Gout Education Society

Roundtable Consensus Paper

Exploring the Link Between Gout & Renal Health: A Roundtable Discussion

Raising Awareness & Reinforcing Treatment Adherence

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Introduction

Gout is an extremely serious and potentially debilitating disease that affects more than 9.2 million Americans. It is the most common form of inflammatory arthritis, yet it is widely misunderstood and poorly treated. While serious on its own, gout is even more dangerous when combined with other health issues. The connection between gout and renal health is especially important and will be highlighted in the following sections.

Gout is caused by hyperuricemia—high levels of uric acid in the blood above 6.8 mg/dL. This buildup of serum uric acid (sUA) can lead to crystal formation and deposition in and around joints—ultimately leading to painful flares and destructive arthritis. Kidneys have an intricate system of organic acid and specific uric acid transporters that normally maintain sUA levels in a range that doesn't favor urate precipitation and crystal formation. Disruption of normal transporter function in the proximal convoluted tubule by genetic mutations, pharmacologic interference or diminished glomerular filtration from any cause can lead to hyperuricemia.

When patients have renal disease, gout treatment becomes much more complex but also makes control of hyperuricemia more imperative. If patients do not receive proper care and treatment for both gout and their renal disease, both conditions are likely to worsen at an accelerated pace.

Regarding gout and renal health, it is important to build patient awareness—and knowledge of the need for ongoing treatment for better patient outcomes. Research from the Gout Education Society has revealed:

- Three out of four Americans don't know that gout is associated with renal health.
- Six out of 10 Americans with gout don't get their sUA levels checked regularly, and two-thirds don't take daily uric acid-lowering medications.
- Four in 10 gout sufferers say gout is more painful than having kidney stones, reinforcing a need for treatment plans to address both gout and kidney health.

The Gout Education Society (www.GoutEducation.org) is dedicated to raising awareness about gouty arthritis and providing education to both the public and professional community. Since its inception in 2005, the society has shared and followed the guidelines for gout according to the American College of Rheumatology (ACR)—recommending that people with gout aim for a uric acid level of 6.0 mg/dL or below to optimize patient treatment.

To understand the link between gout and renal health and improve public education, the Gout Education Society hosted a virtual roundtable discussion after the virtual ACR Annual Meeting on Nov. 20, 2020, with rheumatologists, nephrologists and industry organizations.

Gout, Renal Disease and Other Comorbidities: Overview and Impact

Data from the National Health and Nutrition Examination Survey (NHANES) showed that gout affected around 9.2 million Americans, with a prevalence of 3.9%.[1] In this population of American gout patients, 71% also suffered from chronic kidney disease (CKD) stage 3 or worse, and 20% had CKD stage 4 or higher, (16% in men and 31% in women). Additionally, 71% were hypertensive; 56% were obese; 26% were diabetic; and 24% suffered from nephrolithiasis.

Additionally, patients with CKD have an approximately threefold elevated risk of developing gout.[2,3] The association between estimated glomerular filtration rate (eGFR) and gout is nonlinear, with a sharp increase in prevalence of gout for patients with eGFR <60 ml/min/1.73m^2; there is approximately a two- to threefold increase in prevalence of gout for each 30 ml/min/1.73m^2 decrease in eGFR.[4] Gout also increases the rate of progression of CKD.[5] Thus, CKD is a key comorbidity in gout and vice versa.

Does CKD modify the severity of gout? This has not been extensively studied. However, a handful of papers indicate that reduced glomerular filtration rate (GFR) is correlated with earlier onset of tophaceous gout and the tophus burden in gout. For example, Nicola Dalbeth, MBChB, MD, FRACP, FRSNZ, and her team published a paper[6] examining the relationship between GFR (creatinine clearance) and the number of tophi. They found a correlation between reduced GFR and the number of tophi, particularly stage 4 CKD, where the multivariate risk for a higher number of tophi goes up to 12. This suggests that patients with CKD and gout have a greater tophus burden (Figure 1).

