OPINION

The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD

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Abstract | Hyperuricaemia is common among patients with chronic kidney disease (CKD), and increases in severity with the deterioration of kidney function. Although existing guidelines for CKD management do not recommend testing for or treatment of hyperuricaemia in the absence of a diagnosis of gout or urate nephrolithiasis, an emerging body of evidence supports a direct causal relationship between serum urate levels and the development of CKD. Here, we review randomized clinical trials that have evaluated the effect of urate-lowering therapy (ULT) on the rate of CKD progression. Among trials in which individuals in the control arm experienced progressive deterioration of kidney function (which we define as ≥4 ml/min/1.73 m² over the course of the study — typically 6 months to 2 years), treatment with ULT conferred consistent clinical benefits. In contrast, among trials where clinical progression was not observed in the control arm, treatment with ULT was ineffective, but this finding should not be used as an argument against the use of uric acid-lowering therapy. Although additional studies are needed to identify threshold values of serum urate for treatment initiation and to confirm optimal target levels, we believe that sufficient evidence exists to recommend routine measurement of serum urate levels in patients with CKD and consider initiation of ULT among those who are hyperuricaemic with evidence of deteriorating renal function, unless specific contraindications exist.

The relationship between elevated serum urate (uric acid) levels — such as those observed in patients with gout — and kidney impairment, has long been a topic of interest to nephrologists. A post-mortem analysis from 1960, before the introduction of effective urate-lowering therapy (ULT), found that approximately 50% of patients with gout had some evidence of impaired kidney function and nearly all patients showed some evidence of glomerular, vascular or tubulointerstitial scarring on autopsy[1]. This study also found that, depending on the severity and duration of gout, between 18% and 30% of patients died of end-stage renal disease[1]. During this period, the presence of kidney disease among patients with gout was thought to be a complication of gout ('gouty nephropathy'), and was primarily attributed to the presence of urate crystals in the kidney, which were often concentrated in the outer medullary regions[1].

However, In the 1980s, a shift in viewpoint occurred, with the proposal that gout-associated kidney disease was most likely the consequence of hypertension or ageing-associated renal decline and that the elevation in serum urate level was a secondary process, resulting from decreased renal excretion owing to this loss of kidney function[2–5]. Thus, the presence of elevated serum urate was not considered important in either the pathogenesis or progression of chronic kidney disease (CKD), and treatment of hyperuricaemia in patients with kidney disease was recommended only for the management of gout, uric acid kidney stones, or the rare condition of tumour lysis syndrome, in which the kidney becomes overwhelmed by massive urate crystalluria[6]. Treatment of 'asymptomatic' hyperuricaemia was not recommended, especially because the principal ULT at the time was allopurinol, which occasionally induced a serious hypersensitive reaction and for which there was the additional concern that toxicity might be enhanced in the setting of CKD or diuretic use[7,8]. Owing to the concern that measurement of serum urate levels might trigger indiscriminate initiation of ULT and its potential toxic effects, serum urate was removed from the routine autoanalyzer-based chemistry (sequential, multiple analysis computer) panel used by hospitals. By the 1990s, the role of serum urate in cardiovascular and kidney disease fell into oblivion, with little mention in the published literature.

Renewed interest in the role of serum urate in CKD emerged around the millennium, when a review of the epidemiological studies identified assumptions in the interpretation of study findings relating to the relationship between urate level and CKD[9]. For example, much of the kidney disease in patients with gout was attributed to the presence of hypertension[3] without consideration of the possibility that hyperuricaemia might be involved in the pathogenesis of both hypertension and kidney disease[9–11]. The presence of hypertension was also assumed to cause CKD in all cases where hypertension was present, even though it is well known that hypertension does not cause CKD in 100% of cases. Concerns that these earlier epidemiological studies were flawed were exposed by new experimental studies showing that soluble urate was pro-inflammatory at clinically relevant concentrations in cell culture[12–14] and could mediate inflammation in animal models of kidney disease and metabolic syndrome[15–17]. Experimental hyperuricaemia was also shown to alter renal haemodynamics, leading to both systemic and intraglomerular hypertension[18–21]. Increasing serum urate in experimental models was also found to increase the severity of cisplatin-induced

acute kidney injury and to both induce and accelerate kidney injury in models of CKD[12,16–18,20].

In addition to the potential role of systemic hyperuricaemia in the pathogenesis of kidney disease, studies over the past couple of years have suggested that intermittent uricosuria might also induce tubular injury, either because of the direct effects of urate crystals in the tubules or the effects of high soluble concentrations of urate on the phenotype of tubular cells[22–25].

Findings from these experimental studies were further supported by newer epidemiological studies that showed that the presence of hyperuricaemia independently predicted the development of CKD (reviewed in REFS[26–28]), including in individuals with normal kidney function[29]. The observation that hyperuricaemia preceded and predicted the development of CKD has fundamentally challenged the concept that its presence in patients with CKD was simply a result of impaired excretion and retention in the setting of reduced kidney function. Pilot studies have also suggested that lowering serum urate might slow the progression of CKD[30,31].

However, countering these findings are genetic studies that report a lack of association between genetic loci associated with hyperuricaemia and CKD[32,33], and meta-analyses[34–41] that have yielded discordant findings with regard to the benefits of ULT in patients with CKD. Furthermore, an umbrella analysis[42] that took into account multiple lines of evidence, including observational studies, controlled trials and Mendelian randomization studies, also concluded that there was insufficient evidence to support a causal relationship between serum urate levels and CKD. These findings have created uncertainty with regard to the true role of uric acid in the development and progression of CKD and whether ULT is warranted[26,43].

