurinol group while the placebo group gained 2 kg over the 8-week study period.[75] A third study showed that the benefit of allopurinol in adolescents with primary hypertension was additive to the effects of an ACE inhibitor.[76] These studies suggest that xanthine oxidase inhibitors might be a useful therapy in childhood-onset hypertension.

### Hypertension in adults in the absence of kidney disease

A randomized trial of 120 subjects randomized to febuxostat or placebo in adults with hyperuricemia and hypertension reported that the lowering of serum urate in the hypertensive general population did not lower ambulatory BP in the overall analysis. However, there was a significant reduction in BP in the prespecified group with normal kidney function.[77] In this trial, approximately 40% of subjects were on blockers of the RAS.[77] In another study of older (mean age 68 years) subjects with a recent transient ischemic attack or stroke, a randomized trial comparing allopurinol to placebo showed a greater fall in BP in the allopurinol group along with less progression of carotid intimal thickness at 12 months.[78] In a 3-year study of type 2 diabetic subjects with hyperuricemia and normal kidney function, the use

**Table 1.** Brief summary of clinical trials of lowering BP in hypertension

| Subjects | Agent | Effects | Reference |
|---|---|---|---|
| Children and adolescent with hypertension | AP | A reduction in BP, plasma renin activity and systemic vascular resistance | 43 |
| Prehypertensive obese adolescents | AP | A reduction in BP and body weight | 75 |
| Adolescent with primary hypertension | AP (with ACEi) | A reduction in BP<br>(further reduction with ACEi) | 76 |
| Hypertensive adults | Fx | Fail to lower BP except in those with normal kidney function<br>(40% subject were on RAS inhibitor) | 77 |
| Older subjects with recent ischemic attack or stroke | AP | A reduction in BP<br>Less progression of carotid intimal thickness | 78 |
| Type 2 diabetic with normal renal function | AP | Improvement in blood pressure, kidney function, insulin resistance, and inflammation | 79 |
| Prehypertensive with mild hyperuricemia | AP | Dipping pattern of BP were observed | 80 |
| Gouty patients | Pegloticase | A reduction in BP | 81 |
| Normotensive subjects | | Minor reduction in systolic BP in subject with asymptomatic hyperuricemia | 82,83,84 |
| Normotensive subjects with anti-hypertensive agents | XO inhibitor | No effect on BP<br>A reduction in plasma renin activity and plasma aldosterone in hyperuricemic subjects | 85,86 |
| Hypertensive and CKD patients | Febuxostat | A reduction in BP | 87 |
| CKD subjects | Removing AP | BP and renal function got worse in subjects who were not on RAS inhibitors. | 88 |
| Volunteers on low fructose diet | AP | A reduction in BP and serum UA | 89 |
| Overweight | Low fructose diet (with AP) | A reduction in BP<br>(BP was further reduced with AP) | 80 |

of allopurinol was associated with an improvement in BP as well as kidney function, insulin resistance (HOMA-IR), and inflammation (hs-CRP levels).[79] Another placebo-controlled study reported that allopurinol could lower ambulatory systolic BP in prehypertensive subjects with modest elevations in serum urate (mean serum urate 6–6.2 mg/dl) over 4 weeks compared with placebo, and this was associated with an increase in a dipping pattern of BP and greater weight loss.[80] A post hoc analysis of a study in subjects with gout also reported an improvement in BP in subjects receiving pegloticase every 2 weeks who were responders (meaning their serum urates fell significantly in response to treatment) compared with the controls. Importantly, in these hyperuricemic subjects serum urate levels tended to fall to less than 3 mg/dl.[81]

Uric acid lowering therapy has also been given to individuals whose BP was in the normal range, either because they were normotensive or because they were receiving anti-hypertensive agents. The lowering of serum urate does not appear to significantly lower BP in normouricemic subjects with normal BP, nor is there an effect on plasma renin activity,[83] while minor reductions in systolic BP were observed in subjects with asymptomatic hyperuricemia and normal BP.[82,84] Likewise, hypertensive subjects with normal blood pressures on anti-hypertensive treatment also do not show further improvement in BP with xanthine oxidase inhibition,[85,86] although in the study in which mean serum urate values were in the hyperuricemic range, some reduction in plasma renin activity and plasma aldosterone was observed.[86] These studies suggest that xanthine oxidase inhibitors are unlikely to lower BP in normotensive subjects, especially if the individuals are not hyperuricemic.

