

URIC ACID IN CHRONIC KIDNEY DISEASE: A CLINICAL APPRAISAL

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ABSTRACT

A consistent body of evidence supports an independent association between uric acid (UA) level and the risk of chronic kidney disease (CKD) in humans. It has been observed in experimental data that UA is capable of inducing renal damage through several pathways, including activation of the renin-angiotensin-aldosterone system (RAAS), oxidative stress, and inflammation. Treatment with urate lowering agents and RAAS inhibitors prevented renal insult mediated by UA in animal models. Both of the xanthine oxidase inhibitors available in clinical practice, allopurinol and febuxostat, were efficient in controlling gout flares. However, data from randomised controlled trials are still inconsistent in relation to their benefit for slowing CKD progression. This review discusses the metabolism of urates in humans as well as the experimental and clinical evidence linking UA to CKD. Current evidence about the effect of allopurinol and febuxostat on CKD progression is also considered.

Keywords: Uric acid (UA), chronic kidney disease (CKD), allopurinol, febuxostat, humans.

INTRODUCTION

Stepwise mutations of the uricase promoter gene occurred in lesser and great apes between 9 and 15 million years ago. Uricase silencing led to an inability in hominoids to convert uric acid (UA) into allantoin, which is disposable via renal excretion; this led to higher circulating levels of UA compared with their ancestors.¹ Increased UA concentration, induced by poor nutritional salt intake, may have been adjuvant in the tertiary development of bipedal locomotion. The maintenance of high blood pressure through activation of the renin-angiotensin-aldosterone system (RAAS), afferent arteriosclerosis, and increased salt sensitivity are suggested as the main favourable adaptive responses offered by uricase silencing during the Miocene period.² The contemporary Western diet, which is richer in proteins, alcohol, and fructose, compared with the presumed nutritional profile of the Quaternary period, may have led to an

excessive load of UA with potential disadvantageous effects thereafter (a maladaptive response).³

Gout represents the traditional consequence of UA excess in contemporary subjects as they are predisposed to UA deposition in joints and soft tissues. Several trials have demonstrated how lowering UA synthesis by the administration of xanthine oxidase inhibitors was effective in reducing the incidence of gout flares.⁴⁻⁸ More recently, observational studies have linked UA to a variety of unfavourable outcomes, such as cardiovascular disease,^{9,10} hypertension,^{11,12} metabolic syndrome,¹³ diabetes,¹⁴ mortality,^{10,15} and chronic kidney disease (CKD).¹⁶ This review will consider the metabolism of UA in humans and the experimental and clinical evidences linking UA to CKD. The discussion will also cover the potential benefits offered by xanthine oxidase inhibitors on CKD progression.

URIC ACID METABOLISM IN HUMANS

UA is the final enzymatic end product of purine metabolism in humans. UA is derived from the endogenous degradation (500–600 mg/day) of adenosine triphosphate, nucleic acids, and amino acids, as well as from nutrients (100–200 mg/day) rich in proteins, alcohol, and fructose.^{3,17} Transformation of xanthine into UA by xanthine oxidase represents the last reaction of the purine catabolic pathway. The synthesis of UA mainly occurs in the liver and intestine, with less production observed in peripheral tissues such as the muscle, the kidney, and the endothelium.¹⁸ UA is thereafter excreted in urine (70%), and in biliary fluid to a lesser extent (30%).^{17,18} Almost all of the circulating UA is filtered by glomeruli. Although the handling of UA in the proximal convoluted tubule (PCT) is far more complex, including pre-secretory reabsorption, secretion, and post-secretory reabsorption in the first, second, and third segment of PCT, respectively,¹⁷ it is accepted that the PCT reabsorbs almost 90% of the filtered UA,¹⁹ principally through the action of the urate anion transporter (URAT) 1, glucose transporter (GLUT) 9, and organic anion transporters 1 and 3.^{17,20} Notably, GLUT and URAT are inhibited by probenecid and benzbromarone,¹⁷ while losartan and angiotensin II receptor blockers can inhibit URAT1.^{17,21}

Circulating UA exists as a urate anion at the physiological pH due to its pK_a of 5.75, while it is present in urine at pH of 5–6 in its acidic form.²⁰ The solubility limit of circulating UA corresponds to 6.8 mg/dL at 37°C and decreases at colder temperatures, reaching 4.5 mg/dL at 30°C. Hyperuricaemia is variably defined as serum UA levels >6.8 mg/dL or 7.0 mg/dL in adults,^{22,23} while guidelines for gout management recommend to lower serum UA below 6 mg/dL.²⁴