In this Perspectives article, we focus on reasons why clinical trials of ULT have shown inconsistent results in terms of renoprotection in patients with CKD. We propose that sufficient evidence now exists that implicates hyperuricaemia as a true causal risk factor for CKD based on a cumulative body of clinical studies, anchored by solid experimental studies that underpin key physiological mechanisms, and supported by clinical trials that show effective slowing of CKD progression with ULT intervention. We further suggest that this evidence is sufficiently robust to stimulate a change in clinical practice with initiation of ULT in patients with CKD unless specific contraindications exist. Although more rigorous clinical studies are encouraged to confirm the benefits of ULT in CKD, we propose that routine screening for hyperuricaemia should be considered in patients with CKD as part of clinical practice and that treatment with ULT should be initiated where hyperuricaemia is detected.

Mechanistic insights

A fundamental strength of experimental studies lies in the identification of mechanistic pathways that might explain how both serum urate and urinary uric acid might cause CKD (FIG. 1). Knowledge of key pathophysiological processes is crucial for the design of clinical trials and for the determination and interpretation of key outcomes that potentially explain why some studies fail and others succeed. Although evidence-based medicine is a powerful tool, failure to consider the underlying physiology identified by experimental studies may lead to misinterpretation of study results.

One key aspect is the recognition that hyperuricaemia contributes to the development of hypertension, which in turn can cause kidney injury, but that it needs to be regarded in the context of other processes that may coexist in individuals with CKD. Pathophysiological studies in animal models show that hyperuricaemia induces hypertension by activating vasoactive and inflammatory processes that favour sodium retention, vascular constriction and elevated blood pressure (reviewed elsewhere[44]). However, the physiological effects of high serum urate levels to raise blood pressure might not always be evident in individuals with hyperuricaemia if they are taking agents that block the biological actions of hyperuricaemia, just as the effects of elevated plasma renin activity might not be evident in a patient with hypertension treated with an angiotensin-receptor blocker (ARB) or angiotensin-converting-enzyme (ACE) inhibitor.

Uric acid activates the renin–angiotensin–aldosterone system. Experimental studies show that uric acid is a potent activator of the renin–angiotensin–aldosterone system (RAAS). It activates prorenin receptors in proximal tubular cells of the kidney that stimulate the intrarenal RAAS, as well as increasing renal renin expression, plasma renin activity, serum aldosterone levels, and intracellular angiotensin II levels[18,45–47]. Blocking the RAAS effectively lowers blood pressure and reduces glomerular, tubular and vascular injury in rats with experimental hyperuricaemia[19]. A clinical trial in young adults with new-onset hypertension also showed that allopurinol can markedly reduce plasma renin activity[48], whereas another study showed that lowering uric acid levels in hyperuricaemic, hypertensive adults led to a significant decrease in plasma renin activity and plasma aldosterone levels[49]. A further study in patients with CKD showed that cessation of allopurinol therapy had minimal effects on kidney function and blood pressure for those maintained on an ACE inhibitor or an ARB, but was associated with a marked deterioration of kidney function and blood pressure among those not receiving RAAS blockade[50]. Thus, a principal mechanism by which ULT acts is by reducing RAAS activation.

Importantly, uric acid also activates other important vasoconstrictors, such as endothelin and thromboxane, while suppressing vasodilatory pathways such as nitric oxide[17]. Of note, one study in rats with fructose-induced metabolic syndrome reported synergistic effects of allopurinol and captopril on blood pressure, abdominal fat and dyslipidaemia[51]. Thus, some evidence suggests that ULT might provide additional metabolic protection beyond the use of RAAS blockers alone, but the benefits of allopurinol on renal function among patients with hyperuricaemia are predicted to be most evident among individuals not on RAAS inhibitors. From a clinical perspective, clinicians need to know whether lowering the serum urate level provides additional benefits over standard RAAS blockade therapy, and thus most studies to date have given allopurinol as an add-on therapy to RAAS blockade.

Cellular effects. Most experimental studies suggest that the primary metabolic and renal effects of uric acid are mediated by intracellular urate (reviewed elsewhere[52]). This mode of action is distinctly different from the processes involved in gout, whereby the extracellular deposition of crystalline uric acid in the joint space activates an inflammatory response[53]. One of the key intracellular mechanisms by which uric acid acts is via stimulation of NADPH oxidase and its translocation to mitochondria[54–56], resulting in increased intracellular oxidative stress, despite the fact that extracellular uric acid can act as an antioxidant[57]. Intracellular oxidative stress induces the production of inflammatory proteins such as monocyte chemoattractant protein-1, stimulates innate immune pathways, triggers proliferation of vascular smooth muscle cells and induces vasoactive responses[12,13,17,58]. Since increased extracellular uric acid levels increase