### Hypertension in the setting of kidney disease

Several studies that have evaluated the effect of lowering serum urate on BP in subjects with CKD have not noted any significant BP lowering effect compared with controls.[91–93] One study of subjects with stage 2 and stage 3 CKD did note a greater change in systolic BP in the febuxostat group (−13 mm Hg) compared with the control group (−4 mm Hg) although differences in final absolute BP did not reach significance.[87] On the basis of the experimental studies, the reason may relate to immune mechanisms becoming dominant in driving BP in subjects with kidney disease, and also because inhibitors of the RAS are commonly used in subjects with kidney disease and may mimic some of the effects of xanthine oxidase inhibitors. Indeed, Talaat and el-Sheikh[88] performed an interesting study in which subjects with CKD who were on allopurinol were taken off allopurinol for 12 months to determine if it had any effect on BP. The striking finding was a marked increase in systolic and diastolic BP with a worsening of kidney function in the subjects with CKD who were not on RAS blockade, whereas those who were on ACE inhibitors or angiotensin receptor blockers (ARBs) remained stable. Furthermore, Shi *et al.*[90] performed a randomized clinical trial in subjects with IgA nephropathy in which use of RAS inhibitors was not allowed, and in this study a significant decrease in BP occurred in the

subjects given allopurinol who were not on antihypertensive agents along with a reduction in anti-hyperpertensive agents in those who were on medication, whereas no effect on BP was observed in the control group.

### The effect of modulating uric acid levels by diet or direct infusion of uric acid

Soluble uric acid has also been administered intravenously to humans, but despite raising serum urate by more than 2 mg/dl, acute changes in BP were not found.[94] Similarly, clinical trials in which inosine has been given orally to subjects with multiple sclerosis or Parkinson's disease have not observed an effect of raising serum uric acid on BP.[95,96] In contrast, when intracellular urate is increased, such as by fructose,[97] a hypertensive response can be observed.[98] Perez-Pozo *et al*. performed a trial in which 200 g of fructose was given daily for 2 weeks to with or without allopurinol. The group receiving fructose alone had a marked rise in serum urate as well as a rise in clinic BP that were both prevented in the group receiving allopurinol.[89] Madero *et al*. conducted a pilot study with overweight subjects in which a low fructose diet or isocaloric control diet was given for 4 weeks. The low fructose group showed a reduction in BP that was further decreased when the subjects were additionally treated with allopurinol for 4 weeks.[80] These studies suggest that intracellular urate may be more important in the BP response that simply raising serum urate.

### Special settings

Lead intoxication is known to cause saturnine gout and to be associated with hyperuricemia, hypertension, and kidney disease.[99] It is not known if the hypertension associated with lead poisoning in humans is amenable to urate lowering therapy, although in experimental animals the hypertension is uric acid-dependent.[100] In addition, some of the cardiovascular benefits of SGLT2 inhibitors[101] and of losartan (an ARB)[102] may relate to their ability to also lower serum urate.

## ADDITIONAL BENEFITS

Some studies suggest additional benefits of lowering serum urate, including possible beneficial effects on insulin resistance and HbA1c values, on weight gain, and on kidney function.[75,79,103,104] Some studies also suggest the benefit on cardiovascular and kidney outcomes is best observed if the treatment using a xanthine oxidase inhibitor is maintained for 3 years or more.[79,103,105] Currently, there is a large placebo-controlled study evaluating whether allopurinol use provides additional cardiovascular benefit in subjects with preexisting ischemic heart disease (the ALL-HEART study).[106]

