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Hyperuricemia, Acute and Chronic Kidney Disease, Hypertension, and Cardiovascular Disease: Report of a Scientific Workshop Organized by the National Kidney Foundation

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Abstract

Urate is a cause of gout, kidney stones, and acute kidney injury from tumor lysis syndrome, but its relationship to kidney disease, cardiovascular disease, and diabetes remains controversial. A scientific workshop organized by the National Kidney Foundation was held in September 2016 to review current evidence. Cell culture studies and animal models suggest that elevated serum urate concentrations can contribute to kidney disease, hypertension, and metabolic syndrome. Epidemiologic evidence also supports elevated serum urate concentrations as a risk factor for the development of kidney disease, hypertension, and diabetes, but differences in methodologies and inpacts on serum urate concentrations by even subtle changes in kidney function render conclusions uncertain. Mendelian randomization studies generally do not support a causal role of serum urate in kidney disease, hypertension, or diabetes, although interpretation is complicated by nonhomogeneous populations, a failure to consider environmental interactions, and a lack of understanding of how the genetic polymorphisms affect biological mechanisms related to urate. Although several small clinical trials suggest benefits of urate-lowering therapies on kidney function, blood pressure, and insulin resistance, others have been negative, with many trials having design limitations and insufficient power. Thus, whether uric acid has a causal role in kidney and cardiovascular diseases requires further study.

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Introduction

The association of serum urate with kidney, cardiovascular (CVD), and metabolic disease has been described since the 19th century, but whether urate metabolism has a role in these diseases is controversial. Experimental and clinical evidence were presented at a Scientific Workshop held by the National Kidney Foundation in September 2016. We present a meeting summary and discuss current controversies.

Serum Urate Regulation

Urate is the end product of nucleic acid metabolism and is also generated during the breakdown of high-energy nucleotides (eg, adenosine triphosphate [ATP]). It is generated intracellularly by xanthine oxidoreductase (XOR) and transported into and exists in the circulation as plasma sodium urate. Intracellular urate concentration likely varies, but may be orders of magnitude lower than it is in serum.[1]

In most mammals, serum urate concentrations are low (1–3 mg/dL [60–180 μM]) due to the enzyme uricase, which degrades uric acid to 5-hydroxyisourate and allantoin. Humans and apes lack uricase due to inactivating mutations that occurred during hominoid evolution,[2,3] resulting in higher circulating urate concentrations. The lower range of urate concentrations, described in people consuming traditional non-Western diets, is 2 to 4 mg/dL (120–240 μM).[4] Serum urate concentrations are higher in industrialized populations (3–8 mg/dL [180–480 μM]), reflecting diets richer in purines and fructose (both of which generate urate), greater alcohol intake, increased prevalence of factors that reduce kidney urate excretion (eg, insulin resistance, renal vasoconstriction associated with hypertension, and decreased kidney function),[4] and interpopulation genetic differences.[5]

In humans, serum urate is excreted by the kidney (two-thirds) and gut (one-third). Some circulating urate is also removed by reaction with oxidants or nitric oxide. Urate production by XOR contributes to serum concentrations,[6] but the molecular physiology of epithelial urate transport is most relevant to the genetics of hyper- and hypouricemia.[7]

Kidney Urate Excretion

Urate is freely filtered at the glomerulus, followed by reabsorption and secretion in the proximal tubule. However, reabsorption is dominant, resulting in fractional urate excretion ≤ 10% (Fig 1).

Urate reabsorption in the proximal tubule occurs by urate/monocarboxylate exchange (Fig 1A). Organic monocarboxylate reabsorption by the apical sodium/monocarboxylate cotransporters SMCT1 and SMCT2[8,9] results in higher intracellular concentrations of anions that exchange with luminal urate by means of urate-anion exchangers (Fig 1A). Higher concentrations of SMCT substrates (including nicotinate, pyrazinoate, lactate, and ketones) in the circulation can lead to hyperuricemia[10–13] arising from elevated apical uptake of these filtered anions, greater intracellular concentrations in proximal tubular cells, and increased apical urate/anion exchange.[14] In humans, URAT1 is the main apical urate/anion exchanger.[15] The “orphan” organic anion transporter known variously as ORCTL3 or OAT10 also

mediates urate/nicotinate and urate/pyrazinoate exchange.[16] Human OAT4 reportedly functions as an apical urate/anion exchanger[17]; however, unlike OAT10 and URAT1, OAT4 exchanges urate with divalent organic anions. At the basolateral membrane, GLUT9 (glucose transporter 9) is the sole pathway for urate exit during urate reabsorption. Initially identified as a fructose transporter,[18] GLUT9 functions instead as a urate uniporter.[19]

A separate set of transporters function in urate secretion (Fig 1B). At the basolateral membrane, OAT1 and OAT3 transport urate into proximal tubular cells.[20] This basolateral uptake is driven by intracellular concentration of divalent anions that exchange with urate by means of OAT1 and OAT3. Uptake of these anions is mediated by the sodium-dependent dicarboxylate transporter NaDC3 (Fig 1B). Efflux at the apical membrane is mediated by the ATP-driven pumps MRP4 (multidrug resistance protein 4)[21] and ABCG2.[22,23] There are also electrogenic apical urate transporters (NPT1[24,25] and NPT4[26]) that function in secretion.