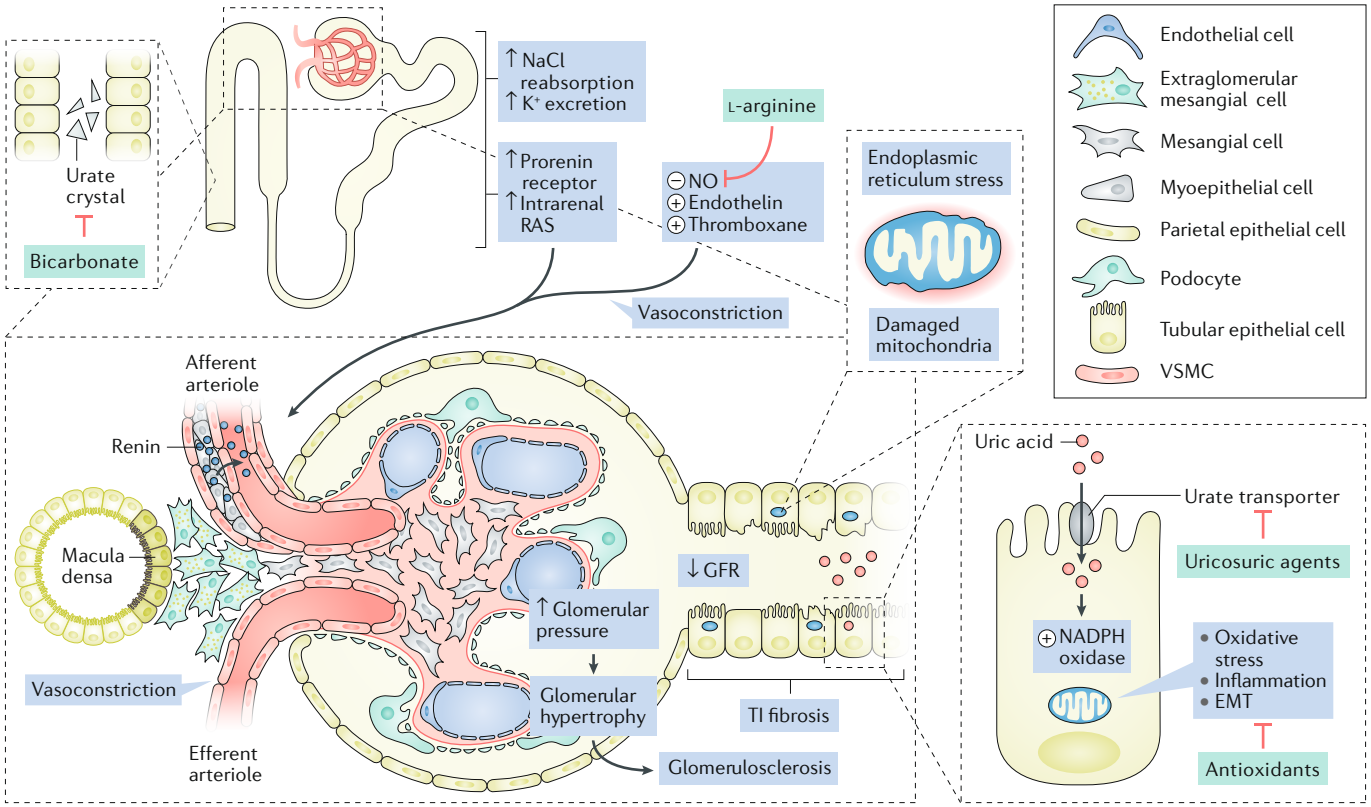

Fig. 1 | **Effects of uric acid on the kidney.** A major mechanism by which hyperuricaemia causes hypertension and chronic kidney disease (CKD) is by activation of the renin–angiotensin–aldosterone system (RAAS). Hyperuricaemia stimulates renin expression by the myoepithelial cells of the afferent arteriole; uric acid also stimulates prorenin receptors in proximal tubular cells that activate the intrarenal angiotensin system. Activation of the RAAS and other vasoconstrictors (endothelin and thromboxane) and suppression of vasodilators (nitric oxide) causes systemic and renal vasoconstriction, resulting in reduced renal plasma flow. Afferent arteriolar hypertrophy develops, impairing autoregulation and leading to an ineffective afferent vasoconstrictive response with transmission of systemic pressure to the glomeruli, which might promote progression of CKD. Stimulation of NADPH oxidase by intracellular urate might also cause oxidative stress, leading to mitochondrial dysfunction, the production of inflammatory cytokines and proliferation of vascular smooth muscle cells. Uricosuria and urate crystals might also cause tubular damage through direct mechanisms or through inflammation mediated by the inflammasome, oxidative stress and epithelial-to-mesenchymal transition. The effects of uric acid on the kidney might be mitigated by substances such as ULT, angiotensin-converting-enzyme inhibitors, L-arginine, bicarbonate and antioxidants. Uricosuric agents have the benefit of blocking urate uptake into cells but the disadvantage of increasing urine uric acid and potentially increasing the risk of uric acid crystalluria. EMT, epithelial–mesenchymal transition; GFR, glomerular filtration rate; NaCl, sodium chloride; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; RAS, renin–angiotensin system; TI, tubulointerstitial; VSMC, vascular smooth muscle cells.

intracellular uric acid levels via urate transporter-mediated uptake[55], an elevated serum urate level is generally a proxy for elevated intracellular uric acid. However, the endogenous production of uric acid, such as by xanthine oxidase during fructose metabolism[59], could drive biologic responses even when serum urate levels are not particularly elevated[14,56]. Intracellular effects of uric acid can be blocked by uricosuric agents such as probenecid (which inhibits urate transporters in the apical membrane of the proximal tubule, thereby blocking the cellular uptake of urate but not its endogenous production), antioxidants such as *N*-acetyl cysteine, tempol and ascorbate, L-arginine (which stimulates the vasodilator nitric oxide, thereby counteracting the vasoconstrictive effects of intracellular urate), and certain flavonoids such as quercetin (which inhibit inflammatory pathways stimulated by intracellular uric acid)[12,55,56,60].