## SAFETY CONCERNS

Currently, all uric acid-lowering therapies have potential toxicities. For example, allopurinol can result in a hypersensitivity syndrome similar to a Stevens–Johnson reaction, and this is observed almost exclusively in individuals who carry the HLA-B*58 genotype, especially Chinese Han people (3–7%), followed by African Americans (3%) and Caucasians (0.5%). We recommend genotyping Asian individuals before initiating allopurinol in this group. Febuxostat does not appear to carry this risk. However, a secondary endpoint analysis in the Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Morbidities (CARES) Study reported that in subjects at cardiovascular risk, febuxostat carried greater risk for cardiovascular mortality than allopurinol.[107] In particular, febuxostat was associated with a higher risk for sudden cardiac death than allopurinol (2.7% vs. 1.8%). This has led to an FDA black box warning on the use of febuxostat in subjects at cardiovascular risk, which characterizes many subjects with hyperuricemia. However, this study was associated with an excessively high dropout (57%) rate, and an analysis of the cardiovascular mortality documented that many of the events occurred when febuxostat or allopurinol were stopped, with an 18-fold increased rate in the first 30 days following withdrawal.[108] This suggests that the withdrawal of xanthine oxidase inhibitors might be associated with a rebound effect. One possibility is that chronic inhibition of xanthine oxidase might lead to increased xanthine oxidase expression that leads to an exuberant response when the inhibitors are withdrawn. Based on the study by Talaat and el-Sheikh,[88] this might relate to enhanced stimulation of the RAS, and argues for placing an individual on an ACE inhibitor or ARB if a xanthine oxidase inhibitor is stopped in a subject at cardiovascular risk.

Other uric acid lowering therapies may also carry some risk. For example, uricosuric agents (especially if given alone) can result in uric acid kidney stones or rarely acute kidney injury, possibly related to the effects of high urinary urate levels with or without crystal formation.[109] In contrast, recombinant uricase (such as rasburicase or pegylated uricase) can be associated with allergic reactions resulting from an immune response to the uricase peptides that can rarely result in anaphylaxis and may also impair efficacy.[110]

## EVOLUTIONARY CONSIDERATIONS

The mutation of uricase in the *Homo* lineage occurred during a period when our ancestors were starving and close to extinction in Europe, and may have occurred as a survival mechanism to maintain BP and enhance fat stores.[111] Recent studies suggest that there is a primary survival pathway used by many species that is mediated by either dietary or endogenously produced fructose. This pathway is initiated by a drop in cellular energy associated with the stepwise degradation of ATP and the generation of uric acid that leads to a reduction in mitochondrial metabolism with an increased stimulation of glycolysis.[112] Studies suggest that the uricase mutation, which approximately doubled serum uric acid from 1–2 to 3–4 mg/dl, acted to amplify this pathway as a survival mechanism at a time when food (and especially fructose) was scarce.[9]

A trade-off of the uricase mutation was the reduced ability to control serum and intracellular urate levels, and in the setting of high fructose, and umami-rich high purine foods led

to hyperuricemia with its risk for extracellular urate deposition (gout and kidney stones) and high intracellular urate levels (increasing the risk for obesity, diabetes, and hypertension). Indeed, while intracellular urate may drive some of kidney hemodynamic effects (glomerular hypertension and systemic vascular resistance),[27,113] the necessity for kidney excretion increases the risk for urate crystalluria and acute kidney injury, especially in the setting of heat stress, dehydration, diabetes, or increased purine load.[114–116] This may be why certain polymorphisms that lower serum urate by increasing urate excretion can be associated with increased risk for CKD.[117]

It has also been suggested that the uricase mutation increased extracellular anti-oxidant activity due to the ability of uric acid to scavenge peroxynitrite (to form triuret) and to react with singlet oxygen ($^1O_2$), lipid-derived radicals and ferric iron (urate-$Fe^{3+}$-urate).[118,119] In the latter reaction, uric acid serves to diminish the oxidizing potential of $Fe^{3+}$ and thus may reduce overall oxidant burden. While the reaction with $1O_2$ and lipid radicals does appear protective, uric acid generates oxygen-free radicals when it binds to peroxynitrite[120] or participates in myeloperoxidase (MPO)-based reactions.[121] The antioxidant activity of uric acid has been proposed to provide neural protection, and that in conditions, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease, the presence of a low serum urate may increase risk for the disease and/or its progression. However, recent studies suggest that uric acid levels are high in the sera and cerebral spinal fluid of subjects with multiple sclerosis and reflect mitochondrial dysfunction[122,123] and is consistent with the lack of beneficial effect observed with inosine therapy to raise uric acid in this disorder.[124] Likewise, while serum urate levels were originally reported to be low in Alzheimer's disease, this may reflect the effect of chronic disability to impair adequate food intake, and meta-analyses suggest no difference in serum uric acid in this condition.[125] Indeed, in Alzheimer's disease there may be evidence for intracerebral activation of fructose metabolism resulting in cerebral insulin resistance and mitochondrial dysfunction, with potential toxic effects of intracerebral urate.[126–129] Only in Parkinson's disease is there any evidence that low serum urate may confer risk and that orally administered inosine may provide benefit by raising serum urate, at least in women.[130]

