KI REPORTS
KIReports.org

Uric Acid and Chronic Kidney Disease: Still More to Do

Richard J. Johnson[1], Laura G. Sanchez Lozada[2], Miguel A. Lanaspa[1], Federica Piani[3] and Claudio Borghi[3]

[1]Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA; [2]Department of Cardio-Renal Physiopathology, Instituto Nacional de Cardiología "Ignacio Chavez," Mexico City, Mexico; and [3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Gout and hyperuricemia are present in 25% and 60% of patients with chronic kidney disease (CKD), respectively. Despite the common association, the role of uric acid in the progression of kidney disease and in metabolic complications remains contested. Some authorities argue that the treatment of asymptomatic hyperuricemia in CKD is not indicated, and some have even suggested hyperuricemia may be beneficial. Here, we review the various arguments both for and against treatment. The weight of the evidence suggests asymptomatic hyperuricemia is likely injurious, but it may primarily relate to subgroups, those who have systemic crystal deposits, those with frequent urinary crystalluria or kidney stones, and those with high intracellular uric acid levels. We recommend carefully designed clinical trials to test if lowering uric acid in hyperuricemic subjects with cardiometabolic complications is protective.

Kidney Int Rep (2023) **8,** 229–239; https://doi.org/10.1016/j.ekir.2022.11.016
KEYWORDS: chronic kidney disease; gout; hyperuricemia; metabolic syndrome; systemic inflammation

Hyperuricemia (defined as a serum uric acid level >7 mg/dl in males and >6 mg/dl in women) is common in CKD. This is because hyperuricemia is common in type 2 diabetes and hypertension, which are conditions that cause CKD, and also because CKD results in reduced urinary excretion of uric acid. As a consequence, the prevalence of gout increases from 1% to 2% of adults with normal kidney function to 32% of those with stage 4 CKD. Hyperuricemia prevalence also increases from 11% among those with normal kidney function to 80% among those with stage 4 CKD.[1] The converse is also true. CKD stage 2 or higher is present in 70% of subjects with gout and 50% of those with hyperuricemia.[2]

It is therefore important to understand if high uric acid levels modify kidney or metabolic outcomes. This is especially true because hyperuricemia is an independent predictor of CKD and metabolic diseases,[3–5] including in subjects who are healthy without any morbidities.[6] There is also a direct relationship of serum uric acid level with prevalence of hypertension, diabetes, and CKD (Figure 1).[7,8]

Today, there remains controversy over the role of uric acid in CKD and cardiometabolic outcomes. Several groups have suggested that asymptomatic hyperuricemia in CKD is benign and should not be treated, or may even be beneficial.[9–12] Here, we present our countering viewpoint with recommendations for how to move forward. For purposes of the discussion, our analysis will be separately about those who have gout and CKD, and those with asymptomatic hyperuricemia and CKD.

Gout and CKD

Gout is classically treated with urate-lowering agents to reduce the risk for recurrent arthritic attacks and joint damage.[13] It has remained controversial whether lowering serum uric acid in gout has an effect on kidney disease or cardiovascular events. However, there are at least 3 arguments that strongly suggest that lowering uric acid in subjects with gout may be beneficial for CKD and/or cardiovascular events. All these are based on the fact that urate crystals are known to be very proinflammatory, and known to induce local inflammation that is mediated by activation of inflammasomes and the release of interleukin-1.[14]

The first argument is that urate crystals are known to deposit not only in joints, but also in other tissues,[15]

Correspondence: Richard J. Johnson, Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, 12700 East 19th Avenue, RC-2 Research Building, Room 7012, Mail Stop C281, Aurora, Colorado 80045, USA. E-mail: richard.johnson@ucdenver.edu

Received 4 October 2022; revised 14 November 2022; accepted 21 November 2022; published online 5 December 2022

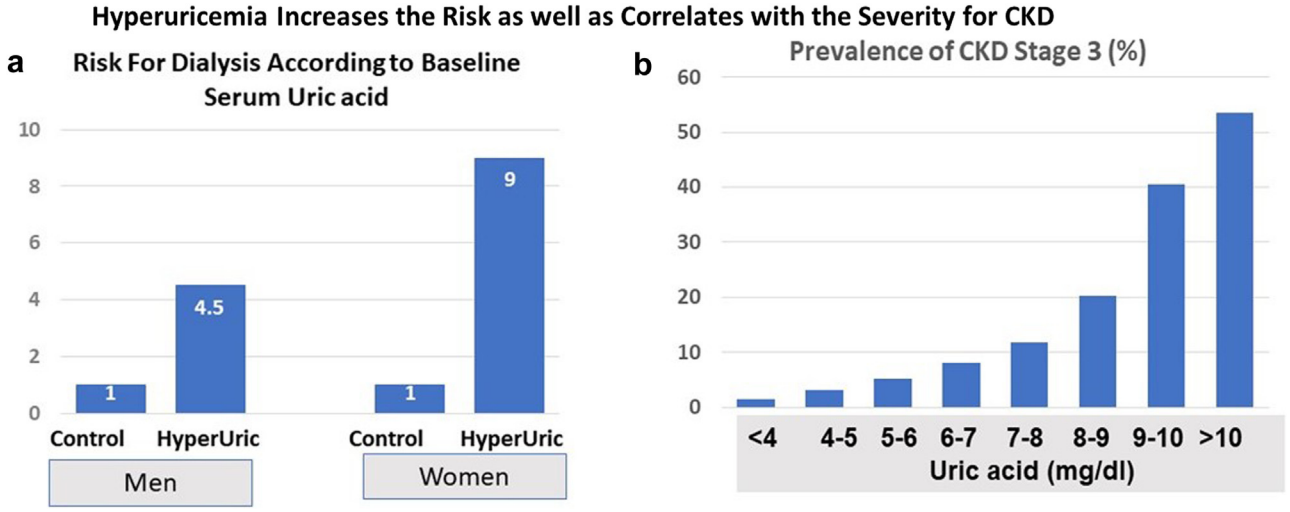

Figure 1. Relationship of Serum Uric acid with CKD. (a) A study in which more than 48,000 Japanese that were 20 years or older who were followed for 7 years. After controlling for baseline serum creatinine and other variables, the presence or absence of baseline hyperuricemia (defined as >7 mg/dl in men and >6 mg/dl in women) markedly increased the risk for developing end stage kidney disease requiring dialysis. (b) A figure based on the study of 5707 participants aged 20 years and older from the National Health and Nutrition Examination Survey 2007–2008. There is an exponential relationship of serum uric acid levels with CKD. (a) Adapted from Iseki *et al.*[7] and (b) Adapted from Zhu *et al.*[8] CKD, chronic kidney disease; HyperUric, hyperuricemia.

and one of the favored sites is in the collecting ducts of the kidney.[16] As urine concentrates, it also acidifies, and this can lead to urate crystallization. Some urate crystals adhere to the tubular epithelium, where they can cause local inflammation that leads to rupture of the tubular wall with the crystals escaping into the interstitium.[17] This can be associated with marked local inflammation with macrophage infiltration.[18] Subjects with gout have reduced fractional excretion of uric acid. Nevertheless, they excrete large amounts of uric acid, especially following ingestion of a purine-rich[19] or fructose-rich[20] meal.