Haemodynamic effects. Experimentally, hyperuricaemia results in mild systemic hypertension with an increase in systemic vascular resistance that is primarily mediated by activation of the RAAS[19]. This activation is associated with renal vasoconstriction, which reduces renal blood flow, but tends to maintain glomerular filtration rate (GFR) owing to the development of afferent arteriolar disease, which results in a reduced afferent vasoconstrictive (autoregulatory) response[21]. The afferent arteriolopathy is characterized by arteriolar hypertrophy and is driven largely by RAAS activation and oxidative stress; the impaired autoregulation results in increased transmission of systemic blood pressure to the glomerulus, resulting in elevated glomerular hydrostatic pressure[19,21,61]. These haemodynamic effects are thought to have a key role in mediating the progression of kidney disease.

Crystalline effects. Although many of the effects of urate are driven by intracellular actions, the oral ingestion of certain purines may result in the rapid synthesis of uric acid, with a transient increase in serum urate and acute uricosuria[62] (FIG. 2). Similarly, transient increases in serum urate can occur in humans in a variety of conditions, including heat stress[22] and rhabdomyolysis[63]. The increase in serum urate results in acute elevations in urinary uric acid that may precipitate urate crystal formation if the urine is acidic, as commonly occurs in the dehydrated state. Chronic glycosuria also results in uricosuria, possibly due to exchange of glucose for uric

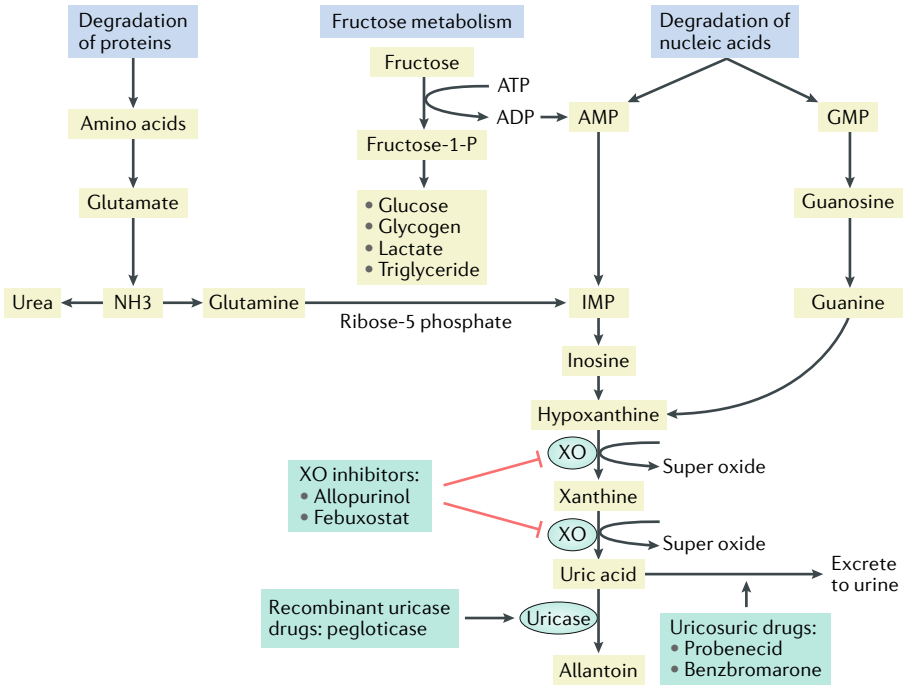

Fig. 2 | **Purine nucleotide degradation and fructose metabolism generate uric acid.** Uric acid is the final product of the metabolic pathway of purine nucleic acids. Fructose metabolism also leads to the production of uric acid. The xanthine oxidase (XO) inhibitors, allopurinol and febuxostat, block the conversion of hypoxanthine and xanthine to uric acid, and also reduce production of superoxide and hydrogen peroxide. Pegloticase is a recombinant porcine-like uricase that converts uric acid to allantoin. Once converted, allantoin is easily solubilized in water and excreted in the urine. Uricosuric medications, such as probenecid and benzbromarone, inhibit reabsorption of uric acid by the renal tubules and increase excretion of uric acid in urine. IMP, inosine monophosphate; NH3, ammonia.

acid by the apical SLC2A9b transporter[64], and may also result in formation of urinary uric acid crystals[24,65].

Once formed, urate crystals may induce an inflammasome-mediated inflammatory response in the kidney, possibly due to the crystals functioning as danger-associated molecular patterns[66,67] and/or through direct activation of the inflammasome[68], whereas the uptake of soluble uric acid by tubular epithelial cells might induce oxidative stress, epithelial-to-mesenchymal transition and stimulate inflammatory pathways[25,69–71]. Some evidence suggests that the crystalluria and tubular injury can be reduced by administration of bicarbonate, which alkalinizes the urine and improves urate solubility[23].

Uric acid effects on blood pressure. It is well-known that removal of an adrenal adenoma will not resolve hypertension in patients with primary hyperaldosteronism once renal microvascular disease has developed[72]. Similarly, hypertension induced by unilateral renal artery stenosis can initially be cured by removal of the ischaemic kidney, but hypertension will persist if substantial microvascular injury to the other kidney has occurred[73]. The development of low-grade kidney interstitial inflammation involving T cells and macrophages has been shown to mediate persistent hypertension even after the initiating hypertensive stimulus is removed (reviewed elsewhere[74]). Typically, this latter hypertension shows a marked rise in blood pressure in response to a high salt diet (termed 'salt-sensitive' hypertension) and is associated with a relative impairment in salt excretion compared with that of normotensive animals[74]. Hence, it is not surprising that hypertension induced by hyperuricaemia is initially responsive to ULT, but as renal vascular disease and interstitial inflammation develop, the hypertension becomes salt-sensitive and dependent on the kidney[75]. Thus, one would expect that the beneficial effect of ULT on hypertension would more likely be observed in patients with early hypertension and preserved renal function[76], especially in the setting of a low sodium diet.