Likewise, countervailing associations between uric acid and stroke have been realized where hyperuricemia is reported to be predictive of an ischemic event as well as poorer outcomes[131,132] whereas intravenous administration of uric acid post stroke (with and/or without TPA) appears to afford benefit.[131,133] A potential explanation for protective effects of uric acid in stroke may be its antioxidant capacity as described above; however, the fact that UA, itself, is an xanthine oxidase (XO) inhibitor may also play a role. For example, XO inhibition by UA has been shown in human plasma ($IC_{50}$ = 300 μM)[134,135] well-within the physiologic range and thus, this product-based inhibition may produce salutary actions in an ischemic and subsequently reperfused setting where XO has been reported to be a major source of oxidant generation. In summary, the role assumed by uric acid in these disease processes may be determined not only by its concentration, but importantly by its abundance in the circulation vs. its presence in the intracellular compartment.

## SUMMARY

The role of uric acid in the pathogenesis of human disease depends on whether the increase in urate concentration is inside the cell, where it may have a role in hypertension and metabolic disease, or outside the cell, where it causes extracellular urate depositions diseases, such as gout and nephrolithiasis. The observation that genetic scores for serum urate predict sudden cardiac death[62] and diabetic vascular disease[63] may relate to the ability of extracellular urate to deposit in plaque and to form crystalline deposits in coronary and other major blood vessels where it may also act as a nidus for calcification.[136] Indeed, the observation for increased sudden cardiovascular death following withdrawal of xanthine oxidase inhibitors[108] may relate to the rapid rebound of serum urate with its potential for crystallization at sites of plaque similar to a gout attack or possibly a surge in plasma renin activity. High serum uric acid may also predispose to increased urinary excretion that can be exacerbated with purine loads or fructose intake[114] which could lead to kidney injury especially in the setting of dehydration or heat stress. Intracellular urate will also be more likely elevated when serum urate is elevated, due to the ability of urate to enter into cells *via* specific transporters.[137] Thus, extracellular uric acid may also carry cardiometabolic risk, despite intracellular urate having the dominant role. Dissociation of intracellular and extracellular levels is possible, and increased intracellular urate production may be driven by either polymorphisms in urate transporters or by diet (fructose, glutamate and purine rich foods, high glycemic carbohydrates and high salt diets). The complex relationship between extracellular and intracellular urate concentration is central in the interpretation of the controversies raised by apparently contrasting studies on the pathogenic role of uric acid levels in primary hypertension.

## FINAL RECOMMENDATIONS

We believe that young Frederick Mahomed was correct when he suggested in the 1870s that uric acid might have a contributory and causal role in primary hypertension.[1] We suspect that the rise in hypertension over the last century largely reflects the rise in sugar and salt intake and other components of the western diet that can influence intracellular urate levels. Reducing sugar, fructose, and salt intake,[80,138–140] and increasing water intake to suppress vasopressin[141] have emerged as potential strategies that deserve further investigation. The mechanisms and strategies for decreasing intracellular urate require further study. At this time, specific recommendations cannot be given, but it is reasonable to initiate urate lowering therapy in subjects with hyperuricemia and hypertension provided the patient is aware of the associated safety risks of using the various therapies. In the event that the xanthine oxidase inhibitor are to be discontinued, awareness of the rebound of serum urate

levels is needed and we suggest slowly weaning the dose while maintaining the individuals on RAS blockers.

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## DISCLOSURE

R.J.J. has equity with XORTX Therapeutics which is a startup company generating novel xanthine oxidase inhibitors. R.J.J., M.A.L., and L.G.S. are also members of Colorado Research Partners LLC that is developing novel inhibitors of fructose metabolism. P.B. has acted as a consultant for Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi, Novo Nordisk, and Horizon Pharma. P.B. serves on the advisory board of XORTX and Boehringer Ingelheim. All support was outside the submitted work. All other authors have indicated they have no relationships relevant to this article to disclose.

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