Indeed, in the days before urate-lowering treatment was available, autopsies of patients with gout showed an almost universal presence of kidney disease, characterized by arteriolosclerosis, focal segmental glomerulosclerosis, and chronic tubulointerstitial disease,[16,21] and as many as 20% or 25% of gouty subjects would have markedly reduced kidney function.[22] Most strikingly, urate crystals were found in 90% of autopsies, always concentrated in the outer medulla.[21] In contrast, kidney biopsies rarely document urate crystals[23] because the biopsies are of the cortex where uric acid crystals are sparse. In addition, urate crystals are often washed out during the fixation process unless special techniques, such as using alcohol fixation and the De Galantha stain, are used.

It is not known how common urate crystals are present in the kidneys of gout patients today. Newer techniques such as the dual energy computed tomography (DECT) scans have been suggested as a method to detect their presence.[24] However, there are technical issues in performing and analyzing scans, and adjustments need to be performed for each organ evaluated, and the art of performing DECT scans on kidneys is still being refined. Nevertheless, another approach that has been recommended is the use of renal artery ultrasound to determine if there is enhanced echogenicity in the renal medulla associated with crystal deposition. A hyperechoic medulla by ultrasound is considered strongly suggestive of urate crystal deposition and has been reported to be present in one-third of subjects with gout.[25]

The second argument to treat gout not just for the risk of recurrent gout attacks is because there is now evidence that urate crystals may be directly involved in the atherosclerotic process. Specifically, DECT scans adjusted for evaluating blood vessels have had the surprising discovery that urate crystals are common in the aorta and coronary arteries of subjects with gout. Indeed, urate crystals are present in the blood vessels of 75% to 86% of patients with gout, with nearly 30% of gout subjects having crystals in their coronary arteries.[26,27] The primary sites seem to be in areas of atherosclerotic plaque, which has been confirmed by histologic studies.[28–30] Urate crystals have also been colocalized with sites of vascular calcification.[26] Urate crystals are likely to stimulate inflammasomes in the lesions similar to that of cholesterol crystals, and this is expected to increase the risk for plaque extension or rupture.[31] These findings could explain why both hyperuricemia and gout are associated with cardiovascular mortality in both epidemiology and Mendelian randomization studies.[32–34]

The third argument relates to the observation that urate crystal deposits can result in not just local inflammation but also in systemic inflammation, and the latter is recognized as a contributing factor for progressive kidney disease as well as cardiovascular events.[35,36] A striking finding in gout is that resolution of an acute attack is not associated with resolution of urate crystals because they will persist until the next attack (i.e., the "intercritical period").[37] These "silent crystals" can still be associated with evidence for systemic inflammation that may have an indirect role in the progression of kidney disease and cardiovascular events.[38] Indeed, both elevated monocyte counts and high levels of highly sensitive C-reactive protein levels are found in patients with a history of gout.[39,40] Some studies have found that allopurinol treatment can lower highly sensitive C-reactive protein levels.[41] Furthermore, targeting inflammation by giving antibodies to interleukin-1 can reduce highly sensitive C-reactive protein and cardiovascular events in individuals at risk of cardiovascular disease.[42,43]

We believe these arguments are strong enough to recommend urate-lowering in all subjects who suffer from gout, and treatment could be dietary or involve a nutraceutical or drug; however, the goal would be to lower serum uric acid levels to <6 mg/dl.

Hyperuricemia and CKD

Initially there was strong evidence that hyperuricemia in the absence of gout might be driving CKD. This was supported both by epidemiologic studies,[3,44] experimental studies[45,46] and pilot clinical trials.[47] However, 2 large clinical trials, known as the prevention of early renal loss in type 1 Diabetes and CKD-FIX (Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase), were published in the same issue of the New England Journal of Medicine and found no benefit of allopurinol in slowing renal progression.[48,49] This initially led several groups, including the Caring for Australians and New Zealanders with Kidney Impairment Guidelines Committee to suggest that there is now conclusive evidence not to treat asymptomatic hyperuricemia in CKD.[9,12]

We believe this conclusion is premature. The prevention of early renal loss and CKD-FIX studies tested whether lowering uric acid was beneficial but not whether treating hyperuricemia is beneficial, because both studies included large numbers of patients with normal serum uric acid levels. Normal uric acid levels are not expected to significantly increase the risk for CKD (see Figure 1).

Both studies were also intention-to-treat analyses. These analyses count all treated subjects even if they discontinued treatment because of problems with compliance or side effects. In this case, approximately 17.5% to 30% of subjects dropped out before completion of the trial. The fact that this happened in both treatment and placebo groups suggest it was largely not because of the drug but rather because of general characteristics of the population being studied, or perhaps because of general concerns or preset opinions that allopurinol might be associated with high side effects. Therefore, the trial was not actually testing the hypothesis that asymptomatic hyperuricemia might be driving CKD, but rather tested whether allopurinol treatment reduced progression of kidney disease when including issues such as compliance, side effects, and other factors.

The CARI guidelines have some additional problems. For example, the criteria they used in their studies did not require the presence of hyperuricemia (allowing any serum uric acid level), nor did it require the presence of CKD,[9] yet the question being addressed was whether treating asymptomatic hyperuricemia in CKD was beneficial. Their conclusion that treatment was not beneficial was also at odds with the meta-analysis they used for their study. The latter had concluded that lowering serum uric acid was beneficial in reducing the decline in estimated glomerular filtration rate and blood pressure.[50]

More recently, the ALLHEART study was published in which older patients (age >60 years) with a history of ischemic heart disease and no gout were randomized to allopurinol or placebo and followed for almost 5 years without any discernible benefit on subsequent cardiovascular events.[51] However, similar to the other trials, patients with normal uric acid levels were included (the mean serum uric acid was 5.6 mg/dl) and gout was excluded. Likewise, there was a large (57%) dropout which were included in the analysis because it was an intention-to-treat study, such that it was not truly testing whether the treatment of hyperuricemia is beneficial on cardiac endpoints.