Evidence from clinical trials

We identified 22 randomized clinical trials that have assessed the effect of lowering serum urate in patients with CKD (defined as estimated GFR (eGFR) <60 ml/min/1.73 m^2 but not receiving dialysis), and that included baseline eGFR and final (post-treatment) eGFR or serum creatinine level (TABLES 1,2). Although many of these trials reported the benefit of ULT to renal outcomes[30,31,49,77–87], others were considered negative[88–96]. Many of these trials have also been analysed in meta-analyses, the conclusions of which have also been variable, with some reporting that ULT likely confers a clinical benefit in patients with CKD[36–39,41], whereas others, including a 2017 Cochrane Review, express uncertainty, noting insufficient sample size, heterogeneity in study design, short follow-up times and variability in results[34,35]. A key scientific question is why some studies have shown clinical benefit whereas others have not, for if lowering serum urate level confers true benefit and protects kidney function, then there should be consistency in the clinical effect across CKD populations.

Although it remains possible that the variation in clinical results could mean that ULT does not provide a consistent benefit in all patients with CKD and hyperuricaemia, we sought to evaluate the trials from another perspective. Specifically, one possible explanation for the disparity in results relates to variability in the absolute rates of CKD progression within the population tested. Depending on the burden of risk factors and the extent to which these factors are controlled in a clinical population, rates of CKD progression measured in terms of eGFR decline may vary from minimal or no progression (for instance, a rate of eGFR decline of 0.5–1.5 ml/min/1.73 m^2 per year) to more rapid progression (for instance, rates of eGFR decline of >4 ml/min/1.73 m^2 per year). Given improvements in the management of aetiological factors and comorbidities, such as hypertension and diabetes, rates of eGFR decline among patients with early-stage CKD are much lower than they were two decades ago[97]. If the goal of a trial is to show that ULT slows renal progression, the studies need to be sufficiently large and/or of adequate follow-up to show statistically significant and clinically relevant CKD progression in the control group. Simply put, a study to prevent myocardial infarction will be negative regardless of therapy if no one in either the placebo or the treatment group has a myocardial infarction. Thus, if there is no difference in eGFR between the treatment and control groups at the study end point owing to a lack of progression of CKD in the control group, the study should be considered indeterminate, not negative, and should not be included in meta-analyses under the pretence that it was negative.

Table 1 | **'Interpretable' studies of ULT in patients with CKD**

Study design	Population	*n*	Design	Duration (months)	ΔeGFR or ΔsCr in the control group over the study period	ΔeGFR or ΔsCr in the treatment group over the study period	Net change with treatment	[a]*P* value	Ref.
Parallel RCT	CKD (eGFR <60)	T57; C56	Allo versus usual Tx	24	ΔeGFR −3.6	ΔeGFR +1.4	• ΔeGFR +5.0 • Improved	0.000	31
Follow-up RCT (post hoc)	CKD (eGFR <60)	T56; C51	Allo versus usual Tx	84	ΔeGFR −13.3	ΔeGFR −6.5	• ΔeGFR +6.8 • Improved	0.001	77
Parallel RCT	CKD (eGFR <60 or proteinuria >0.5 g/day) with HUA	T45; C41	Allo versus usual Tx	6	ΔeGFR −2.8	ΔeGFR +2.7	• ΔeGFR +5.6 • Improved	<0.05	78
Parallel, open-label RCT	[b]HTN with HUA	T30; C30	Feb versus non-Tx	6	ΔeGFR −3.4	ΔeGFR +3.7	• ΔeGFR +7.1 • Improved	[c]T: <0.001; C: 0.22	49
Parallel, placebo RCT	CKD (eGFR 15–60)	T45; C48	Feb versus placebo	3	ΔeGFR −4.4	ΔeGFR +3.2	• ΔeGFR +7.6 • Improved	0.05	87
Parallel, placebo RCT	HUA	T20; C18	Rasburicase versus placebo	8	ΔCCr −0.9	ΔCCr +12.7	• ΔCCr +13.8 • Improved	<0.001	79
Parallel RCT	Type 2 DN (eGFR 30–60) with HUA	T72; C64	Allo versus usual Tx	24	sCr +2.05	sCr +0.87	• ΔsCr −1.18 • Improve	<0.05	80
Parallel, open-label RCT	Proteinuria >0.5 g/day and/or sCr >1.35	T25; C26	Allo versus usual Tx	12	sCr +1.03	sCr +0.29	• ΔsCr −0.74 • Improved	0.08	30
Parallel RCT	sCr 1.5–3.0 with serum urate >7 mg/dl	T15; C17	Allo versus non-Tx	12	sCr +0.68	sCr +0.07	• ΔsCr −0.61 • Improved	[c]T: 0.35; C: <0.001	81
Parallel RCT	CKD (sCr 1.36–4.52) with HUA	T24; C23	Allo versus usual Tx	12	sCr +1.12	sCr +0.35	• ΔsCr −0.77 • Improved	<0.05	82
Parallel RCT	CKD (sCr 1.59–5.0) with HUA	T26; C25	Allo versus usual Tx	12	sCr +0.66	sCr −0.04	• ΔsCr −0.70 • Improved	<0.05	83
Parallel RCT	CKD (sCr 1.59–5.0) with HUA	T28; C29	Allo versus usual Tx	12	sCr +0.57	sCr −0.12	• ΔsCr −0.69 • Improved	<0.05	84
Parallel RCT	CKD (sCr 1.59–5.0) with HUA	T29; C28	Allo versus usual Tx	12	sCr +1.97	sCr +0.97	• ΔsCr −1.00 • Improved	<0.05	85
Parallel RCT	Non-diabetic patients with eGFR 30–59 and HUA	T53; C52	Allo versus usual Tx	24	[d]24 out of 53	[d]11 out of 52	Improved	0.013	86