Gut Urate Excretion

Urate is also transported in the gut, where as much as one-third can be degraded by uricolytic bacteria. Mechanisms for urate transport in the gut are uncertain, but both GLUT9 and ABCG2 transport urate into the gut, and knockout of intestinal GLUT9 can cause hyperuricemia.[27] Knockout of ABCG2 results in hyperuricemia and “overload” uricosuria.[28]

Definition of Hyperuricemia

Hyperuricemia is defined as serum urate concentrations > 7 mg/dL (>420 μM) in men and >6 mg/dL (>360 μM) in women. For children and adolescents, a concentration ≥ 5.5 mg/dL (≥330 μM) is considered abnormal.[29] Serum urate concentrations are lower in premenopausal women due to the uricosuric effects of estrogen, and following menopause, urate increases to concentrations similar to those observed in men. The concentration of 7 mg/dL (420 μM) is viewed as abnormal because it nearly matches the solubility of urate in water; however, urate is more soluble in plasma and concentrations may be >10 mg/dL (>600 μM) without crystal deposition.

In gout, hyperuricemia results from both dietary purine excess[30] and reduced urinary urate excretion. In the steady state, urinary excretion reflects the rate of production; notably, the fractional excretion of urate can increase rapidly in response to a purine load.[30]

Biological Actions of Urate

Antioxidant Effects

Urate can function as an antioxidant, especially in the extracellular environment.[31] Urate reacts with superoxide to generate allantoin and with peroxynitrite to form triuret. These effects may be important in neurologic disease, in which acute administration of urate reduces neurologic injury in models of ischemic stroke[32] or multiple sclerosis.[33] In contrast, the reaction of urate with peroxynitrite generates aminocarbonyl and triuretcarbonyl radicals,[34] and the reaction with myeloperoxidase generates the pro-oxidant urate hydroperoxide.[35]

Immune Effects

Urate may aid the immune response by release from dying cells, facilitating recognition of apoptotic cells by dendritic cells and activation of CD8 cells.[36,37]

Proinflammatory Effects

Although urate is an extracellular antioxidant, intracellular urate functions as a pro-oxidant, stimulating reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[38–41] The effects of exogenous urate on cells can be prevented if cellular uptake of urate is prevented by probenecid (an organic anion transport inhibitor). Likewise, biological effects of endogenously produced urate can be prevented by blocking its synthesis with XOR inhibitors (XORIs).[39,42]

Urate exerts autocrine, paracrine, and endocrine effects. High intracellular urate concentrations stimulate mitogen activated protein kinases, proinflammatory transcription factors (nuclear factor κB [NF-κB]), growth factors, vasoconstrictive substances (angiotensin II, thromboxane, and endothelin), chemokines, and mitochondrial dysfunction.[39,43–45] Urate also reduces endothelial nitric oxide bioavailability by a variety of mechanisms and inhibits endothelial cell proliferation and migration.[44,46–48] High urate concentrations induce proximal tubular dysfunction with release of inflammatory chemokines, vascular cell muscle proliferation, fat synthesis in hepatocytes, oxidative stress in islet cells, and decreased adiponectin synthesis in adipocytes.[39,49–53]

Models of Hypertension and Kidney Injury

The classic model of hyperuricemia in the rat involves administering a uricase inhibitor (oxonic acid) to double or triple serum urate concentration. Hyperuricemic rats develop modest hypertension mediated by activation of renal and systemic renin-angiotensin-aldosterone systems (RAAS), oxidative stress, and loss of endothelial nitric oxide.[54–57] Over time, microvascular and inflammatory changes in the kidney drive hypertension independent of serum urate concentrations.[58] Afferent arteriolar disease also results in impaired renal autoregulation with glomerular hypertension while simultaneously reducing renal blood flow.[59] These effects can both cause chronic kidney disease (CKD)[60] and accelerate existing CKD[43] with histologic and renal hemodynamic features similar to those observed in persons with longstanding gout and/or hypertension.[61] Experimental studies also confirmed a role of urate in animal models of diabetic kidney disease, calcineurin inhibitor nephrotoxicity, and acute kidney injury (AKI) (Table 1).[43,54,55,59,62–64,66–76]

Although many effects of urate appear to be mediated by its intracellular action, kidney injury in humans can occur with hyperuricosuria, especially in the setting of urate crystalluria and acidic urinary pH. Soluble urate and urate crystals activate inflammasomes, causing local inflammation and tubular injury.[77,78] Hyperuricosuria and/or hyperuricemia may also play a role in AKI (eg, rhabdomyolysis and radiocontrast administration).[74,79,80] Figure 2 summarizes mechanisms by which urate induces kidney damage through crystal-independent and crystal-dependent mechanisms. Figure 3 shows a possible mechanism for urate-induced hypertension.

Fructose and Metabolic Syndrome

Fructose is distinct from most energy sources in its ability to induce features of metabolic syndrome.[81] Experimental studies suggest that this occurs secondary to a decrease in ATP concentrations during fructose metabolism that leads to intracellular urate generation, mitochondrial oxidative stress, and inhibition of adenosine monophosphate (AMP)-activated protein kinase.[39,52,82,83] Urate also stimulates aldose reductase (which can lead to more fructose generation) and fructokinase (which amplifies the pathway).[53,84] Reducing serum and intracellular urate concentrations has been found to block features of metabolic syndrome in fructose-dependent and -independent models.[85,86] The side effects of thiazides to induce features of metabolic syndrome could also be prevented by lowering serum urate concentrations with allopurinol.[87]

The observation that knocking down the urate transporter GLUT9 in the intestine causes hyperuricemia and metabolic syndrome that can be ameliorated by XORIs further supports a role for uric acid in the causality of metabolic syndrome.[27] In contrast, with hepatic knockout of GLUT9, hyperuricemia develops without hypertension or metabolic syndrome.[88]

An Evolutionary Perspective

The observation that parallel inactivating mutations occurred in uricase during the Oligocene and Miocene epochs in the ancestors of humans and great apes and also in lesser apes suggests a survival advantage to higher serum urate concentrations.[2,3] Various hypotheses have been proposed, including the possibility that urate may have carried a survival advantage as an antioxidant[31] or as a means to help increase blood pressure (BP) during a period when salt intake was low[58] or to help store fat during a time of global cooling when fruit was less available.[89] Viewed in this context, the uricase mutation may have functioned as a “thrifty gene,” being protective during periods of starvation in the past, but harmful with ample access to food.