URIC ACID AND CHRONIC KIDNEY DISEASE PROGRESSION: MECHANISMS

The solubility of UA in urine is highly dependent on several factors beyond uricosuria. This also exposes individuals with normal renal excretion of urates to the risk of renal stones, irrespective of concomitant predisposing conditions such as persistently low urinary pH or reduced urine volume. Although UA nephrolithiasis represents the most known cause of renal disease, a recent body of evidence was reported on how UA

overload may induce asymptomatic kidney damage through crystal independent pathways including oxidative stress, activation of RAAS, reduced synthesis of nitric oxide, and inflammation.²⁵

Hyperuricaemic rats developed hypertension and ischaemic renal injury independent of urate crystal deposition.²⁶ Notably, hyperuricaemia was associated with increased renal vascular resistance and reduced tubular excretion of sodium, mediated by increased synthesis of renin and a reduced synthesis of nitric oxide.²⁶ Hypertension was consequently prevented by the administration of allopurinol, enalapril, and L-arginine.²⁶ Arteriopathy of the afferent glomerular vessels improved after administration of enalapril but not after administration of hydrochlorothiazide despite a similar blood pressure control, revealing that UA induced renal vascular damage independently from the hypertensive mechanism.²⁷ Furthermore, correcting high UA levels through the administration of febuxostat improved afferent arteriolar morphology and tubulointerstitial fibrosis, reduced proteinuria, and preserved renal function in rats with CKD.²⁸

Apoptosis of proximal tubular cells occurred under exposition to high UA levels *in vitro*, due to its pro-oxidant effects mediated by the upregulation of nicotinamide adenine dinucleotide phosphate oxidase and NOX-4.²⁹ Apoptotic events were prevented by the addition of URAT1 blockers (probenecid and losartan), showing that UA may elicit oxidative effects at an intracellular level.²⁹ Furthermore, repeated experimental data has demonstrated how UA may induce renal damage through the activation of proinflammatory cascades, mediated by tumour necrosis factor alpha, cyclo-oxygenase, and inflammatory transcription factor nuclear factor kappa B.³⁰ This hypothesis was confirmed by the renal protective effect elicited by allopurinol in diabetic rats, resulting from the inhibition of an inflammatory cascade triggered by intracellular adhesion molecule 1 in tubular epithelial cells.³¹

UA may also contribute to CKD progression through indirect processes. UA has been proposed as a promoter of the cardiorenal metabolic syndrome, which is currently defined as an interactive milieu of risk factors for CKD and cardiovascular disease, including insulin resistance, obesity, dyslipidaemia, hypertension, and diastolic dysfunction.²⁵ Repeated experimental data raised evidence on how UA may induce the synthesis

of lipids and insulin resistance, both of which are involved in the onset of metabolic syndrome, resulting in a higher risk of CKD.³² UA-dependent intracellular and mitochondrial oxidative stress resulted in a relevant induction of hepatic lipogenesis.³³ UA-induced oxidative and inflammatory reactions in the adipocytes of fructose-fed rats, leading to insulin resistance and an unbalanced leptin-adiponectin ratio, were improved by allopurinol administration.^{34,35} Oxidative stress was reported in insulin-secreting islet cells exposed to a high concentration of UA, raising the risk of islet dysfunction.³⁶ Furthermore, normalisation of circulating UA levels with febuxostat reduced renal vasoconstriction and afferent arteriolar area, and improved insulin sensitivity as well as blood and glomerular pressure in rats affected by metabolic syndrome.^{32,37}

Xanthine oxidase inhibitors have also been suggested as the cause of organ damage attributed to high UA levels.^{18,32} The pro-oxidant effects of xanthine oxidase are well known; however, no studies have investigated the effect of xanthine oxidase on CKD progression independent of the action of UA in humans.

URIC ACID AND CHRONIC KIDNEY DISEASE: OBSERVATIONAL DATA

The association between UA and the risk of CKD has been repeatedly investigated in observational studies.^{16,18} A recent meta-analysis by Li et al.¹⁸ reported a significant association between hyperuricaemia and new onset CKD in five studies (odds ratio [OR]: 2.11; 95% confidence interval [CI]: 1.70–2.619). A 6% higher risk of incident CKD was observed for each 1 mg/dL increase of UA (OR: 1.06; 95% CI: 1.04–1.08).¹⁸ Subgroup analysis revealed a slightly stronger association between UA levels and CKD in Western populations compared with Asian populations, potentially accounted for by the higher purine intake in the Occidental compared with the Eastern diet.¹⁸ The risk of CKD progression was also addressed in a large cohort of volunteers in California over a median follow-up of 25.7 years.³⁸ Subjects in the fourth quartile of UA levels (6.00–14.90 mg/dL) had a 2-fold increased risk of requiring dialysis or renal transplantation compared with those in the lowest quartile (0.10–4.17 mg/dL; hazard ratio [HR]: 2.15; 95% CI: 1.65–2.77).³⁸ More recently, UA levels >6.5 mg/dL were retrospectively associated with the risk of progression to end-stage renal