Randomized trials of urate-lowering therapy (ULT) in patients with chronic kidney disease (CKD stage 3 or higher) except for one study in which the estimated glomerular filtration rate (eGFR) decreased by ≥4 ml/min/1.73 m^2 in the control group over the study period, and/or the difference in eGFR between the control and treatment groups was ≥5 ml/min/1.73 m^2 over the study period, and/or serum creatinine (sCr (in mg/dl; multiply by 88.4 to obtain value in μmol/l)) increased by ≥0.2 mg/dl (18 μmol/l) in the control group. [a]*P* values result from a direct comparison of the control group versus the treatment group except for two studies. [b]The participants in this study included individuals without CKD; 26 out of 60 participants had CKD stage 3 or higher. [c]*P* value results from a within-group comparison. No analytic data for direct comparison between groups were reported. [d]Number of patients showing deterioration in kidney function (annualized decline of eGFR −1.9 ml/min/1.73 m^2). Allo, allopurinol; C, control group; CCr, creatinine clearance (in ml/min/24 h); DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate (in ml/min/1.73 m^2); Feb, febuxostat; HTN, hypertension; HUA, hyperuricaemia; T; treatment group; Tx, treatment.

The 22 clinical trials available can therefore be separated into two groups, according to whether the control group showed evidence of clinically relevant progression of CKD (defined here as a eGFR decline ≥4 ml/min/1.73 m^2 over the course of the study), which in our opinion enables sufficiently valid comparisons of treatment and non-treatment arms[30,31,49,77–87] (TABLE 1), or whether the control group did not show clinically relevant progression of CKD (defined here as eGFR decline <4 ml/min/1.73 m^2 over the course of the study), which in our opinion does not allow the effect of treatment to be determined[88–96] (TABLE 2). We considered a threshold of 4 ml/min/1.73 m^2 over the study period (median 12 months; range 3–84 months) to determine progression versus non-progression of CKD from a clinical intervention perspective, as a change in kidney function of ≥4 ml/min/1.73 m^2 would be viewed by many clinicians as being clinically meaningful in the context of disease management. In a surprising number of trials, patients in the treatment group actually showed an improvement in kidney function[31,49,78,79,84,87] (which would not generally be predicted in CKD in which chronic scarring is a prominent feature). Thus, we also considered studies of ULT to be positive if the final difference in eGFR between the treatment and control arms was ≥5 ml/min/1.73 m^2, even if eGFR decline in the control group was <4 ml/min/1.73 m^2 over the study period. When eGFR measurements were unavailable, we considered an increase in serum creatinine level of ≥0.2 mg/dl (≥18 μmol/l) in the control group to be clinically relevant. Although studies with a very large sample size might provide sufficient power to detect small differences in rates of CKD progression, in populations in which progression rates are very low, such clinical trials generally take several years to demonstrate statistically meaningful differences. In addition, we posit that the clinician is much more interested in clinically meaningful changes in kidney function as

Table 2 | **Non-interpretable studies of ULT in CKD**

Study design	Population	*n*	Design	Duration (months)	ΔeGFR or ΔsCr in control group over the study period	ΔeGFR or ΔsCr in treatment group over the study period	Net change with treatment	*P* value	Ref.
Parallel, double-blind placebo RCT	CKD stage 3 with HUA	T219; C222	Feb versus placebo	25	ΔeGFR −0.97	ΔeGFR +0.48	• ΔeGFR +1.45 • Improved	NS	88
Parallel RCT	CKD (eGFR 30–60) with HUA	T62; C60	Topiroxostat versus placebo	22	ΔeGFR −0.46	ΔeGFR +0.64	• ΔeGFR +1.1 • Improved	NS	89
Parallel RCT	CKD (eGFR 30–59)	T52; C63	Allo versus usual Tx	12	ΔeGFR −2.2	ΔeGFR +1.7	• ΔeGFR +3.9 • Improved	Not reported	90
Parallel, double-blind placebo RCT	CKD (eGFR 15–50) with gout (ACR criteria) and serum urate >7 mg/dl	T17; C15	Feb versus placebo	12	ΔeGFR −2.05	ΔeGFR +0.33	• ΔeGFR +2.38 • Improved	NS	91
Parallel RCT	CKD stage 3 (eGFR 30–60) and LVH	T25; C26	Allo versus placebo	9	ΔeGFR +0.2	ΔeGFR +0.2	• ΔeGFR 0 • No Change	NS	92
Parallel, double-blind placebo RCT	Type 2 DN (eGFR 30–60) with HUA	T39; C37	Feb versus placebo	6	ΔeGFR −3	ΔeGFR −3	• ΔeGFR 0 • No Change	NS	93
Parallel RCT	IgAN with HUA, non-nephrotic, sCr <3 mg/dl	T21; C19	Allo versus usual Tx	6	ΔeGFR +5.3	ΔeGFR +3.7	• ΔeGFR −1.6 • Worsened	NS	94
Parallel, open-label RCT	CKD stage 3 with HUA	T21; C19	Feb versus non-Tx	3	eGFR −0.4	ΔeGFR −1.3	• ΔeGFR 0.9 • Worsened	NS	95
Parallel placebo RCT	Type 2 DN with CKD (proteinuria >500 mg/day and sCr <3 mg/dl)	T20; C20	Allo versus placebo	4	ΔsCr +0.00	ΔsCr +0.10	• ΔsCr +0.1 • Worsened	NS	96