One might hope that meta-analyses might help resolve the issues, but even here there remains confusion, because some recent studies suggest that treatment of asymptomatic hyperuricemia in CKD does slow progression,[52,53] whereas others are mixed or indeterminant,[50,54,55] and some are negative.[56] Some meta-analyses show benefit with only specific urate-lowering drugs, such as febuxostat.[57,58] One possible explanation for the mixed data is that there may be

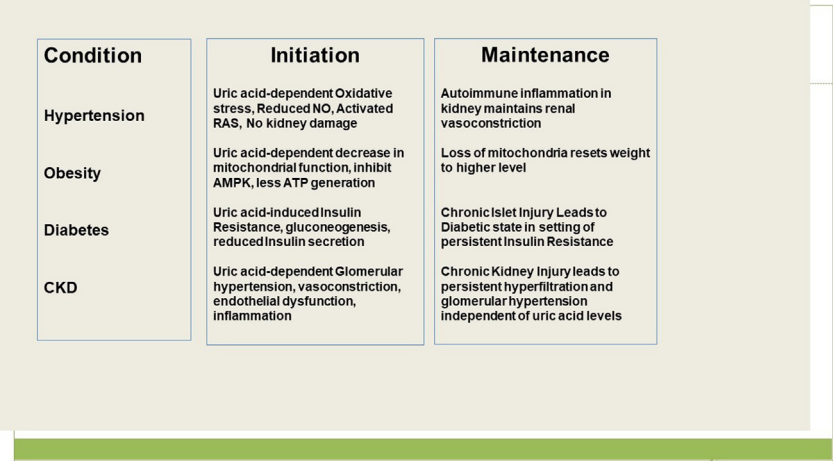

Figure 2. Uric acid may be more Important in the Initiation of Metabolic Diseases Rather than the Maintenance. AMPK, adenosine monophosphatase-activated protein kinas; ATP, adenosine trisphosphate; CKD, chronic kidney disease; NO, nitric oxide; RAS, renin angiotensin system.

subgroups that particularly benefit from treatment. In the next section, we propose specific groups that we believe might be most likely to respond to urate-lowering therapy.

Subgroups in Which Asymptomatic Hyperuricemia may be Most Likely to Drive CKD and Cardiac Disease

The first group to consider would be patients with asymptomatic hyperuricemia who may harbor "silent" crystals in their joints, blood vessels, or kidneys (similar to the argument provided in the gout section). Approximately 15% of hyperuricemic subjects who do not have gout still have urate deposits in their blood vessels when evaluated by DECT scan.[26] Some patients may also harbor crystals silently in their joints or kidneys. Studies that include DECT scanning or renal ultrasound may help identify this subgroup.

A second group would be subjects with recurrent urate crystalluria or kidney stones. Crystalluria can stimulate inflammasomes in renal tubular cells leading to local inflammation and injury that can accelerate CKD.[11,59–61] One mechanism for the crystalluria would be the presence of a low urinary pH, such as may occur with dehydration, because uric acid is very insoluble in acidic urine. A low urinary pH predicts the development of CKD.[62] This may also explain the benefit of bicarbonate therapy to slow CKD, and we reported that bicarbonate therapy can solubilize urate crystals and reduce biomarkers of renal tubular injury in diabetic subjects.[63] Heat stress-associated urate crystalluria is also common in subjects with Mesoamerican nephropathy where it might be driving kidney damage,[64,65] and uricosuria accompanies rhabdomyolysis where it has been suggested to play an ancillary role.[66] Indeed, both allopurinol and bicarbonate therapy are protective in experimental rhabdomyolysis-associated kidney injury.[67,68]

Although urate crystalluria is largely driven by low urinary pH, some individuals will show "overproduction" uricosuria. Recently, this was shown to be mediated by reduced intestinal uric acid excretion, especially by inhibition of the adenosine triphosphate-binding cassette subfamily G member 2 urate transporter.[69,70] The adenosine triphosphate-binding cassette subfamily G member 2 transporter is expressed in both the kidney and intestine, but polymorphisms that are associated with reduced function (such as the Q126X variant [that has near absent function] and the Q141K [which has half-function]) result in reduced intestinal elimination with increased renal excretion.[70] New studies suggest that individuals carrying these variants are at higher risk for progression of CKD.[69,71] Dietary mechanisms may also be operative. Fructose, for example, also blocks adenosine triphosphate-binding cassette subfamily G member 2 in the intestine, reducing intestinal uric acid excretion,[72] while increasing urinary excretion,[73] reducing urinary pH,[74] and reducing urine volume.[75] Dietary intake of high purine foods can also cause transient uricosuria[19] that might be important in mediating kidney injury.

Asymptomatic hyperuricemic patients with kidney stones may also be candidates for having recurrent uricosuria. Kidney stones are common in subjects with gout, being present in one-third of subjects when evaluated by helical computerized tomography, although two-thirds of these patients were not aware they had stones. Of interest, the subjects with kidney stones had worse kidney function and lower urine pH than those who did not have stones.[76] Therefore, one might consider evaluating subjects with hyperuricemia to determine if they have stones, because this may

Potential Clinical Trials

Study	Comparison	Outcome	Stratification and Duration
Gout with DECT positive urate crystals in vasculature	Pegloticase vs High Dose Xanthine Oxidase Inhibitor vs Standard of Care	Cardiovascular Events, Vascular Calcification, Renal progression	2 years No restriction on baseline kidney function
Gout with uric acid levels > 7mg/dl despite standard of care	High Dose Xanthine oxidase therapy vs pegloticase vs standard of care	Renal progression, CV events, Vascular events and calcification	2 years No restriction on baseline kidney function
Hyperuricemia with type 2 diabetes or metabolic syndrome (perhaps elevated plasma XO activity)	Xanthine oxidase inhibitor versus placebo	Kidney progression, CV events, metabolic outcomes	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)
Hyperuricemia with Kidney Stones, Hyperuricosuria, or ABCG2 polymorphisms	Xanthine oxidase inhibitor vs placebo vs bicarbonate therapy	Progression of Kidney disease, kidney stones	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)
Hyperuricemia and polycystic kidney disease	Xanthine oxidase inhibitor vs placebo	Renal progression, use of BP medications	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)
Hyperuricemia with elevation of CRP and endothelial dysfunction	Xanthine oxidase inhibitor vs pegloticase vs placebo	CV events, progression of kidney disease	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)

Figure 3. Examples of potential clinical trials to investigate the role of uric acid in cardio-renal diseases. BP, blood pressure; CRP, C-reactive protein; CV, cardiovascular; DECT, dual energy computed tomography; XO, xanthine oxidase.

represent a group with an increased risk for CKD progression.

The importance of urate crystalluria in causing kidney injury was recently elucidated in patients with uricosuria and hypouricemia because of the loss of urate transporters in their kidneys.[77,78] In both experimental models and humans, the use of allopurinol to reduce uricosuria is associated with protection from kidney injury.[77,79]

A third group of subjects might be those who have increased intracellular levels of uric acid occurring in their livers or kidneys. In the liver, intracellular uric acid is thought to mediate oxidative stress to the mitochondria that drives metabolic effects like insulin resistance, hepatic fat accumulation, and elevation in blood pressure.[80] Interestingly, this is associated with dietary measures such as intake of fructose or purine-rich foods; howver, it can also occur with block in intestinal uric acid excretion.[71] Another condition might by polycystic kidney disease, in which the enlarging cysts are likely stimulating local uric acid generation. In autosomal polycystic kidney disease, serum uric acid levels are high and correlate with progression, whereas pilot studies suggest that lowering serum uric acid may be protective.[81,82]