Epidemiology

Epidemiologic Studies

Many studies have evaluated whether serum urate is independently associated with CKD, hypertension, and metabolic syndrome/type 2 diabetes.[90,91] Many studies are limited by disparate covariate adjustment strategies and exposure and outcome definitions, which introduce uncertainty when attempting to integrate evidence. Nevertheless, longitudinal studies have shown that elevated serum urate concentration is independently associated with hypertension in 22 of 23 published studies, including 2 meta-analyses.[92–94] The relation of serum urate with the development of hypertension meets Bradford Hill criteria for a likely causal relation (Box 1).[29,54,62,95–97]

In 23 of 24 published studies, including meta-analyses,[98–100] higher serum urate concentrations are independently associated with metabolic syndrome and type 2 diabetes in men, women, or both and may also be independently associated with obesity.[101] Serum urate concentration was reported to independently predict incident CKD in 17 of 18 published

studies and in meta-analyses in people with and without diabetes.[102–107] However, serum urate is not consistently associated with progression of CKD in patients with pre-existing CKD (reviewed in[108]). Hyperuricemia also predicts AKI following surgery or radiocontrast exposure.[79,109]

In contrast, serum urate concentration is not consistently associated with CVD,[110–112] likely reflecting complex causal linkages among potential risk factors used in multivariable analysis.[113] Nevertheless, one study found hyperuricemia to be associated with hypertension, obesity, and CKD in Japanese adults who at baseline did not have elevated Quételet (body mass) index, had normal BP, and had normal glucose tolerance.[114]

A major problem with these epidemiologic studies is that serum urate concentrations are affected by kidney function, and the relationship may be subject to confounding by other factors.[113,115,116] A confounder is associated with both the exposure and the outcome, but does not constitute the causal pathway between exposure and outcome. Epidemiologic studies attempt to account for confounding through multivariable adjustment and other strategies; however, if there is residual confounding, the association between serum urate and CKD may be significant even in the absence of causality.[113] For example, if the true risk factor for CKD were oxidative stress (which is not directly measured) rather than hyperuricemia, the presence of hyperuricemia as a proxy for oxidative stress could lead to the incorrect conclusion that hyperuricemia causes CKD. Box 2 summarizes factors affecting the association of urate with outcomes in observational studies and clinical trials.

Mendelian Randomization Studies

Genome-wide association studies (GWAS) have identified approximately 30 loci controlling serum urate.[117,118] The loci with the strongest effects encode uric acid transporters (eg, GLUT9, ABCG2, and URAT1)[117,118] or regulatory transporter-associated proteins (eg, PDZK1).[117,119] In general, loss-of-function mutations in reabsorptive urate transporters cause hypouricemia,[15,117,120–123] whereas loss-of-function mutations in secretory transporters result in hyperuricemia.[23,26,28] Other loci with weaker effects encode genes involved in glycolysis, consistent with a role for hepatic metabolism in urate homeostasis. However, for most loci, causal genes and causal variants have not been identified. Predictably, many of the urate-controlling loci are associated with gout.[117,124,125]

The identification of genetic polymorphisms that influence serum urate concentrations has allowed investigation of whether these polymorphisms also increase the risk for hypertension or kidney disease. Specifically, large populations in which GWAS have been performed can be used to develop a “genetic score” to identify individuals with genetic predisposition to hyperuricemia and gout (as evidence for validation), CKD, hypertension, and type 2 diabetes. Because persons with urate-raising and urate-lowering genetic variants have been exposed to these variants since conception and provided that genetic variants are not themselves associated with confounders or do not exhibit pleiotropic effects, these Mendelian randomization studies can mitigate confounding.[126]

Using this approach, many adequately powered studies have been unable to find associations between a genetic urate score with hypertension,[117,127] type 2 diabetes,[127–129] or the

development of CKD,[127,130,131] arguing against a causal role of urate in these disease states. However, the absence of associations in these studies does not conclusively dismiss causality. First, intracellular urate drives its metabolic and vascular effects (rather than extracellular concentrations or crystal deposition), and polymorphisms that affect serum urate may not have the same effect on intracellular and hepatic urate.[27,88,132] Second, environment and/or diet can influence the effects that genetic polymorphisms exert on urate disposition.[133,134] Third, most published studies focus on polymorphisms involved in renal urate handling without considering alternative pathways. For example, genetic polymorphisms of XOR have been linked with CVD.[135,136] Finally, the inability to show an association does not mean that lowering serum urate concentrations may not have beneficial effects on hypertension or CKD; inhibitors of the renin-angiotensin system (RAAS), for example, are beneficial in the management of hypertension and CKD despite GWAS failing to identify genetic polymorphisms of the RAAS associated with hypertension and CKD.