All randomized clinical trials of urate-lowering therapy (ULT) in patients with chronic kidney disease (CKD) in which estimated glomerular filtration rate (eGFR) decreased by <4 ml/min/1.73 m^2 over the study period in the control group, and/or the difference in eGFR between control and treatment was <5 ml/min/1.73 m^2 over the study period, and/or the increase in serum creatinine (sCr (in mg/dl; multiply by 88.4 to get value in μmol/l)) was <0.2 mg/dl (18 μmol/l) in the control group. Studies are considered non-interpretable owing to minimal progression of CKD in controls. ACR, American College of Rheumatology; Allo, allopurinol; C, control group; CCr, creatinine clearance (in ml/min/24 h); DM, diabetes mellitus; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate (in ml/min/1.73 m^2); Feb, febuxostat; HF, heart failure; HTN, hypertension; HUA, hyperuricaemia; IgAN, IgA nephropathy; LVH, left ventricular hypertrophy; NS, not significant; T, treatment group; Tx, treatment.

opposed to minimal differences that are statistically significant[98].

In our opinion, stratifying studies according to the absolute rates of CKD progression in the control groups reveals the true clinical benefit of ULT in slowing the progression of CKD (TABLE 1). 14 of the 22 studies were considered to be 'interpretable studies' in that they showed progression of CKD in control groups. One study[49] included patients with mild CKD (only 26 of the 60 participants had CKD stage 3 or higher; nevertheless, patients in the control arm of that study showed deterioration of eGFR of −3.4 ml/min/1.73 m^2 over the 6-month study period, and the final difference in eGFR between the treatment and the control group was ≥5 ml/min/1.73 m^2. In 12 of the 14 'interpretable studies', patients in the treatment group had significantly higher eGFR than patients in the control group, although two studies were analysed only for within-group comparison, for which the *P* values between control group and treatment group were different[49,81].

Conversely, studies deemed to be non-interpretable owing to a lack of progression in the control group are all non-significant with no difference in the rate of renal progression between patients in the treatment and control groups (TABLE 2). One explanation for this lack of difference between treatment and control groups could be that the observational period was short (<1 year) in some studies. Studies in which the observational period was ≥1 year but did not demonstrate a benefit of ULT could reflect a high standard of care[88,89,91]. Of note, 'non-interpretable' studies of longer duration (≥12 months) had a tendency towards improved kidney function in the treatment group, whereas ULT tended to result in slightly worse renal function in studies of shorter duration (≤6 months). These differences are probably due to an acute reduction in kidney function that occurs with initiation of ULT[94] owing to its haemodynamic action to reduce glomerular pressure[21], a process similar to that of ACE inhibitors and SGLT2 inhibitors.

Taken together, we believe that these data provide strong evidence that lowering serum urate levels slows the deterioration of kidney disease in hyperuricaemic patients with non-dialysis-dependent CKD, who progress at rates of eGFR decline of >4 ml/min/1.73 m^2 over a period of 1–2 years, especially for CKD stage 3 or higher. As most patients in these trials were receiving a standard of care with RAAS inhibitors, the studies support the addition of ULT to the routine management of patients with hyperuricaemia and CKD stage 3 or higher. However, the optimal threshold of serum urate prompting initiation of ULT and the target serum urate level required to achieve maximal clinical benefit deserve further exploration.

Considerations for the use of ULT

Safety of ULT. ULT is not FDA-approved for the treatment of CKD; thus, the decision to initiate therapy must involve careful discussions with the patient regarding the pros and cons of treatment and the safety of each urate-lowering agent. The first

step should be to reduce dietary foods that might contribute to the development of hyperuricaemia, such as sucrose and foods with a high purine content. Sucrose and high fructose corn syrup are sweeteners that contain fructose, which generates uric acid during its metabolism, whereas high purine-containing foods such as beer and shrimp also increase uric acid from the stepwise degradation of purines to uric acid (FIG. 2). Unfortunately, reducing fructose and purine intake typically reduces serum urate by only 0.5–2.0 mg/dl (30–120 μmol/l)[99,100]. Where possible, medications that induce hyperuricaemia as an adverse effect (such as thiazide diuretics) should be stopped or reduced. If hyperuricaemia persists, we recommend that xanthine oxidase inhibitors be considered as the primary class of ULTs for patients with CKD. Concerns have been raised about the use of the xanthine oxidase inhibitor allopurinol, owing to the risk of potentially fatal hypersensitive reactions[101]. A 2011 report recognized that allopurinol hypersensitivity is observed mainly in patients who carry the HLA-B*58:01 genotype[102]. Although this HLA genotype is rare in individuals of European ancestry (<1%), it is more common in African–Americans (4%), and in individuals of Asian descent, especially in Han Chinese (10–15%). Therefore, it has been recommended to genotype African–Americans and Asians before starting allopurinol[103].

There is also concern that allopurinol might be associated with a higher risk of nephrotoxicity in patients with hyperuricaemia and CKD than in those without CKD, owing to the rapid accumulation of xanthine, which could potentially crystallize in the urine and cause tubular injury. This concern has lessened following the publication of a 2018 study that showed that initiation of allopurinol therapy (≥300 mg per day) among patients with newly diagnosed gout was associated with a lower risk of renal function decline than non-initiation of therapy[104]. Nevertheless, we recommend initiating allopurinol therapy at a low dose (50 mg/day) and to increase the dose every several weeks until a dose of 300 mg/day is achieved. If a skin rash develops on treatment, allopurinol hypersensitivity should be considered likely, the drug must be discontinued immediately and the primary physician or responsible specialist contacted.