disease (ESRD) among 803 CKD patients (HR: 3.39; 95% CI: 1.55–7.42).³⁹ Similar results, but with a significant gender interaction, were reported among 48,177 adults in Okinawa.⁴⁰ Hyperuricaemic women (UA levels >6 mg/dL) presented an independent higher risk of progression toward ESRD compared with normouricaemic women (HR: 5.77; 95% CI: 2.31–14.21).⁴⁰ In the multivariate Cox analysis in men, hyperuricaemia was not a significant risk factor for ESRD (UA levels >7.0 mg/dL),⁴⁰ however data concerning differences in UA toxicity between males and females remains conflicted. The prevalence of hyperuricaemia and gout were higher in males^{41,42} and several authors reported a greater association between UA and CKD in men.^{43,44} Furthermore, the meta-analysis by Li et al.¹⁸ showed a descriptively higher risk of CKD for each 1 mg/dL increase of UA in males (OR: 1.43; 95% CI: 1.05–1.94) compared with females (OR: 1.21; 95% CI: 1.04–1.41).

The aforementioned link between high UA levels and CKD is not universally confirmed. In the Mild to Moderate Kidney Disease Study (MMKD), the association between UA levels and progression of CKD, defined as the doubling of serum creatinine or dialysis need, lost significance after adjustment for basal kidney function.⁴⁵ A *post hoc* analysis of the Modification of Diet in Renal Disease (MDRD) study did not confirm any association between UA levels and the risk of kidney failure in Stage 3–4 CKD patients.⁴⁶ Several factors accounting for this negative result were proposed by the authors, such as the enrolment of patients with considerable risk factors for CKD progression, the presence of patients randomised to the low blood pressure group with consequent delayed kidney failure potentially mediated by strict blood pressure control and, thirdly, the adjustment for measured glomerular filtration rate (GFR).⁴⁶ Thus, several authors have raised the hypothesis that UA should be taken as a marker of reduced GFR rather than a potential effector of renal damage, accounting for the inconsistent association between UA and CKD progression after adequate adjustments for GFR.¹⁸ More recently, a polymorphism of GLUT9 was strongly associated with serum UA levels and with a significant risk of CKD progression.⁴⁷

A negative association between UA and CKD has also been reported. In a retrospective cohort of 94,422 patients in Taiwan, a minority of 50 patients with UA levels <2.0 mg/dL presented a higher risk of CKD progression.⁴⁸ More recently,

Kanda et al.⁴⁹ showed a U-shaped association between UA level and loss of kidney function in healthy subjects.⁴⁹ Oxidative stress induced by renal hypouricaemia was suggested as a potential mechanism underlying the loss of GFR due to UA levels <2.0 mg/dL. Although the real impact of hypouricaemia on renal function remains unknown, these preliminary data raise concerns about the adequacy of a 'the lower the better' approach to UA targets in CKD.

XANTHINE OXIDASE INHIBITORS: OVERVIEW AND LESSON FROM GOUTY PATIENTS

Two classes of drugs are currently available to reduce UA levels: xanthine oxidase inhibitors (allopurinol and febuxostat) and uricosuric agents (probenecid, benzbromarone, and sulfapyrazone).

Allopurinol works as a purine substrate for xanthine oxidase, blocking the synthesis of xanthine and UA.⁵⁰ Allopurinol is thereafter hydroxylated by xanthine oxidase to its active catabolite oxypurinol, which is considered more active than allopurinol as it is more stable, more easily available, and has a longer half-life.⁵¹ Allopurinol is also transformed into other nucleotide derivatives by hypoxanthine-guanine phosphoribosyltransferase and orotate phosphoribosyltransferase.⁵⁰ Allopurinol and its metabolites are then capable of inhibiting T cell function, which may result in allopurinol hypersensitivity syndrome.⁵² Furthermore, allopurinol and oxypurinol accumulation may lead to tissue injury with secondary immune reaction, induced by antigen release.⁵³ Metabolism of allopurinol is based on hepatic conversion to oxypurinol, which is then excreted in urine. Renal patients are thus exposed to a higher risk of allopurinol toxicity, requiring proper dose adjustments.⁵⁰ Although the approved dose of allopurinol ranges from 50–800 mg, the mean delivered dose corresponds to 300 mg,⁵⁴ with even lower dosages in renal patients leading to a risk of inadequate efficacy.⁵⁵

Febuxostat is differentiated from allopurinol by several characteristics. The non-purine based structure of febuxostat delivers selective inhibition of both the reduced and the oxidative form of xanthine oxidase.⁵⁰ Febuxostat is metabolised by liver enzymes to acyl-glucuronide, generating only a minimal amount of oxidative metabolites. Compared with allopurinol, febuxostat provides a

stronger and quicker reduction of UA levels without exposing renal patients to drug accumulation.⁵⁰