Other Mendelian randomization studies have identified associations of genetic polymorphisms that influence serum urate concentrations with hypertension, obesity, metabolic syndrome, CVD, or CKD.[137–143] These studies differ from others because they either focus on more homogeneous populations, such as Italian[144,145] or Native American populations,[139,146] or assess interactions of the genetic score with potential confounders, such as body mass index[147] or asymmetric dimethylarginine concentrations.[138]

GWAS Loci Predicting Both CKD and Serum Urate Concentration

A GWAS has identified approximately 50 loci associated with estimated glomerular filtration rate (eGFR) and CKD.[148] Of these, 9 are also associated with serum urate concentrations (Table 2), none of which encode urate transporters. Interestingly, patterns are the same for most shared loci, suggesting that (as yet unidentified) genetic variants associated with serum urate and kidney function are likely to be the same. However, there is inconsistency in the direction of effect, with the serum urate–increasing allele associated with better kidney function in some cases and worse kidney function in others. These data suggest that shared pathologic mechanism(s) between effectors of kidney function and determination of hyperuricemia further complicating interpretation.

Clinical Trials

Hypertension

Studies of the role of urate in hypertension have largely focused on children and adolescents, reflecting experimental studies showing that hyperuricemia has its greatest effect on BP early in life, before kidney microvascular and inflammatory changes occur.[55,58] Adolescents with primary hypertension have elevated serum urate concentrations (>5.5 mg/dL) in nearly 90% of cases, correlating directly with systolic BP (SBP).[29] A small pilot study reported that lowering serum urate concentration to <5.0 mg/dL (<300 μM) normalized BP in 86% of patients compared to 3% during the placebo phase.[96] A double-blind randomized study in which obese prehypertensive adolescents were given placebo, probenecid (a uricosuric), or allopurinol (an XORI) showed a significant decrease in BP in both the probenecid -and allopurinol-treated groups, and lowering serum urate concentration was associated with less

weight gain.[149] The therapeutic equivalence of probenecid and allopurinol suggests that urate-lowering mediated the effect. A third double-blind placebo-controlled study in older (>65 years) patients after ischemic stroke who had prehypertension found that treatment with allopurinol in patients with normal serum urate concentrations resulted in a decrease in clinically assessed SBP and central SBP and a reduction in carotid intimal thickness compared to placebo.[150] Allopurinol lowered SBP and diastolic BP in obese middle-aged adults with prehypertension and modestly elevated serum urate concentrations (6.0–6.2 mg/dL [360–372 μM]).[151] One study of asymptomatic hyperuricemia (serum urate ≥ 8 mg/dL [≥480 μM]) found a decrease in SBP with improvement in eGFR following allopurinol treatment compared to placebo.[152] In contrast, 2 double-blind placebo-controlled trials found that lowering serum urate concentrations in patients with modestly elevated serum urate concentrations (6–7 mg/dL [360–480 μM] range) did not lower BP, although interpretation is limited by the fact that the mean blood pressure of participants was in the normotensive range prior to starting therapy.[153–155]

Chronic Kidney Disease

Small studies have reported that treatment with XORIs can slow CKD progression.[156–161] A double-blind placebo-controlled trial randomly assigned 93 hyperuricemic patients with CKD stage 3 or higher to febuxostat (or placebo) for 6 months.[158] Febuxostat attenuated the decline in kidney function, with 38% showing a >10% decline in eGFR versus 54% in the placebo group (P = 0.004). Febuxostat also lowered SBP (−13 vs −4 mm Hg).[158]

Two randomized trials reported that lowering serum urate concentrations with allopurinol could slow CKD progression in patients with CKD stage 3,[156,157] with one trial showing a reduction in cardiovascular events.[157,162] In another trial, 109 hyperuricemic patients with CKD stage 3 or higher and who had previously undergone cardiac surgery were randomly assigned to allopurinol or febuxostat for 6 months. Febuxostat reduced serum urate concentrations and led to favorable effects on SBP, eGFR, and albuminuria.[163] Post hoc analyses of other studies also suggest beneficial effects of lowering serum urate concentrations with febuxostat and/or allopurinol on kidney function in patients with gout and CKD stage 2.[159,160] In contrast, 3 studies (in patients with diabetic nephropathy,[164] immunoglobulin A nephropathy,[165] and stage 3 CKD[166]) reported no change in eGFR with allopurinol/febuxostat. Of note, these studies were either limited in duration (12 weeks)[164,166] or enrolled patients with stable CKD.[165] Interestingly, beneficial effects on BP[165,166] and albuminuria[164,166] were still observed.

Acute Kidney Injury

Several studies have investigated whether lowering serum urate concentrations may prevent AKI. One clinical trial of hyperuricemic patients undergoing cardiac surgery reported that urate lowering with rasburicase resulted in lower concentrations of the kidney tubular injury marker urine neutrophil-associated lipocalin but no difference in postoperative serum creatinine concentrations.[167] In 2 trials comparing hydration to hydration plus allopurinol in the prevention of radiocontrast nephropathy, none of the 169 participants receiving allopurinol with hydration developed AKI (defined as worsening of serum creatinine by >25%) compared to 35 of the 170 (20%) participants receiving saline solution alone.[168,169]

Insulin Resistance and Metabolic Syndrome

Urate-lowering therapy in hyperuricemic patients has been reported to improve insulin resistance or fasting glucose concentrations.[170–172] A double-blind crossover trial that randomly assigned patients to benzbromarone or placebo found that patients with heart failure and hyperuricemia showed an improvement in insulin resistance (as assessed by Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) after 8 weeks.[170] In contrast, another study found that allopurinol attenuated the increase in BP resulting from a high-fructose diet, but did not improve insulin resistance.[173]