Relationship between creatinine clearance levels and the number of tophi: Poisson regression analysis

Creatinine clearance (ml/min)	Unadjusted relative risk estimate (95% CI)	Unadjusted P	Multivariate* adjusted relative risk estimate (95% CI)	Multivariate* adjusted P
>90	1.0 (ref)	-	1.0 (ref)	-
>60-90	2.6 (1.1-5.9)	0.025	2.5 (1.1-5.8)	0.031
>30-60	7.2 (3.3-15.7)	<0.001	6.1 (2.8-13.7)	<0.001

**adjusted for ethnicity, corticosteroid use, diuretic use and colchicine use.*

Figure 1

Case Study #1: Issues in Uric Acid Homeostasis Relevant to Managing CKD Patients

This 67-year-old patient was seen in the renal clinic for CKD follow-up. His baseline creatinine had fluctuated over the years, recently varying from 2.1 to 2.4 mg/dL. His creatinine had been 1.6 mg/dL seven years prior to this clinic visit and 1.0 mg/dL 17 years prior. He had modest proteinuria, about 0.3 grams per day by urine protein/creatinine ratios. His comorbidities included gout and congestive heart failure (CHF). He had recently been admitted for a CHF exacerbation, requiring treatment with both loop and distal tubular diuretics. This resulted in superimposed acute kidney injury (AKI), with a peak creatinine of 3.2 mg/dL. His diuresis was associated with a serum urate level of 13.0 mg/dL and a gout flare.

His other comorbidities included a 20-year history of type 2 diabetes, obesity, obstructive sleep apnea and hypertension. He was taking more than a dozen medications, including a relatively high dose of furosemide (80 mg bid), metolazone (5 mg qod), niacin (1,000 mg daily), colchicine (0.6 mg daily) and allopurinol (100 mg daily for recent gout flares), as well as a low dose of aspirin (ASA) (81 mg daily).

His physical exam was notable for significant truncal obesity and hypervolemia, with evidence of pulmonary edema and peripheral edema. His lab results revealed an eGFR of 16 with creatinine of 3.8 mg/dl. His serum urate (SU) level was 9.1 mg/dL, despite modest amounts of allopurinol. His parathyroid hormone (PTH) was also 305 with replete vitamin D level.

The first question to consider is why this patient is so hyperuricemic. The relevant factors include the following:

1 Metabolic syndrome

Hyperuricemia and gout have a strong association with metabolic syndrome, insulin resistance and type 2 diabetes.[7–9] Physiological euglycemic hyperinsulinemia induced by insulin infusion (6 pmol/min/kg) in healthy volunteers acutely reduces urinary urate excretion,[10–12] suggesting a key role for hyperinsulinemia in the pathogenesis of hyperuricemia.

2 CKD

As noted above, there is a strong association between gout and CKD. CKD clearly leads to hyperuricemia—for example, 86% of gout patients with a SU of over 10.0 mg/dL have an eGFR less than 90 ml/min/1.73m^2.[13]

3 Hyperparathyroidism

This patient had significant secondary hyperparathyroidism. There is a strong association between hyperuricemia and hyperparathyroidism, with normalization of SU after parathyroidectomy.[14–16] A uremic mouse model of secondary hyperparathyroidism suggested that downregulation of ABCG2 was responsible for development of hyperuricemia, with administration of cinacalcet normalizing serum urate.[17]

4 Niacin and ASA therapy

This patient's therapy with both niacin and ASA contributed to his hyperuricemia. Several monovalent anions have anti-uricosuric effects at low concentrations, due to "trans-activation" of apical urate-anion exchange.[17] These anions are all substrates for the apical, proximal tubular sodium-coupled monocarboxylate transporters SMCT1 and SMCT2. Reabsorption of the anions, which are also substrates for the URAT1/OAT10 urate-anion exchangers, increases apical urate-anion exchange and leads to hyperuricemia.[18] Pharmacological doses of niacin (nicotinate), a strong transactivator of both URAT1 and OAT10,[19] can cause hyperuricemia and lead to gout flares.[20] Aspirin doses up to 1 to 2 g/day reduce uric acid excretion, contributing to hyperuricemia, whereas higher doses are uricosuric;[21] the latter effect is attributed to "cis-inhibition" of apical urate-anion exchange.[18]

5 Diuretic therapy

Urate homeostasis is clearly modulated by changes in whole-body extracellular fluid volume. Prior studies have confirmed a relationship between proximal tubular salt and urate handling—short- and long-term salt restriction have been shown to cause hyperuricemia with a rapid reversal occurring with salt loading.[22–24] In rats, extracellular volume depletion leads to a rise in SU and a decreased clearance of urate that is unrelated to changes in GFR. The relevant mediators have not been fully characterized.