A major mechanism by which hyperuricemia induces its effects on the kidney is likely via its vascular effects. Uric acid has been shown experimentally to mediate endothelial dysfunction by both reducing biologically available nitric oxide and inducing oxidative stress.[83–85] Although not all studies are positive, most clinical studies suggest that xanthine oxidase inhibitors can improve endothelial dysfunction.[86] Uric acid can also enter into vascular smooth muscle cells via specific transporters,[87,88] where it drives proliferation and proinflammatory pathways.[87,89,90] Hyperuricemia is especially correlated with disease of the afferent arteriole in both experimental animals[45] and in humans.[91] Experimentally, this is associated with renal vasoconstriction, altered renal autoregulation, and increased glomerular hydrostatic pressure.[92] Serum uric acid also correlates with high renal afferent arteriolar resistance in humans.[93]

Measuring intracellular uric acid levels is difficult. However, determining plasma xanthine oxidase activity might be an alternative way to identify these patients. Elevated plasma xanthine oxidase activity has been reported to identify subjects with CKD who are at risk for cardiovascular events[94] and may be superior to serum uric acid in predicting metabolic disorders.[95,96]

Other Arguments

Some have argued that uric acid may be beneficial because it can function as an antioxidant.[97] However, uric acid is pro-oxidative inside cells because it activates nicotinamide adenine dinucleatide phosphate oxidase and also because it can generate radicals such as hydroperoxide, peroxynitrite-radicals, and myeloperoxidase-based radicals.[98,99] When uric acid quells the production of hypochlorous acid by

neutrophils, the overall oxidative stress remains the same because of increased production of superoxide.[100] Indeed, the overall effects of soluble uric acid are proinflammatory.[98,100–102]

Some groups have reported that hyperuricemia induced by inosine may protect against kidney disease.[11,103,104] However, inosine has been shown to be anti-inflammatory because it activates adenosine receptors[105–107] and generates hypoxanthine, the latter that can be recycled to IMP and eventually adenosine triphosphate.[108] Importantly, in the studies evaluating if uric acid is beneficial in kidney disease, the investigators did not determine if allopurinol treatment would reverse this protection. Other groups have shown that the anti-inflammatory effects of inosine are enhanced by administering allopurinol.[109,110]

Another issue has been the concern that febuxostat might increase the risk for cardiovascular mortality because it was associated with more cardiovascular events in the CARES trial.[111] Other studies could not affirm this association.[112] Moreover, there was no placebo group in the CARES study, and studies of allopurinol suggest it may reduce mortality risk in the general population,[113] with a trend toward protection in subjects with CKD.[114]

An additional argument is that most Mendelian randomization studies have not been able to show that genetic polymorphisms that increase serum uric acid translate into increased risk for CKD,[115–118] despite this being shown in other Mendelian randomization studies for hypertension,[119] coronary artery disease,[34] or cardiovascular events.[33] However, serum uric acid is not the critical factor, given that the factors driving kidney disease may relate more to urine uric acid, urine pH, presence or absence of urate crystals in the kidney, and intracellular serum uric acid levels, especially in the liver and kidney. Although intracellular uric acid and serum uric acid levels are often correlated, they can also be dissociated.[120] In addition, some urate transporters, such as SLC2A9, may have divergent effects on serum uric acid depending on which target organ is evaluated,[121,122] suggesting that genetic polymorphisms altering SLC2A9 function could have opposing biologic effects depending on the target organ that could confound Mendelian randomization studies.

Finally, an important consideration is that what initiates disease might be different from what drives it (Figure 2). For example, experimental studies suggest that experimental hyperuricemia causes a rise in blood pressure because of effects of uric acid; however, over time there is the induction of an autoimmune inflammatory response in the kidney that maintains the hypertension.[123] Likewise, experimental hyperuricemia is associated with glomerular hypertension and renal vasoconstriction that is dependent on uric acid levels, but as CKD develops, glomerular hypertension is driven by a reduction in nephron number.[124] Similarly, there is evidence that fructose-induced hyperuricemia initially causes a reversible insulin resistance; however, overtime there is progressive injury to the islets resulting in islet dysfunction and a loss in insulin secretory ability.[125] There is also evidence that long-standing mitochondrial oxidative stress may lead to a loss of mitochondria that may have persistent effects.[126] Thus, the timing for when uric acid is lowered may be important. Similarly, to see a benefit in established disease, one might have to treat for a long time, and there is some evidence that the benefit of lowering uric acid is greatest if treatment is prolonged for 2 years or more.[127]

Summary

Asymptomatic hyperuricemia is common in subjects with CKD. Although the CKD-FIX and prevention of early renal loss studies did not report benefit of allopurinol in slowing the progression of kidney disease, they did not specifically address the role of hyperuricemia. We suggest that there may be some specific subgroups of subjects with asymptomatic hyperuricemia that would benefit, including those with documented crystal deposition in joints, blood vessels, and the kidneys; those with documented recurrent urate crystalluria or with kidney stones; and those who have evidence for elevated liver or kidney uric acid levels (possibly noted by high plasma xanthine oxidase activity). Examples of some proposed trials are shown in Figure 3. The addition of these carefully designed studies are needed to determine the role of uric acid in the progression of CKD.

DISCLOSURE

RJJ has equity with Colorado Research Partners LLC, has stock with XORTX Therapeutics, and is a consultant for Horizon Pharma. MAL and LGI have equity with Colorado Research Partners LLC. CB has research grants from Servier and Alfasigma and serves as a consultant for Servier, Novartis, Novo Nordisk, Alfasigma, Sanofi, and Menarini. FP declares no competing interests.

ACKNOWLEDGMENTS

Funding

Supported in part by NIH grant DK121496.