Finally, one study randomly assigned patients with type 2 diabetes and asymptomatic hyperuricemia (n = 176) to allopurinol or placebo for 3 years. The allopurinol-treated group had lower SBP and diastolic BP, less worsening of HOMA-IR and serum triglyceride concentration, lower albuminuria, higher eGFR, and fewer cases of new-onset diabetic nephropathy (defined as urine albumin excretion > 200 μg/min[4.9% vs 10%).[161]

Additional Issues With Use of XORIs

XORIs are ideal urate-lowering agents because they block production and will reduce both intra- and extracellular urate. In contrast, uricosuric agents may block urate uptake into cells,[38,44] but will not block intracellular urate production, such as occurs during fructose metabolism. Because most of the cardiovascular and kidney effects of urate are thought to be mediated by intracellular urate, XORIs are thought to be superior to uricosurics in blocking urate's biological effects. Nevertheless, interpretation of studies using XORIs are confounded because the conversion of hypoxanthine and xanthine to urate by XOR results in the production of oxidants. Thus, blocking XOR also reduces oxidative stress that may be independent of urate. One study reported that XORIs could improve endothelial dysfunction, whereas probenecid could not,[174] and other studies also suggest that XOR may also be induced by oxidants generated from other sources (such as from mitochondria or NADPH oxidase) to amplify local oxidative stress.[175] Nevertheless, the benefit of XOR inhibition on fat accumulation in cultured hepatocytes can be blocked by adding urate back to the incubation mixture.[39] Uricosuric agents have also been reported to improve BP and insulin resistance in 2 studies.[149,170]

Summary

When considering clinical trials of urate-lowering therapy in hypertension, it appears that the effects of urate-lowering therapy on BP are most likely to be observed among patients with hyperuricemia (especially if serum urate is >8 mg/dL [>476 μM]) when baseline SBP is >130 mm Hg and GFR is normal. Likewise, when considering trials of urate-lowering therapy and effects on CKD progression, it appears there may be benefits in patients with hyperuricemia and in longer duration trials sufficient to see non–hemodynamically-mediated changes in eGFR.

Angiotensin-converting enzyme (ACE) inhibitors and other blockers of the RAAS may impact the association between urate and kidney outcomes, with experimental studies and clinical studies of humans suggesting that hyperuricemia affects both blood pressure and kidney function in part by activation of the RAAS.[41,55,96] In this regard, withdrawal of

allopurinol in one study of patients with CKD resulted in worsening of BP and more rapid CKD progression only in patients who were not concurrently treated with ACE inhibitors.[176] In addition to the possibility that lowering urate concentrations might down-regulate the RAAS, the angiotensin receptor blocker losartan can also lower serum urate concentration by increasing urine urate excretion. Hence, studies in which agents that block the RAAS are used may obscure effects of urate-lowering therapy and vice versa. Because RAAS blockade is commonly used in CKD, a trial of urate-lowering therapy may be primarily addressing whether decreasing serum urate concentrations provides benefit above and beyond that provided by RAAS inhibitors.

The safety of urate-lowering therapies must be considered. In rare cases, allopurinol can cause a hyper-sensitivity syndrome that resembles Stevens-Johnson syndrome, especially in persons with the HLA-B*58 serotype.[177] There has also been some concern that use of febuxostat may be associated with increased cardiovascular risk compared to allopurinol, resulting in a recent US Food and Drug Administration alert.[178,179] Uricosuric agents may increase the risk for kidney stones; in phase 3 trials, lesinurad caused transient increases in serum creatinine concentrations when used at high doses, and without concomitant XORIs.[180]

In summary, although pilot clinical trials of urate-lowering therapy suggest potential benefits in the treatment of hypertension and prevention of kidney disease and CVD, they have been limited in size and power and have generally used intermediate or surrogate end points. Comparisons of urate-lowering therapy and placebo on top of standard therapies (including RAAS inhibitors) are underway (Table 3) or planned (Box 3) in several adequately powered trials with hard cardiovascular and/or kidney end points. In particular, the Preventing Early Renal Function Loss (PERL) Consortium is randomly assigning 400 adults with type 1 diabetes, mild to moderate CKD with albuminuria, and serum urate concentrations ≥ 4.5 mg/dL to allopurinol or placebo, with allopurinol titrated to reduce serum urate concentrations to <4.5 mg/dL. The primary outcome of this 3-year intervention trial is GFR measured using iohexol, assessed 2 months after intervention washout to diminish the influence of possible hemodynamic effects.[181]

Conclusions

Though hyperuricemia was considered a potential cause of hypertension by Mahomed in the 1870s, after 140 years, the potential causal role of urate in kidney disease and hypertension is still hotly debated. Hyperuricemia is a biomarker for kidney and cardiovascular risk, but serum urate concentration also increases as GFR decreases. Although serum urate concentration is a strong independent risk marker for incident CKD and hypertension, Mendelian randomization studies do not support urate as a causal factor in these conditions. At this time, in concordance with a recent Cochrane review,[182] and given potential toxicities of current treatments, we cannot recommend routine treatment of hyperuricemia in persons with hypertension, kidney disease, or metabolic syndrome/type 2 diabetes. Rather, we must await the results of well-designed and adequately powered clinical trials.

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Box 1.