However, an experimental infusion of angiotensin and norepinephrine in healthy volunteers resulted in respective 50% and 33% drops in the urinary excretion of urate, independent of changes in urine osmolality or GFR, suggesting that these hormones may play a role.[25,26] Loop and thiazide diuretics can also modulate urate transporters,[27,28] however, these effects are likely less important than diuretic-associated volume depletion.

What Is the Etiology of the Patient's CKD?

The patient had many comorbidities that could have contributed to his progressive CKD. Notably, however, with an absence of progressive proteinuria, he was not felt to have classic diabetic nephropathy—a substantial proportion of patients with type 2 diabetes and CKD do not have significant proteinuria, suggesting other underlying renal pathologies.[29] He also had a history of hypertension but with excellent blood pressure control. His recent CHF suggested possible cardiorenal syndrome, but that did not explain his longstanding CKD. One key clue to the cause of this patient's CKD was the positive family history of both CKD/end-stage renal disease (ESRD) and gout. Both brothers had gout, one with CKD and the other with ESRD. They were also both overweight, suggesting shared metabolic syndrome. However, given the hyperuricemia with a strong family history of gout and CKD/ESRD, a genetic screen for uromodulin kidney disease (UKD)[30] was sent. This revealed a heterozygous mutation in uromodulin, generating an I302T mutation. This was a "variant of unknown significance," not reported in kindreds with UKD, but the mutation resides within a disease-associated domain of uromodulin and is predicted to affect function.

What Is UKD?

Patients with UKD frequently (~75%) develop hyperuricemia due to a reduced fractional excretion of urate; 65% also develop gout, typically with an early onset.[30] They can also manifest progressive renal failure and medullary cystic disease. Uromodulin is expressed in the renal thick ascending limb and distal convolute tubule, where it activates the Na-K-2Cl cotransporter NKCC2 and the Na-Cl cotransporter NCC, respectively. UKD-associated mutations in uromodulin result in retention of the protein within renal tubular cells; this inhibits sodium-chloride reabsorption by the thick ascending limb and distal convoluted tubule, leading to hypovolemia and an increased sodium and urate reabsorption in the proximal tubule. Notably, gout is also seen in the related thick ascending limb disorders Bartter syndrome and hereditary hypomagnesemia (Figure 2).