REFERENCES

1. Juraschek SP, Kovell LC, Miller ER 3rd, Gelber AC. Association of kidney disease with prevalent gout in the United States in 1988–1994 and 2007–2010. *Semin Arthritis Rheum*. 2013;42:551–561. https://doi.org/10.1016/j.semarthrit.2012.09.009
2. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009–10. *PLoS One*. 2012;7:e50046. https://doi.org/10.1371/journal.pone.0050046
3. Zhu P, Liu Y, Han L, et al. Serum uric acid is associated with incident chronic kidney disease in middle-aged populations: a meta-analysis of 15 cohort studies. *PLoS One*. 2014;9:e100801. https://doi.org/10.1371/journal.pone.0100801
4. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2011;63:102–110. https://doi.org/10.1002/acr.20344
5. Lv Q, Meng XF, He FF, et al. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. *PLoS One*. 2013;8:e56864. https://doi.org/10.1371/journal.pone.0056864
6. Kuwabara M, Niwa K, Hisatome I, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases: five-year Japanese cohort study. *Hypertension*. 2017;69:1036–1044. https://doi.org/10.1161/HYPERTENSIONAHA.116.08998
7. Iseki K, Ikemiya Y, Inoue T, et al. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis*. 2004;44:642–650. https://doi.org/10.1016/S0272-6386(04)00934-5
8. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. *Am J Med*. 2012;125:679–687.e1. https://doi.org/10.1016/j.amjmed.2011.09.033
9. Stanley IK, Phoon RK, Toussaint N, et al. Caring for Australians and New Zealanders with kidney improvement guidelines: rapid development of urate lowering therapy guidelines for people with CKD. *Kidney Int Rep*. 2022;7:2563–2574. https://doi.org/10.1016/j.ekir.2022.09.024
10. Ma Q, Immler R, Pruenster M, et al. Soluble uric acid inhibits beta2 integrin-mediated neutrophil recruitment in innate immunity. *Blood*. 2022;139:3402–3417. https://doi.org/10.1182/blood.2021011234
11. Sellmayr M, Hernandez Petzsche MR, Ma Q, et al. Only hyperuricemia with crystalluria, but not asymptomatic hyperuricemia, drives progression of chronic kidney disease. *J Am Soc Nephrol*. 2020;31:2773–2792. https://doi.org/10.1681/ASN.2020040523
12. Gonzalez-Martin G, Cano J, Carriazo S, et al. The dirty little secret of urate-lowering therapy: useless to stop chronic kidney disease progression and may increase mortality. *Clin Kidney J*. 2020;13:936–947. https://doi.org/10.1093/ckj/sfaa236
13. Drug and Therapeutics Bulletin. Latest guidance on the management of gout. *BMJ*. 2018;362:k2893. https://doi.org/10.1136/bmj.k2893
14. Martinon F, Petrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440:237–241. https://doi.org/10.1038/nature04516
15. Khanna P, Johnson RJ, Marder B, LaMoreaux B, Kumar A. Systemic urate deposition: an unrecognized complication of gout? *J Clin Med*. 2020;9:3204. https://doi.org/10.3390/jcm9103204
16. Talbott JH, Terplan KL. The kidney in gout. *Med (Baltim)*. 1960;39:405–467. https://doi.org/10.1097/00005792-196012000-00001
17. Cameron JS, Simmonds HA. Uric acid, gout and the kidney. *J Clin Pathol*. 1981;34:1245–1254. https://doi.org/10.1136/jcp.34.11.1245
18. Kim YG, Huang XR, Suga S, et al. Involvement of macrophage migration inhibitory factor (MIF) in experimental uric acid nephropathy. *Mol Med*. 2000;6:837–848. https://doi.org/10.1007/BF03401822
19. Clifford AJ, Riumallo JA, Youn VR, Scrimshaw NS. Effect of oral purines on serum and urinary uric acid of normal, hyperuricemic and gouty humans. *J Nutr*. 1976;106:428–450. https://doi.org/10.1093/jn/106.3.428
20. Raivio KO, Becker A, Meyer LJ, et al. Stimulation of human purine synthesis de novo by fructose infusion. *Metabolism*. 1975;24:861–869. https://doi.org/10.1016/0026-0495(75)90133-x
21. Brown J, Mallory GK. Renal changes in gout. *N Engl J Med*. 1950;243:325–329. https://doi.org/10.1056/NEJM195008312430901
22. Coombs FS, Pecora LJ, Thorogood E, et al. Renal function in patients with gout. *J Clin Invest*. 1940;19:525–535. https://doi.org/10.1172/JCI101156
23. Barlow KA, Beilin LJ. Renal disease in primary gout. *Q J Med*. 1968;37:79–96.
24. Bardin T, Tran KM, Nguyen QD, et al. Renal medulla in severe gout: typical findings on ultrasonography and dual-energy CT study in two patients. *Ann Rheum Dis*. 2019;78:433–434. https://doi.org/10.1136/annrheumdis-2018-214174
25. Bardin T, Nguyen QD, Tran KM, et al. A cross-sectional study of 502 patients found a diffuse hyperechoic kidney medulla pattern in patients with severe gout. *Kidney Int*. 2021;99:218–226. https://doi.org/10.1016/j.kint.2020.08.024
26. Klauser AS, Halpern EJ, Strobl S, et al. Dual-energy computed tomography detection of cardiovascular monosodium urate deposits in patients with gout. *JAMA Cardiol*. 2019;4:1019–1028. https://doi.org/10.1001/jamacardio.2019.3201
27. Barazani SH, Chi WW, Pyzik R, et al. Quantification of uric acid in vasculature of patients with gout using dual-energy computed tomography. *World J Radiol*. 2020;12:184–194. https://doi.org/10.4329/wjr.v12.i8.184
28. Patetsios P, Song M, Shutze WP, et al. Identification of uric acid and xanthine oxidase in atherosclerotic plaque. *Am J Cardiol*. 2001;88:A186. https://doi.org/10.1016/s0002-9149(01)01621-6
29. Patetsios P, Rodino W, Wisselink W, et al. Identification of uric acid in aortic aneurysms and atherosclerotic artery. *Ann N Y Acad Sci*. 1996;800:243–245. https://doi.org/10.1111/j.1749-6632.1996.tb33318.x
30. Nardi V, Franchi F, Prasad M, et al. Uric acid expression in carotid atherosclerotic plaque and serum uric acid are associated with cerebrovascular events. *Hypertension*.