Bradford Hill Criteria for Causality: Urate and Hypertension

1. **Strength** (effect size): An elevated serum uric acid consistently predicts a 1.5- to 2-fold increased risk for hypertension within 5–10 y.[92]
2. **Consistency** (reproducibility): An elevated serum uric acid independently predicts the development of hypertension in 22 of 23 studies.[92]
3. **Specificity:** The risk for developing hypertension in those with elevated serum urate level persists after controlling for other cardiovascular risk factors. In adolescents, new-onset essential hypertension is associated with an elevated serum urate (≥5.5 mg/dL) in 90% of cases; by contrast, hyperuricemia occurs in just 30% of those with secondary hypertension and is rare in normotensive and white-coat hypertensive adolescent patients.[29]
4. **Temporality:** Although not all individuals with hypertension have hyperuricemia, an elevated serum urate frequently precedes the development of hypertension, and in adolescents, 90% with primary hypertension have been reported to have hyperuricemia.[92] These data are most consistent with hyperuricemia being a major cause of hypertension in adolescents.
5. **Biological gradient:** A linear relationship is observed between serum uric acid and level of blood pressure in adolescents with primary hypertension (r=0.80).[29]
6. **Plausibility:** Experimental studies found that hyperuricemia in rats results in hypertension that is mediated by activation of the renin-angiotensin system, induction of oxidative stress, and inhibition of endothelial function.[54–57]
7. **Coherence:** Lowering serum urate in hyperuricemic hypertensive adolescents was observed to correct blood pressure in 86% of cases whose serum urate was lowered to <5 mg/dL.[96] This was also found to be associated with a reduction in plasma renin activity consistent with experimental studies that the hypertension is dependent on the renin-angiotensin system.[54,55]
8. **Experiment:** Rats with experimental hyperuricemia develop hypertension that can be corrected by either a xanthine oxidase inhibitor or an uricosuric agent.[54,62]
9. **Analogy:** Experimentally one can also induce hypertension by stimulation of the renin-angiotensin system, blocking endothelial nitric oxide synthase, or inducing oxidative stress, all mechanisms mediated by uric acid.[97]

Box 2.

Factors Affecting the Association of Serum Urate With Kidney and Cardiovascular Outcomes in Epidemiologic Studies

- Heterogeneity of patients
- Heterogeneity of baseline GFR
- Heterogeneity of risk factors
- Limitations with GFR prediction
- Competing risks (multiple hits) and competing outcomes
- Varying outcome definitions and lack of a core outcomes set
- Varying exposure definitions
- Varying follow-up time
- Adjusting for factors in the causal pathway
- Unmeasured and unadjusted confounding

Abbreviation: GFR, glomerular filtration rate.

Box 3.

Potential RCTs Assessing Urate-Lowering for Kidney Disease and Cardiovascular Disease Benefits

RCT #1: General Population

Population: Patients with asymptomatic hyperuricemia (≥6 mg/dL), HTN, and additional CV or CKD risk

Intervention: XOI fixed or titrated dose, probenecid or lesinurad fixed or titrated dose, placebo

Outcomes: GFR slope, BP change (no. of medications), 30% decline in eGFR; CV outcomes; AEs; urine ACR

Duration: 5 y with a priori–defined longer term posttreatment follow-up

RCT #2: CKD Population

Population: Asymptomatic hyperuricemia (≥6 mg/dL), HTN, and eGFR < 60 mL/min/1.73 m^2 with albuminuria or eGFR < 45 mL/min/1.73 m^2 regardless of albuminuria
Intervention: Allopurinol/febuxostat fixed or titrated dose, placebo

Outcomes: 30% decline in eGFR; composite of ESRD, kidney failure death, or 50% decline in eGFR; CV outcomes; AEs; urine ACR

Duration: 4 y with a priori–defined longer term posttreatment follow-up

RCT #3: AKI Risk Population

Population: Patients at risk for AKI (planned major CV surgery)

Intervention: Allopurinol/febuxostat fixed dose preprocedure for several weeks

Outcomes: AKIN stage 3, AKIN stage 1

Abbreviations: ACR, albumin-creatinine ratio; AE, adverse event; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; (e) GFR, (estimated) glomerular filtration rate; ESRD, end-stage renal disease; HTN, hypertension; RCT, randomized clinical trial; XOI, xanthine oxidase inhibitor.

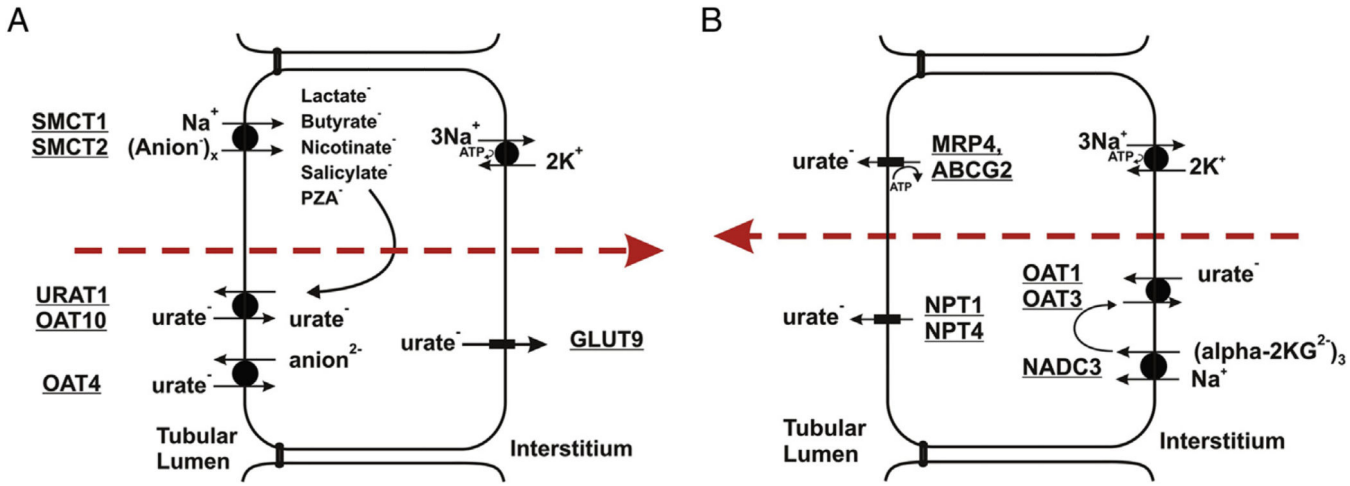

Figure 1.