Intracelluar Retention and Aggregation of Uromodulin in UKD

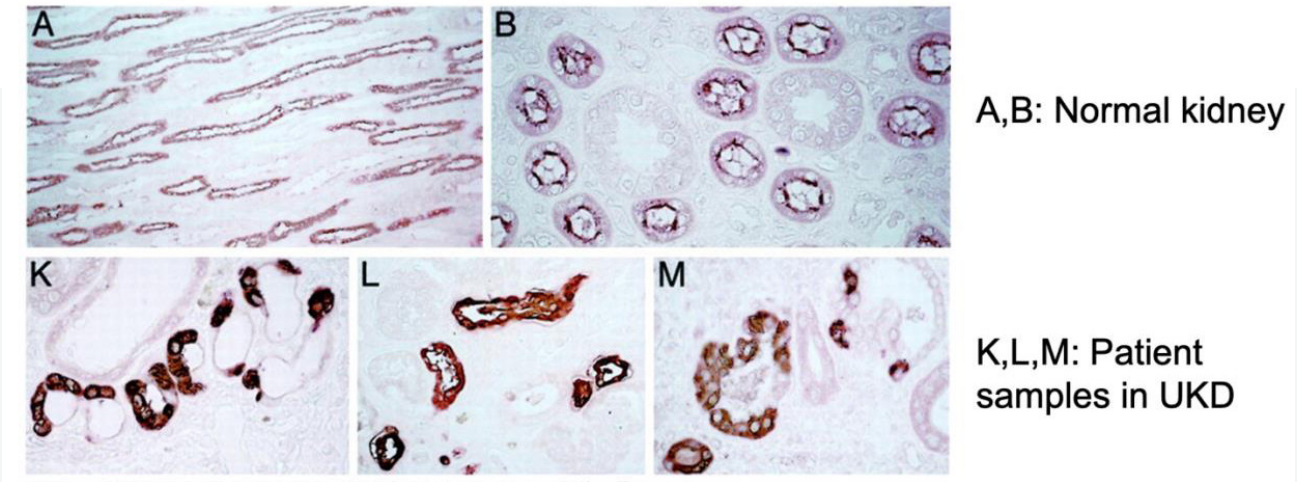


Figure 2

Case Study #2: Patient with Asymptomatic Hyperuricemia

This 66-year-old patient with a history of CKD and dilated cardiomyopathy was initially seen in consultation for postoperative AKI. He was subsequently followed for several years in the renal clinic, with residual stage 3 CKD. Due to a history of hypokalemic hypertension, he underwent workup for primary hyperaldosteronism, with discovery of a renal adenoma and laparoscopic adrenalectomy. Soon after, he was found to have normocalcemic primary hyperparathyroidism, leading to parathyroidectomy. After adrenalectomy, the patient's blood pressure was well-controlled.

Notably, his SU was consistently 10.0 to 11.0 mg/dL over several years, with no joint symptoms. This is relevant because there is a 10% greater yearly likelihood of developing gout when a patient has a uric acid of 10.0 mg/dL or higher (Figure 3).[2]

Though the patient did not develop gout during several years of follow-up, it is not considered appropriate treatment for a patient like this to be treated with allopurinol or other urate-lowering therapies in the absence of clinical gout. Dual energy CT (DECT) studies show that about 20% of patients with asymptomatic hyperuricemia have detectable monosodium-urate deposits consistent with tophi; however, the tophus burden is much lower than it is in patients with actual gout.[31]

After an eight-month treatment hiatus due to COVID-19, the patient was seen again. His eGFR was now in the mid-20s, he had lower back pain (which was relieved by physiotherapy) and, importantly, he had bumps over some of his finger pads that were sensitive to touch. Within a few months, the bumps had gotten progressively worse and were tender to touch. Upon examination in the renal clinic, the bumps were identified as tophi. His sUA was 10.8 mg/dL, though he still did not have any joint symptoms.