Trials that have compared allopurinol and febuxostat in patients with gout have provided significant outcomes.^{4–8} Although febuxostat lowered UA levels in a greater proportion of patients and to a greater extent than allopurinol, none of the trials demonstrated a significant difference in the incidence of gout flare and tophi reduction between the treatment arms.^{4–8} Notably, the absolute risk of gout flares was highly sensitive to the length of follow-up, reaching a rate of flares close to zero after 40 months of treatment.^{6,7} Urate lowering therapy was followed by a transitory increase of gout flares, especially in patients receiving febuxostat at high dosage;^{4–8} this inspired an experimental extension of prophylaxis with low dose colchicine \leq 6 months in the more recent CONFIRMS trial.⁸ Liver function test abnormalities were a common cause of drug discontinuation; the few cardiovascular events were not attributed to the study drug.^{4–8} Notably, the APEX trial included a minority of 35 patients with serum creatinine 1.5–1.9 mg/dL.⁵ None of the 10 patients randomised to allopurinol 100 mg/day achieved UA levels <6 mg/dL, compared with 44%, 45%, and 60% of those receiving febuxostat 80 mg, 120 mg, and 240 mg, respectively.⁵ The CONFIRMS trial included 35% of patients with mild or moderate renal impairment (defined as an estimated creatinine clearance of 60–89 mL/min and 30–59 mL/min, respectively).⁸ Patients were randomised in a 1:1:1 fashion to febuxostat 40 mg, febuxostat 80 mg, and allopurinol (300 mg/day for subjects with normal renal function and mild renal impairment or 200 mg in the presence of moderate renal impairment). The proportion of subjects with mild-to-moderate renal impairment achieving UA levels <6 mg/dL was higher in the treatment arm with febuxostat 80 mg (71.6%) compared with those with febuxostat 40 mg (49.7%) and allopurinol (42.3%) ($p < 0.001$ for each comparison). *Post hoc* analysis of the FOCUS trial estimated an improvement of 1 mL/min of GFR for every 1 mg/dL reduction of UA level.⁵⁶

XANTHINE OXIDASE INHIBITORS AND CHRONIC KIDNEY DISEASE PROGRESSION: CLINICAL TRIALS

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines declared that there was a lack of evidence to support or refute the use

of urate lowering agents in renal patients in order to delay the progression of CKD.⁵⁷ Although the evidence remains inconclusive, recent investigations added encouraging results on the topic. The meta-analysis by Bose et al.⁵⁸ included eight randomised controlled trials comparing the effect of allopurinol with placebo or no treatment on renal outcomes. There was a slight but significant reduction of creatinine in favour of allopurinol in three trials conducted among CKD patients (-0.4 mg/dL; 95% CI: -0.8-0.0, p=0.03), though treatment with allopurinol was not associated with any benefit in terms of GFR change, proteinuria, and progression to ESRD.⁵⁸ More recently Goicoechea et al.⁵⁹ randomised 113 CKD patients to allopurinol 100 mg versus standard therapy. After 84 months of follow-up, patients receiving allopurinol experienced a mild but significant reduction in circulating UA level (from 7.8±2.1 mg/dL to 6.6±1.5 mg/dL, p=0.04) and a lower GFR decline (-6.5±1.6 mL/min/1.73 m²) compared with standard therapy (-13.3±5.0 mL/min/1.73 m²). Allopurinol was also associated with a lower risk of cardiovascular events (HR 0.43; 95% CI: 0.21-0.88).⁵⁹ Sircar et al.⁶⁰ randomised 108 CKD patients to febuxostat 40 mg versus placebo. Six months of treatment with febuxostat was associated with a stronger reduction in UA levels (from 9.0±2.0 to 5.2±1.5 mg/dL) and

with improvement of GFR (+3.2 ml/min/1.73 m²)⁶⁰ compared with that observed with allopurinol by Goicoechea et al.⁵⁹

CONCLUSIONS

The majority of observational data support an independent association between high UA levels and the risk of CKD. However, conflicting results have also been published in regards to this. Experimental evidence has been reported on how UA may directly induce renal damage through the activation of RAAS, inflammation, and intracellular oxidative cascades. RAAS inhibitors or urate lowering agents were shown to be effective in correcting the renal damage induced by UA in animal models. Several randomised controlled trials thereafter investigated the effect of xanthine oxidase inhibitors on renal outcomes, leading to encouraging, but still inconsistent results. Febuxostat may represent a safe and effective medication for lowering UA levels, avoiding the risk of toxicity, or underpowered efficacy of allopurinol in renal patients. Although UA can be considered as a risk factor as well as an effector of renal damage, currently the strength of evidence remains insufficient to recommend a widespread adoption of xanthine oxidase inhibitors for slowing the progression of CKD.

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