2022;79:1814–1823. https://doi.org/10.1161/HYPERTENSIONAHA.122.19247

31. Strandberg TE, Kovanen PT. Coronary artery disease: 'gout' in the artery? *Eur Heart J*. 2021;42:2761–2764. https://doi.org/10.1093/eurheartj/ehab276
32. Kuo CF, See LC, Yu KH, et al. Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality. *Rheumatol (Oxf Engl)*. 2013;52:127–134. https://doi.org/10.1093/rheumatology/kes223
33. Kleber ME, Delgado G, Grammer TB, et al. Uric acid and cardiovascular events: a Mendelian randomization study. *J Am Soc Nephrol*. 2015;26:2831–2838. https://doi.org/10.1681/ASN.2014070660
34. Wang K, Shi X, Zhu Z, et al. Mendelian randomization analysis of 37 clinical factors and coronary artery disease in East Asian and European populations. *Genome Med*. 2022;14:63. https://doi.org/10.1186/s13073-022-01067-1
35. Amdur RL, Feldman HI, Gupta J, et al. Inflammation and progression of CKD: the CRIC study. *Clin J Am Soc Nephrol*. 2016;11:1546–1556. https://doi.org/10.2215/CJN.13121215
36. Ridker PM. Targeting interleukin-1 and interleukin-6: the time has come to aggressively address residual inflammatory risk. *J Am Coll Cardiol*. 2020;76:1774–1776. https://doi.org/10.1016/j.jacc.2020.08.052
37. Toprover M, Shah B, Oh C, et al. Initiating guideline-concordant gout treatment improves arterial endothelial function and reduces intercritical inflammation: a prospective observational study. *Arthritis Res Ther*. 2020;22:169. https://doi.org/10.1186/s13075-020-02260-6
38. Hammer HB, Rollefstad S, Semb AG, et al. Urate crystal deposition is associated with inflammatory markers and carotid artery pathology in patients with intercritical gout: results from the NOR-Gout study. *RMD Open*. 2022;8:e002348. https://doi.org/10.1136/rmdopen-2022-002348
39. Kocaman SA, Sahinarslan A, Cemri M, et al. Independent relationship of serum uric acid levels with leukocytes and coronary atherosclerotic burden. *Nutr Metab Cardiovasc Dis*. 2009;19:729–735. https://doi.org/10.1016/j.numecd.2008.12.010
40. Grainger R, McLaughlin RJ, Harrison AA, Harper JL. Hyperuricaemia elevates circulating CCL2 levels and primes monocyte trafficking in subjects with inter-critical gout. *Rheumatol (Oxf Engl)*. 2013;52:1018–1021. https://doi.org/10.1093/rheumatology/kes326
41. Kanbay M, Huddam B, Azak A, et al. A randomized study of allopurinol on endothelial function and estimated glomerular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol*. 2011;6:1887–1894. https://doi.org/10.2215/CJN.11451210
42. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. https://doi.org/10.1056/NEJMoa1707914
43. Ridker PM, MacFadyen JG, Glynn RJ, et al. Inhibition of interleukin-1beta by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol*. 2018;71:2405–2414. https://doi.org/10.1016/j.jacc.2018.03.490
44. Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant*. 2013;28:2221–2228. https://doi.org/10.1093/ndt/gft029
45. Kang DH, Nakagawa T, Feng L, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol*. 2002;13:2888–2897. https://doi.org/10.1097/01.asn.0000034910.58454.fd
46. Kosugi T, Nakayama T, Heinig M, et al. Effect of lowering uric acid on renal disease in the type 2 diabetic db/db mice. *Am J Physiol Ren Physiol*. 2009;297:F481–F488. https://doi.org/10.1152/ajprenal.00092.2009
47. Sato Y, Feig DI, Stack AG, et al. The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD. *Nat Rev Nephrol*. 2019;15:767–775. https://doi.org/10.1038/s41581-019-0174-z
48. Doria A, Galecki AT, Spino C, et al. Serum urate lowering with allopurinol and kidney function in Type 1 diabetes. *N Engl J Med*. 2020;382:2493–2503. https://doi.org/10.1056/NEJMoa1916624
49. Badve SV, Pascoe EM, Tiku A, et al. Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med*. 2020;382:2504–2513. https://doi.org/10.1056/NEJMoa1915833
50. Chen Q, Wang Z, Zhou J, et al. Effect of urate-lowering therapy on cardiovascular and kidney outcomes: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2020;15:1576–1586. https://doi.org/10.2215/CJN.05190420
51. Mackenzie IS, Hawkey CJ, Ford I, et al. Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400:1195–1205. https://doi.org/10.1016/S0140-6736(22)01657-9
52. Luo Q, Cai Y, Zhao Q, et al. Effects of allopurinol on renal function in patients with diabetes: a systematic review and meta-analysis. *Ren Fail*. 2022;44:806–814. https://doi.org/10.1080/0886022X.2022.2068443
53. Sapankaew T, Thadanipon K, Ruenroengbun N, et al. Efficacy and safety of urate-lowering agents in asymptomatic hyperuricemia: systematic review and network meta-analysis of randomized controlled trials. *BMC Nephrol*. 2022;23:223. https://doi.org/10.1186/s12882-022-02850-3
54. Tsukamoto S, Okami N, Yamada T, et al. Prevention of kidney function decline using uric acid-lowering therapy in chronic kidney disease patients: a systematic review and network meta-analysis. *Clin Rheumatol*. 2022;41:911–919. https://doi.org/10.1007/s10067-021-05956-5
55. Yu X, Gu M, Zhu Y, Zhang L, Kong W, Zou Y. Efficacy of urate-lowering therapy in patients with chronic kidney disease: a network meta-analysis of randomized controlled trials. *Clin Ther*. 2022;44:723–735.e6. https://doi.org/10.1016/j.clinthera.2022.03.014
56. Liang X, Liu X, Li D, Qin W, Liu Y. Effectiveness of urate-lowering therapy for renal function in patients with chronic kidney disease: a meta-analysis of randomized clinical trials. *Front Pharmacol*. 2022;13:798150. https://doi.org/10.3389/fphar.2022.798150
57. Lin TC, Hung LY, Chen YC, et al. Effects of febuxostat on renal function in patients with chronic kidney disease: a systematic review and meta-analysis. *Med (Baltim)*. 2019;98:e16311. https://doi.org/10.1097/MD.0000000000016311