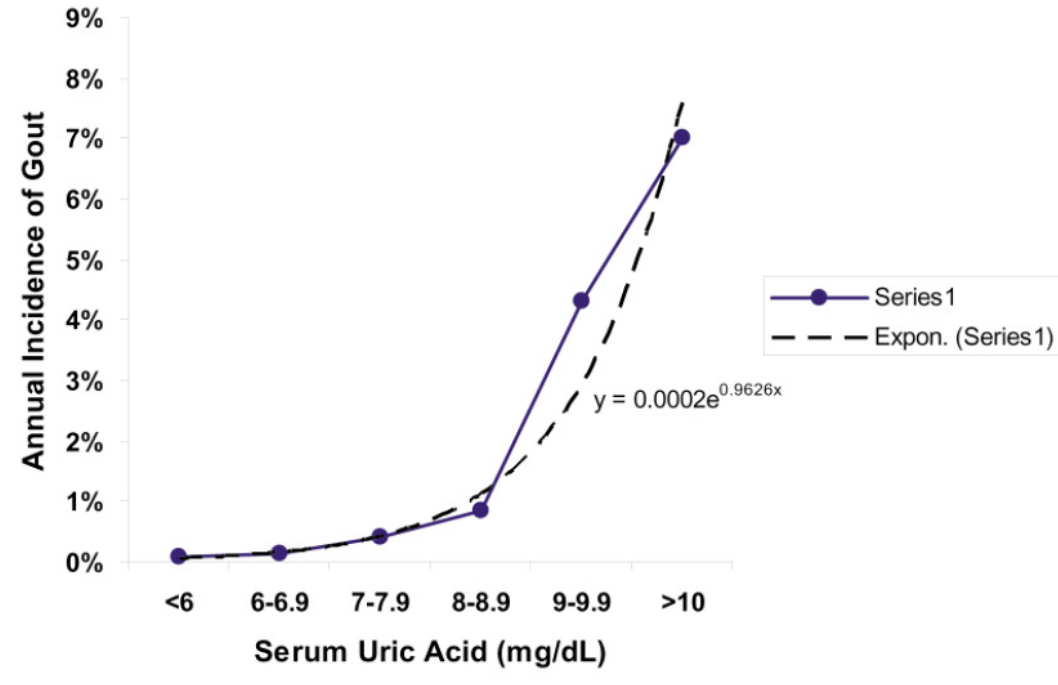


Figure 3

This puzzling picture prompted a referral of the patient to a rheumatologist. While he waited to be seen by a rheumatologist, the patient presented with a left toe abscess with urate crystals seen on incision and drainage by podiatry, in addition to antibiotic therapy. He was also seen by dermatology and had a draining ulcer in his right thumb, where the uric acid paste was visible (Figure 4).

When the patient was seen by a rheumatologist, who assessed him via joint ultrasound, he was started on pegloticase immediately.[32] Even though the patient had no joint symptoms, the rheumatologist saw an urgent need to reduce his uric acid, which was causing rapidly progressive tophi and infectious complications.

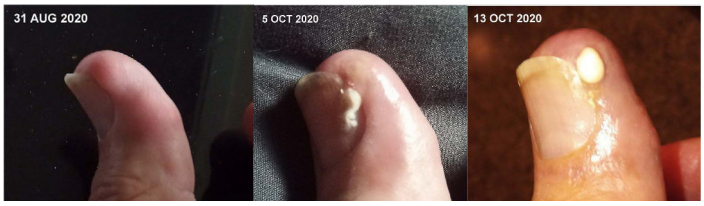


Figure 4

Gout & Renal Health: Exploring Hyperuricemia

The relationship between sUA and kidney disease has been controversial for decades. One reason is that the kidney is a major route to eliminate uric acid, so CKD results in some increase in sUA. However, an elevated sUA also predicts the development of kidney disease. Even with normal kidney function, there is an association of hyperuricemia with an increased risk for kidney disease. Indeed, the overwhelming majority of studies (14 of 15 studies) show that hyperuricemia is an independent risk factor for the development of CKD and for diabetic nephropathy (Figure 5).

Serum Uric Acid Predicts

- **Chronic Kidney Disease…**

Study (year)	Population	F/U	Type	Indep?	Author, Year
Japan	6,403 adults	2 YRS	CKD	Yes	Iseki, 2001
Japan	48,177 adults	10 YRS	ESRD	Women	Iseki, 2004
Thailand	3,499 adults	12YRS	CKD	Yes	Domrongkitchaiporn, 2005
USA	5,808 adults	5 YRS	CKD	No	Chonchol, 2007
Austria	21,457 adults 7YRS	CKD	Yes	Obermayr, 2008	
USA	13,338 adults	8.5YRS	CKD	Yes	Weiner, 2008
Austria	17,375 adults	7 YRS	CKD	Yes	Obermayr, 2008
USA	177,500 adults 25 YRS	ESRD	Yes	Hsu, 2009	
USA	355 type 1 diabetes*	6 YRS	CKD	Yes	Ficociello, 2010
Italy	900 adults	5 YRS	CKD	Yes	Bellomo, 2010
Japan	7,078 adults	5YRS	CKD	Yes	Sonoda, 2011
Taiwan	94,422 adults 3.5 YRS	CKD	Men	Wang, 2011	
Israel	2449 adults	26 YRS	ESRD	Yes	Ben-Dov, 2011
Korea	14,939 adults	10.2YRS	CKD	Yes	Mok, 2012
Italy	1,449 type 2 diabetics	5YRS	CKD	Yes	Zoppini, 2012
Japan	40,000	4YRS	CKD	Yes	Tojama, 2015