Transport pathways for urate in proximal tubule cells. (A) Urate reabsorption. Sodium-dependent anion transport by SMCT1 and SMCT2 increases intracellular concentrations of monovalent anions that exchange with luminal urate (URAT1/OAT10). OAT4 appears to exchange urate with divalent anions. GLUT9 is the exit pathway for urate at the basolateral membrane. (A) Urate secretion. Urate enters the cell at the basolateral membrane by exchange with α-ketoglutarate, mediated by OAT1 and OAT3. At the apical membrane, urate is secreted by MRP4, ABCG2, NPT1, and/or NPT4. Figure is copyright Annual Reviews and is reproduced from Mandal and Mount.[7]

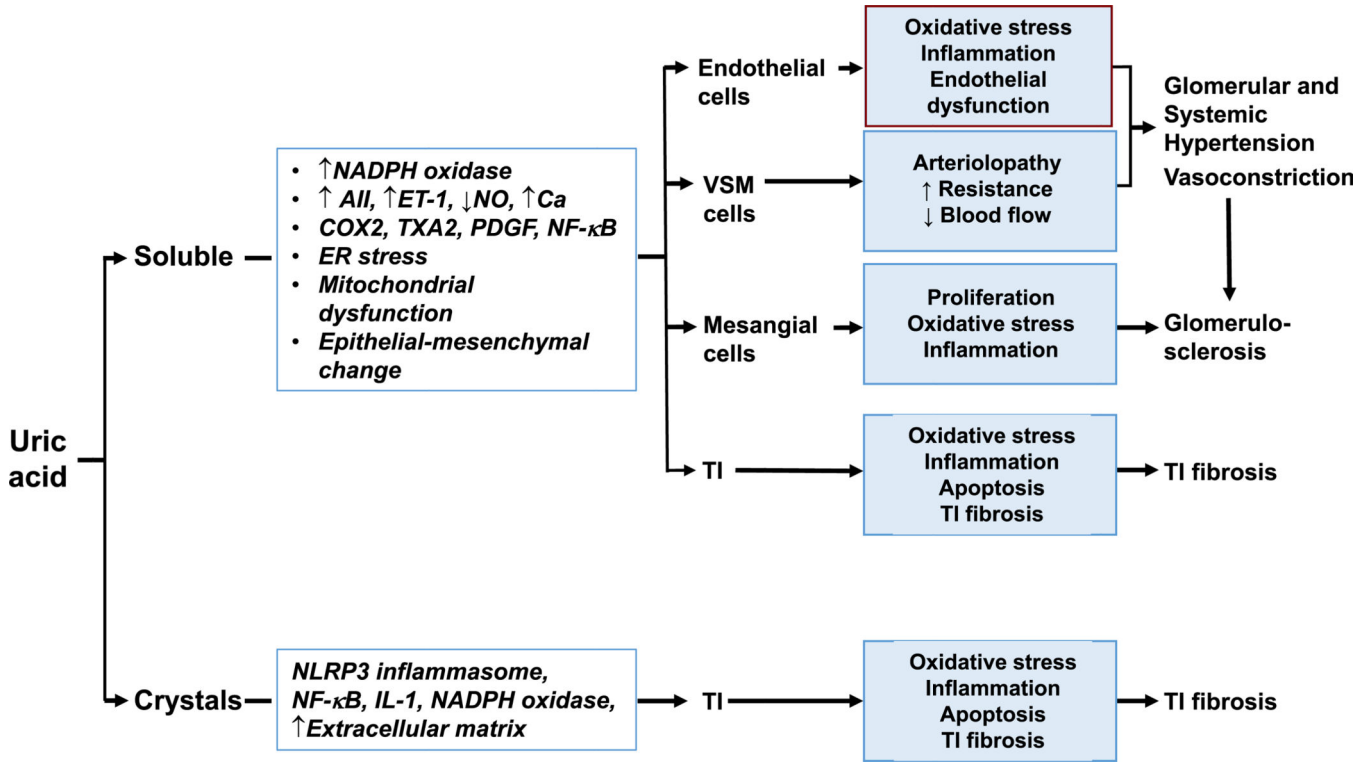

Figure 2.

Potential mechanisms by which urate may cause kidney disease. Urate may induce renal damage in its soluble (crystal-independent) or crystal form. After entering renal cells, soluble uric acid can activate various cascades and responses that lead to damaging inflammatory, proliferative, and maladaptive changes in glomeruli and the tubulointerstitium (TI). Crystalline uric acid seems to be confined to the TI, where it may elicit similar changes. Abbreviation: VSM, vascular smooth muscle.