58. Zheng Y, Sun J. Febuxostat improves uric acid levels and renal function in patients with chronic kidney disease and hyperuricemia: a meta-analysis. *Appl Bionics Biomech*. 2022;2022:9704862. https://doi.org/10.1155/2022/9704862
59. Schepers MS, van Ballegooijen ES, Bangma CH, Verkoelen CF. Crystals cause acute necrotic cell death in renal proximal tubule cells, but not in collecting tubule cells. *Kidney Int*. 2005;68:1543–1553. https://doi.org/10.1111/j.1523-1755.2005.00566.x
60. Shiizaki K, Tsubouchi A, Miura Y, et al. Calcium phosphate microcrystals in the renal tubular fluid accelerate chronic kidney disease progression. *J Clin Invest*. 2021;131:e145693. https://doi.org/10.1172/JCI145693
61. Moe OW. A generic crystallopathic model for chronic kidney disease progression. *J Clin Invest*. 2021;131:e151858. https://doi.org/10.1172/JCI151858
62. Nakanishi N, Fukui M, Tanaka M, et al. Low urine pH Is a predictor of chronic kidney disease. *Kidney Blood Press Res*. 2012;35:77–81. https://doi.org/10.1159/000330487
63. Bjornstad P, Maahs DM, Roncal CA, et al. Role of bicarbonate supplementation on urine uric acid crystals and diabetic tubulopathy in adults with type 1 diabetes. *Diabetes Obes Metab*. 2018;20:1776–1780. https://doi.org/10.1111/dom.13274
64. Wesseling C, Aragon A, Gonzalez M, et al. Heat stress, hydration and uric acid: a cross-sectional study in workers of three occupations in a hotspot of Mesoamerican nephropathy in Nicaragua. *BMJ Open*. 2016;6:e011034. https://doi.org/10.1136/bmjopen-2016-011034
65. Roncal-Jimenez C, Garcia-Trabanino R, Barregard L, et al. Heat stress nephropathy from exercise-induced uric acid crystalluria: a perspective on Mesoamerican nephropathy. *Am J Kidney Dis*. 2016;67:20–30. https://doi.org/10.1053/j.ajkd.2015.08.021
66. Vanholder R, Sever MS, Erek E, Lameire N. Rhabdomyolysis. *J Am Soc Nephrol*. 2000;11:1553–1561. https://doi.org/10.1681/ASN.V1181553
67. Sanchez-Lozada LG, Garcia-Arroyo FE, Gonzaga G, et al. Kidney injury from recurrent heat stress and rhabdomyolysis: protective role of allopurinol and sodium bicarbonate. *Am J Nephrol*. 2018;48:339–348. https://doi.org/10.1159/000494663
68. Gois PH, Canale D, Volpini RA, et al. Allopurinol attenuates rhabdomyolysis-associated acute kidney injury: renal and muscular protection. *Free Radic Biol Med*. 2016;101:176–189. https://doi.org/10.1016/j.freeradbiomed.2016.10.012
69. Ohashi Y, Kuriyama S, Nakano T, et al. Urate transporter ABCG2 function and asymptomatic hyperuricemia: a retrospective cohort study of CKD progression. *Am J Kidney Dis. Forthcoming*. 2022. https://doi.org/10.1053/j.ajkd.2022.05.010
70. Ichida K, Matsuo H, Takada T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun*. 2012;3:764. https://doi.org/10.1038/ncomms1756
71. Johnson RJ. Intestinal hyperuricemia as a driving mechanism for CKD. *Am J Kidney Dis.* Forthcoming. 2022. https://doi.org/10.1053/j.ajkd.2022.08.001
72. Kaneko C, Ogura J, Sasaki S, et al. Fructose suppresses uric acid excretion to the intestinal lumen as a result of the induction of oxidative stress by NADPH oxidase activation. *Biochim Biophys Acta Gen Subj*. 2017;1861:559–566. https://doi.org/10.1016/j.bbagen.2016.11.042
73. Sahebjami H, Scalettar R. Effects of fructose infusion on lactate and uric acid metabolism. *Lancet*. 1971;1:366–369. https://doi.org/10.1016/s0140-6736(71)92208-2
74. Johnson RJ, Perez-Pozo SE, Lillo JL, et al. Fructose increases risk for kidney stones: potential role in metabolic syndrome and heat stress. *BMC Nephrol*. 2018;19:315. https://doi.org/10.1186/s12882-018-1105-0
75. Johnson RJ, Stenvinkel P, Andrews P, et al. Fructose metabolism as a common evolutionary pathway of survival associated with climate change, food shortage and droughts. *J Intern Med*. 2020;287:252–262. https://doi.org/10.1111/joim.12993
76. Shimizu T, Kitada H, Umeyama M, et al. Novel evaluation of nephrolithiasis as a complication of gout: a cross-sectional study using helical computerized tomography. *J Urol*. 2013;189:1747–1752. https://doi.org/10.1016/j.juro.2012.11.076
77. Hosoya T, Uchida S, Shibata S, et al. Xanthine oxidoreductase inhibitors suppress the onset of exercise-induced AKI in high HPRT activity Urat1-Uox double knockout mice. *J Am Soc Nephrol*. 2022;33:326–341. https://doi.org/10.1681/ASN.2021050616
78. Kikuchi Y, Koga H, Yasutomo Y, et al. Patients with renal hypouricemia with exercise-induced acute renal failure and chronic renal dysfunction. *Clin Nephrol*. 2000;53:467–472.
79. Bhasin B, Stiburkova B, De Castro-Pretelt M, et al. Hereditary renal hypouricemia: a new role for allopurinol? *Am J Med*. 2014;127:e3–e4. https://doi.org/10.1016/j.amjmed.2013.08.025
80. Lanaspa MA, Sanchez-Lozada LG, Choi YJ, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *J Biol Chem*. 2012;287:40732–40744. https://doi.org/10.1074/jbc.M112.399899
81. Han M, Park HC, Kim H, et al. Hyperuricemia and deterioration of renal function in autosomal dominant polycystic kidney disease. *BMC Nephrol*. 2014;15:63. https://doi.org/10.1186/1471-2369-15-63
82. Helal I, McFann K, Reed B, et al. Serum uric acid, kidney volume and progression in autosomal-dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2013;28:380–385. https://doi.org/10.1093/ndt/gfs417
83. Yu MA, Sanchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. *J Hypertens*. 2010;28:1234–1242. https://doi.org/10.1097/HJH.0b013e328337da1d
84. Sanchez-Lozada LG, Lanaspa MA, Cristobal-Garcia M, et al. Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. *Nephron Exp Nephrol*. 2012;121:e71–e78. https://doi.org/10.1159/000345509
85. Choi YJ, Yoon Y, Lee KY, et al. Uric acid induces endothelial dysfunction by vascular insulin resistance associated with the impairment of nitric oxide synthesis. *FASEB J*. 2014;28:3197–3204. https://doi.org/10.1096/fj.13-247148

86. Kanbay M, Siriopol D, Nistor I, et al. Effects of allopurinol on endothelial dysfunction: a meta-analysis. *Am J Nephrol*. 2014;39:348–356. https://doi.org/10.1159/000360609

87. Kang DH, Han L, Ouyang X, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol*. 2005;25:425–433. https://doi.org/10.1159/000087713

88. Price KL, Sautin YY, Long DA, et al. Human vascular smooth muscle cells express a urate transporter. *J Am Soc Nephrol*. 2006;17:1791–1795. https://doi.org/10.1681/ASN.2006030264

89. Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension*. 2003;41:1287–1293. https://doi.org/10.1161/01.HYP.0000072820.07472.3B

90. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005;16:3553–3562. https://doi.org/10.1681/ASN.2005050572

91. Myllymaki J, Honkanen T, Syrjanen J, et al. Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. *Nephrol Dial Transplant*. 2005;20:89–95. https://doi.org/10.1093/ndt/gfh584

92. Sanchez-Lozada LG, Tapia E, Santamaria J, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int*. 2005;67:237–247. https://doi.org/10.1111/j.1523-1755.2005.00074.x

93. Uedono H, Tsuda A, Ishimura E, et al. Relationship between serum uric acid levels and intrarenal hemodynamic parameters. *Kidney Blood Press Res*. 2015;40:315–322. https://doi.org/10.1159/000368507

94. Gondouin B, Jourde-Chiche N, Sallee M, et al. Plasma xanthine oxidase activity is predictive of cardiovascular disease in patients with chronic kidney disease, independently of uric acid levels. *Nephron*. 2015;131:167–174. https://doi.org/10.1159/000441091

95. Furuhashi M, Matsumoto M, Tanaka M, et al. Plasma xanthine oxidoreductase activity as a novel biomarker of metabolic disorders in a general population. *Circ J*. 2018;82:1892–1899. https://doi.org/10.1253/circj.CJ-18-0082

96. Furuhashi M, Mori K, Tanaka M, et al. Unexpected high plasma xanthine oxidoreductase activity in female subjects with low levels of uric acid. *Endocr J*. 2018;65:1083–1092. https://doi.org/10.1507/endocrj.EJ18-0127

97. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci U S A*. 1981;78:6858–6862. https://doi.org/10.1073/pnas.78.11.6858

98. Patricio ES, Prado FM, da Silva RP, et al. Chemical characterization of urate hydroperoxide, a pro-oxidant intermediate generated by urate oxidation in inflammatory and photoinduced processes. *Chem Res Toxicol*. 2015;28:1556–1566. https://doi.org/10.1021/acs.chemrestox.5b00132

99. Imaram W, Gersch C, Kim KM, et al. Radicals in the reaction between peroxynitrite and uric acid identified by electron spin resonance spectroscopy and liquid chromatography mass spectrometry. *Free Radic Biol Med*. 2010;49:275–281. https://doi.org/10.1016/j.freeradbiomed.2010.04.010