- **…And Diabetic Nephropathy**

Study (year)	Population	F/U	Type	Indep?	Author, Year
Denmark	263 type 1	18 YRS	Albuminuria	Yes	Hovind, 2009
USA	324 type 1	6 YRS	Micro/Albuminuria	Yes	Jalal, 2011
Italy	13,000 type 2 4 YRS	CKD	Yes	De Cosmo, 2015	

Figure 5

While sUA is a strong predictor of CKD, including in a meta-analysis of 13 studies,[33] an elevated sUA does not always predict progression of kidney disease in subjects with established CKD.

The observation that hyperuricemia predicts the development of CKD led to a hypothesis that hyperuricemia or gout may cause CKD. This was supported by animal studies showing that hyperuricemia can both cause CKD and accelerate the progression of CKD. This led to several trials (positive and negative) to determine whether lowering uric acid can slow the progression of CKD.

Trials

Most studies performed lasted from only a few months to several years, which is not enough time for subjects to progress to ESRD. Therefore, most studies have measured kidney function, known as GFR, to determine how well the kidneys are working. Specifically, it estimates how much blood passes through the glomeruli each minute. Glomeruli are the tiny filters in the kidneys that filter waste from the blood.

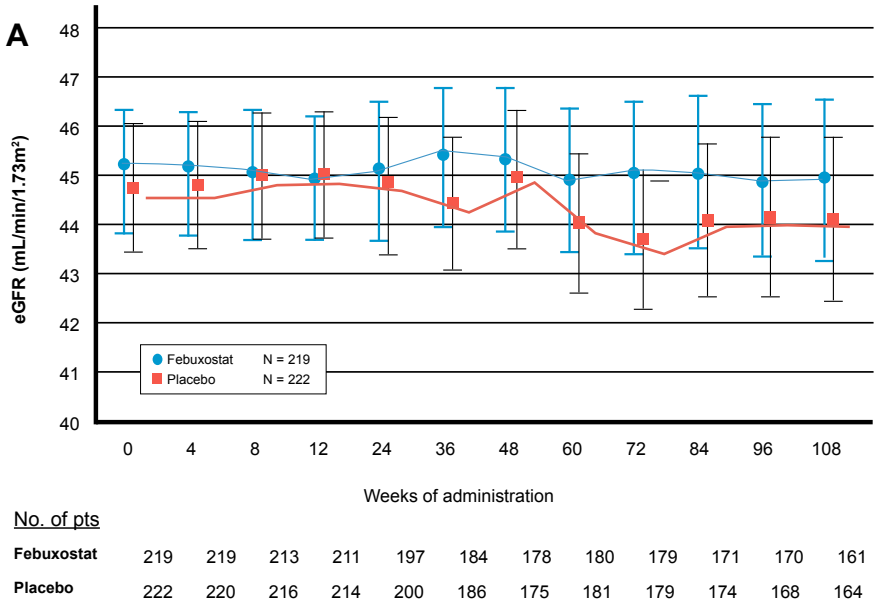


Figure 6

One of the largest trials was the randomized, double-blind, placebo-controlled FEATHER trial [34] with 467 patients with stage 3 CKD and asymptomatic hyperuricemia, which was conducted at 55 medical institutions in Japan. Participants were randomly assigned in a 1:1 ratio to receive febuxostat or placebo for 108 weeks. Of 443 patients who were randomly assigned, 219 and 222, assigned to febuxostat and placebo respectively, were included in the analysis.

There was no significant difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m^2 per year) and placebo (−0.47 ± 4.48 mL/min/1.73 m^2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; P = 0.1). This suggested that lowering uric acid with febuxostat did not show any difference from placebo over the two-year period of the study.

The problem with this study was that the placebo group showed only minimal worsening of their kidney function, which amounted to dropping only about 1 ml per minute GFR in two years. Since the goal of the study was to determine if treatment could prevent progression of the kidney disease, the study could not test this goal, because in essence the control group did not see its kidney disease progress. Therefore, the study was not negative, but rather failed because the placebo group remained healthy (Figure 6).