Despite the risks described above, we recommend allopurinol as first-line therapy on the basis of findings from several clinical studies that suggest that allopurinol might provide cardiac protection in patients with CKD[31,77,92] or gout[105]. Although another xanthine oxidase inhibitor, febuxostat, has an advantage over allopurinol in that its dose does not need to be modified with declining renal function, it has been associated with an increased risk of cardiovascular events and death compared with that associated with allopurinol use[106], although this finding has not been uniformly observed[107]. Of note, there is no evidence to suggest that febuxostat is associated with greater cardiovascular risk than no xanthine oxidase inhibitor treatment, and it is possible that both febuxostat and allopurinol are beneficial but have different degrees of clinical efficacy. Nevertheless, the FDA has issued a 'black box' warning for the use of febuxostat in patients at cardiovascular risk, which includes patients with CKD. Hence, we would not use febuxostat as a first-line agent for the treatment of hyperuricaemia in patients with CKD at this time. Other agents that could be used to lower urate levels in patients with CKD include the recombinant porcine-like uricase pegloticase (which metabolizes uric acid to allantoin), or xanthine oxidase inhibitor combined with a uricosuric agent such as probenecid or lesinurad. Further studies are needed to assess the efficacy and safety of these latter treatments.

Target treatment levels. Although the threshold values of serum urate above which intervention should be initiated are not clearly defined, we propose that ULT is initiated in patients with serum urate levels ≥7 mg/dl (416 μmol/l), and suggest reduction to levels <6 mg/dl (357 μmol/l)[108,109]. However, we recognize that additional studies are required to determine optimal target thresholds for intervention and the extent to which serum urate should be lowered to achieve the greatest clinical benefit.

Should all patients receive ULT? Our analysis of clinical trials suggests there are important benefits of lowering serum urate level in patients with hyperuricaemia and CKD (TABLE 1). However, advances in the management of CKD over the past couple of decades have led to the stabilization of renal function for a large number of patients, resulting in a lack of clinically important disease progression[97] (TABLE 2). In patients with CKD who do not experience clinically relevant progression of kidney disease, ULT should probably not be initiated unless there are other compelling indications such as a history of gout or urate stones, as the potential adverse effects of these agents could potentially confer a greater risk than benefit. We recognize that the quality of the studies performed to date are variable, and it remains reasonable for clinicians to await the results of two large, placebo-controlled clinical trials of ULT in patients with CKD (that is, the CKD-Fix trial in Australia and the PERL study in the USA, from which important data are likely to emerge. The PERL study is particularly interesting as it is a 3-year study that evaluates the benefit of ULT in patients with type I diabetes mellitus and a history of eGFR progression of ≥3 ml/min/1.73 m^2 per year with a relatively low serum urate level (≥4.5 mg/dl (268 μmol/l))[110]. Nevertheless, our recommendation is that serum urate should be measured in all individuals with CKD, and that treatment should be initiated for all patients with CKD who demonstrate evidence of disease progression based on an eGFR trajectory of >4 ml/min/1.73 m^2 over 1–2 years.

Contradictory genetic studies

One remaining question is why Mendelian randomization studies performed to date have failed to identify serum urate as a risk factor for CKD[32,111]. A key element in all of these studies is that the genetic polymorphisms studied are principally involved in urate transport. How these polymorphisms modify intracellular urate is not known, but they are unlikely to influence intracellular xanthine oxidase activity. In addition, few studies have investigated the interaction of genetic polymorphisms affecting serum urate with dietary or environmental factors, despite the well-known fact that dietary sugar and purine intake can stimulate uric acid synthesis (FIG. 2). Moreover, these polymorphisms only explain a small fraction (typically about 6%) of the population variance in serum urate levels[32,111]. Finally, it is well known that important physiological pathways, such as the RAAS, do not necessarily show up in genome-wide association studies as important predictors of hypertension, despite the known physiological relevance of this pathway to hypertension and the known efficacy of RAAS blockers. Thus, despite a lack of genetic evidence, studies showing the benefits of reducing serum uric acid levels for blood pressure using a variety of agents (xanthine oxidase inhibitors, uricosuric agents and recombinant uricase proteins) support the role of uric acid in the development of hypertension[112,113].

Conclusions

The debate on the role of uric acid in CKD dates back to the 1800s, and the scientific field has swayed back and forth with regard to its importance over time. In the past two decades, a compelling body of evidence has emerged – both experimental and clinical — that directly links hyperuricaemia with the development and progression of CKD. In view of this evidence, we would argue that hyperuricaemia has a detrimental impact on kidney function and that treatment of so-called asymptomatic hyperuricaemia to slow or delay the progression of CKD should be a key management strategy. We submit that several knowledge gaps remain with regard to the management of hyperuricaemia and that additional clinical studies are needed to determine the threshold levels for initiation of ULT treatment, optimal target levels for clinical efficacy, and the impact of treatment across the spectrum of CKD and patient subgroups. Nevertheless, we believe that the time has come to recognize serum urate as a true risk factor for CKD that is likely to benefit from effective ULT treatment to protect kidney function.

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Y.S., D.I.F., A.G.S., D.-H.K., L.G.S.-L. and R.J.J. researched data for the article, contributed substantially to discussion of the article's content and wrote the article. All authors contributed to review/editing of the manuscript before submission.

Competing interests
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