100. Carvalho LAC, Lopes J, Kaihami GH, et al. Uric acid disrupts hypochlorous acid production and the bactericidal activity of HL-60 cells. *Redox Biol*. 2018;16:179–188. https://doi.org/10.1016/j.redox.2018.02.020

101. Kono H, Chen CJ, Ontiveros F, Rock KL. Uric acid promotes an acute inflammatory response to sterile cell death in mice. *J Clin Invest*. 2010;120:1939–1949. https://doi.org/10.1172/JCI40124

102. Shi Y. Caught red-handed: uric acid is an agent of inflammation. *J Clin Invest*. 2010;120:1809–1811. https://doi.org/10.1172/JCI43132

103. Ma Q, Honarpisheh M, Li C, et al. Soluble uric acid is an intrinsic negative regulator of monocyte activation in monosodium urate crystal-induced tissue inflammation. *J Immunol*. 2020;205:789–800. https://doi.org/10.4049/jimmunol.2000319

104. Gnemmi V, Li Q, Ma Q, et al. Asymptomatic hyperuricemia promotes recovery from ischemic organ injury by modulating the phenotype of macrophages. *Cells*. 2022;11:626. https://doi.org/10.3390/cells11040626

105. Junqueira SC, Dos Santos Coelho I, Lieberknecht V, et al. Inosine, an endogenous purine nucleoside, suppresses immune responses and protects mice from experimental autoimmune encephalomyelitis: a role for A2A adenosine receptor. *Mol Neurobiol*. 2017;54:3271–3285. https://doi.org/10.1007/s12035-016-9893-3

106. da Rocha Lapa F, de Oliveira AP, Accetturi BG, et al. Anti-inflammatory effects of inosine in allergic lung inflammation in mice: evidence for the participation of adenosine A2A and A3 receptors. *Purinergic Signal*. 2013;9:325–336. https://doi.org/10.1007/s11302-013-9351-x

107. Hasko G, Sitkovsky MV, Szabo C. Immunomodulatory and neuroprotective effects of inosine. *Trends Pharmacol Sci*. 2004;25:152–157. https://doi.org/10.1016/j.tips.2004.01.006

108. Johnson TA, Jinnah HA, Kamatani N. Shortage of cellular ATP as a cause of diseases and strategies to enhance ATP. *Front Pharmacol*. 2019;10:98. https://doi.org/10.3389/fphar.2019.00098

109. Kamatani N, Kushiyama A, Toyo-Oka L, et al. Treatment of two mitochondrial disease patients with a combination of febuxostat and inosine that enhances cellular ATP. *J Hum Genet*. 2019;64:351–353. https://doi.org/10.1038/s10038-018-0558-0

110. Watanabe H, Hattori T, Kume A, et al. Improved Parkinsons disease motor score in a single-arm open-label trial of febuxostat and inosine. *Medicine (Baltimore)*. 2020;99:e21576. https://doi.org/10.1097/MD.0000000000021576

111. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;378:1200–1210. https://doi.org/10.1056/NEJMoa1710895

112. Deng H, Zhang BL, Tong JD, et al. Febuxostat use and risks of cardiovascular disease events, cardiac death, and all-cause mortality: metaanalysis of randomized controlled trials. *J Rheumatol*. 2021;48:1082–1089. https://doi.org/10.3899/jrheum.200307

113. Dubreuil M, Zhu Y, Zhang Y, et al. Allopurinol initiation and all-cause mortality in the general population. *Ann Rheum Dis*. 2015;74:1368–1372. https://doi.org/10.1136/annrheumdis-2014-205269

114. Wei J, Choi HK, Neogi T, et al. Allopurinol initiation and all-cause mortality among patients with gout and concurrent chronic kidney disease: a population-based cohort study. *Ann Intern Med*. 2022;175:461–470. https://doi.org/10.7326/M21-2347

115. Pfister R, Barnes D, Luben R, et al. No evidence for a causal link between uric acid and type 2 diabetes: a Mendelian randomisation approach. *Diabetologia*. 2011;54:2561–2569. https://doi.org/10.1007/s00125-011-2235-0

116. Jordan DM, Choi HK, Verbanck M, et al. No causal effects of serum urate levels on the risk of chronic kidney disease: a Mendelian randomization study. *PLoS Med*. 2019;16:e1002725. https://doi.org/10.1371/journal.pmed.1002725

117. Yang Q, Kottgen A, Dehghan A, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet*. 2010;3:523–530. https://doi.org/10.1161/CIRCGENETICS.109.934455

118. Tin A, Marten J, Halperin Kuhns VL, et al. Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels. *Nat Genet*. 2019;51:1459–1474. https://doi.org/10.1038/s41588-019-0504-x

119. Gill D, Cameron AC, Burgess S, et al. Urate, blood pressure, and cardiovascular disease: evidence from Mendelian randomization and meta-analysis of clinical trials. *Hypertension*. 2021;77:383–392. https://doi.org/10.1161/HYPERTENSIONAHA.120.16547

120. Lanaspa MA, Kuwabara M, Andres-Hernando A, et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. *Proc Natl Acad Sci U S A*. 2018;115:3138–3143. https://doi.org/10.1073/pnas.1713837115

121. DeBosch BJ, Kluth O, Fujiwara H, et al. Early-onset metabolic syndrome in mice lacking the intestinal uric acid transporter SLC2A9. *Nat Commun*. 2014;5:4642. https://doi.org/10.1038/ncomms5642

122. Dinour D, Gray NK, Campbell S, et al. Homozygous SLC2A9 mutations cause severe renal hypouricemia. *J Am Soc Nephrol*. 2010;21:64–72. https://doi.org/10.1681/ASN.2009040406

123. Watanabe S, Kang DH, Feng L, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension*. 2002;40:355–360. https://doi.org/10.1161/01.hyp.0000028589.66335. aa.

124. Sanchez-Lozada LG, Tapia E, Johnson RJ, et al. Glomerular hemodynamic changes associated with arteriolar lesions and tubulointerstitial inflammation. *Kidney Int Suppl*. 2003;(86):S9–S14. https://doi.org/10.1046/j.1523-1755.64.s86.3.x

125. Roncal-Jimenez CA, Lanaspa MA, Rivard CJ, et al. Sucrose induces fatty liver and pancreatic inflammation in male breeder rats independent of excess energy intake. *Metabolism*. 2011;60:1259–1270. https://doi.org/10.1016/j.metabol.2011.01.008

126. Cristobal-Garcia M, Garcia-Arroyo FE, Tapia E, et al. Renal oxidative stress induced by long-term hyperuricemia alters mitochondrial function and maintains systemic hypertension. *Oxid Med Cell Longev*. 2015;2015:535686. https://doi.org/10.1155/2015/535686

127. Liu P, Chen Y, Wang B, et al. Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. *Clin Endocrinol (Oxf)*. 2015;83:475–482. https://doi.org/10.1111/cen.12673