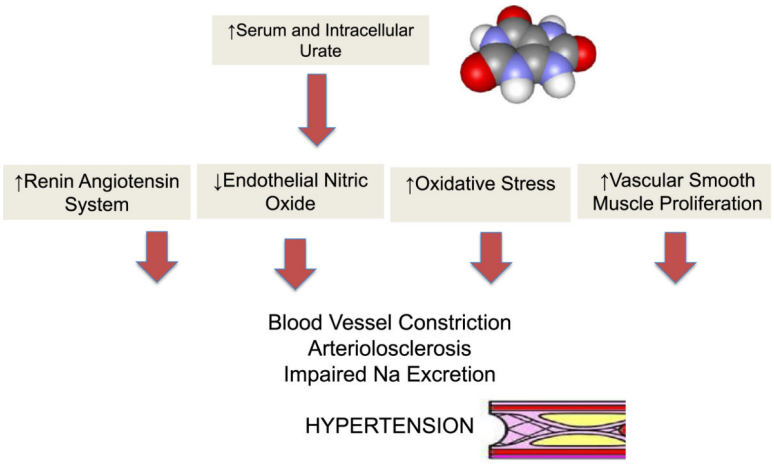

Figure 3.

Mechanism of hyperuricemia-induced hypertension. Hyperuricemia-induced hypertension has been proposed to be a consequence of the effect of serum and/or intracellular urate to stimulate the renin-angiotensin-aldosterone system, lower endothelial nitric oxide, induce oxidative stress, and stimulate vascular smooth muscle cell proliferation, resulting in systemic and renal vasoconstriction and arteriolosclerosis leading to hypertension.

Table 1.

Experimental Models in Which Lowering Serum Urate Prevents or Improves Kidney Injury

Model	Hyperuricemia	UA-Lowering Drug	References
Oxonic acid (rat)	Yes	Allopurinol, febuxostat, benziodarone, thiadiazolopyrimidin-5-one analogue	54, 55, 62–64
Oxonic acid + 5/6 nephrectomy (rat)	Yes	Allopurinol, febuxostat	43, 59, 65
Oxonic acid + cyclosporine (rat)	Yes		66
Tacrolimus-induced nephrotoxicity (rat)	Yes	Febuxostat	67
Cyclosporine-induced nephrotoxicity (rat)	Yes	Allopurinol, benzbromarone	68
Diabetic nephropathy associated with type 1 diabetes (rat)	No	Febuxostat	69
Diabetic nephropathy associated with type 2 diabetes (rat, mouse, in vitro culture)	Yes	Febuxostat, allopurinol	70–72
Spontaneously hypertensive rat	Not reported	Allopurinol	73
Rhabdomyolysis-induced AKI (rat)	Not reported	Allopurinol	74
Oxonic acid + cisplatin-induced AKI (rat)	Yes	Rasburicase	49
Unilateral ureteral obstructive nephropathy (rat)	Yes	Febuxostat	75
Renal ischemia-reperfusion injury (rat)	No	Febuxostat	76

Abbreviations: AKI, acute kidney injury; UA, uric acid.

Table 2.

Shared Loci for eGFR and Serum Urate Control

Locus (function)	SNP Association	Urate	eGFR
A1CF (regulation of lipoprotein synthesis)	Same	↑	↑
BCAS3	Same, additional signal in eGFR	↑	↑
GCKR (glycolysis)	Same	↑	↑
INHBC	Same	↑	↓
LRP2	Different	—	—
PRKAG2 (energy)	Same	↑	↓
STC1	Same	↑	↓
UBE2Q2	Same	↑	↓
VEGFA	Same	↑	↓

Note: Arrows indicate whether the effect allele of the most associated SNP at each locus increases or decreases urate concentrations or eGFR.

Abbreviations: *A1CF*, apolipoprotein B messenger RNA editing enzyme, catalytic polypeptide 1 complementation factor; *BCAS3*, breast carcinoma amplified sequence 3; eGFR, estimated glomerular filtration rate; *GCKR*, glucokinase regulatory protein; *INHBC*, inhibin beta C chain; *LRP2*, lipoprotein-related protein 2; *PRKAG2*, protein kinase adenosine-monophosphate-activated non-catalytic sub-unit gamma 2; SNP, single-nucleotide polymorphism; *STC1*, stanniocalcin 1; *UBE2Q2*, ubiquitin-conjugating enzyme E2 Q2; *VEGFA*, vascular endothelial growth factor A.

Table 3.

Summary of Randomized Clinical Trials in the Field of Serum Urate and Cardiovascular Diseases

CV field	Intervention	Primary Outcomes	ID No. and Status
BP control	Febuxostat vs allopurinol	Clinic BP and ABPM	NCT01701622[a]; terminated (unable to enroll participants)
Coronary endothelial dysfunction	Febuxostat vs placebo	Coronary flow	NCT01763996[a]; completed
BP control	Febuxostat vs placebo	ABPM	NCT01496469[a]; completed
Exercise tolerance in chronic angina	Febuxostat vs placebo	ETT	NCT01549977[a]; terminated
Vascular structure and function (FORWARD)	Febuxostat vs allopurinol	Carotid-femoral PWV	EudraCT 2014–5567-33; enrollment closed
New-onset metabolic syndrome (FAST)	Febuxostat vs placebo	Insulin resistance and features of metabolic syndrome	NCT01654276[a]; ongoing
BP and CV complications (CARES)	Febuxostat vs allopurinol	MACE	NCT01101035[a]; ongoing
Treatment of CHD (ALL-HEARTY)	Allopurionl vs placebo	MACE	EudraCT 2013–003559-39; Ongoing
Cerebrovascular protection (XILO-FIST)	Allopurinol vs placebo	White matter protection	NCT02122718[a]; starting Recruitment
Major CV diseases (FREED)	Febuxostat vs placebo	MACE	NCT01984749[a]; ongoing

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; ETT, exercise tolerance testing; MACE, major adverse cardiovascular events; PWV, pulse wave velocity.

[a]ClinicalTrials.gov.