We realized that other studies also failed not because the treatment did not work, but because the control group did not show the expected worsening of kidney function over time. This led us to propose reanalysis of the literature based on the outcome of the placebo group. An interpretable study [35] was defined in which the control group showed a clinically meaningful decrease in kidney function, defined as a 4 mL per minute change in GFR (Figure 7). Uninterpretable studies were studies in which benefits could not be ascertained because the control group did not show its expected progression (Figure 8). When looked at this way, almost all studies that evaluated the effect of lowering uric acid on the progression of CKD were positive, meaning that they showed a benefit from lowering uric acid levels to slow kidney disease progression.

Subsequent to our analysis, two large, randomized, placebo-controlled studies were published that failed to show a benefit of lowering uric acid on the progression of CKD. These data seriously challenged our analysis.

Interpretable CKD Trials: All 14 Positive

Article	Study design	Design	Duration (months)	ΔeGFR or ΔsCr in Control	ΔeGFR or ΔsCr in Treatment	Net Change with Treatment	p value
Goicoechea	parallel RCT	Allo vs usual Tx	24	ΔeGFR -3.6	ΔeGFR +1.4	ΔeGFR +5.0	P< 0.001
Goicoechea	follow-up RX	Allo vs usual Tx	84	ΔeGFR -13.3	ΔeGFR -6.5	ΔeGFR +6.8	p=0.001
Zhou	parallel RCT	Allo vs usual Tx	6	ΔeGFR -2.8	ΔeGFR +2.7	ΔeGFR +5.6	p<0.05
Tani	Open label RCT	Febuxostat vs non-Tx	6	ΔeGFR -3.4	ΔeGFR +3.7	ΔeGFR +7.1	†T: p<0.001 C: p=0.227
Sircar	placebo RCT	Febuxostat vs placebo	3	ΔeGFR -4.4	ΔeGFR +3.2	ΔeGFR +7.6	p=0.05
Malaguarnera	placebo RCT	Rasburicase vs placebo	8	ΔCCr -0.9 (ml/min/24h)	ΔCCr +12.7 (ml/min/24h)	ΔCCr +13.8	p<0.001
Tan	parallel RCT	Allo vs usual Tx	24	sCr +2.05	sCr +0.87	ΔsCr –1.18	p<0.05
Siu	open-label RCT	Allo vs usual Tx	12	sCr +1.03	sCr +0.29	ΔsCr -0.74	p=0.08
Sarris	parallel RCT	Allo vs non-Tx	12	sCr +0.68	sCr +0.07	ΔsCr -0.61	†T: p=0.35 C: p<0.001
Liu	parallel RCT	Allo vs usual Tx	12	sCr +1.12	sCr +0.35	ΔsCr –0.77	p<0.05
Shen	parallel RCT	Allo vs usual Tx	12	sCr +0.66	sCr -0.04	ΔsCr –0.70	p<0.05
Lei	parallel RCT	Allo vs usual Tx	12	sCr +0.57	sCr -0.12	ΔsCr –0.69	p<0.05
Deng	parallel RCT	Allo vs usual Tx	12	sCr +1.97	sCr +0.97	ΔsCr –1.00	p<0.05
Tuta	parallel RCT	Allo vs usual Tx	24	*24 of 53	*11 of 52	improved	p=0.013

Figure 7

Non-interpretable CKD Trials: All 9 Negative

Article	Study design	Design	Duration (months)	ΔeGFR or ΔsCr in control	ΔeGFR or ΔsCr in treatment	Improvement by treatment	p value
Kimura	parallel, double-blind placebo RCT	Febuxostat vs placebo	25	ΔeGFR–0.97	ΔeGFR +0.48	ΔeGFR +1.45 improved	NS
Hosoya	parallel RCT	Topiroxostat vs placebo	22	ΔeGFR -0.46	ΔeGFR +0.64	ΔeGFR +1.1 improved	NS
Tuta	parallel RCT	Allo vs usual Tx	12	ΔeGFR -2.2	ΔeGFR +1.7	ΔeGFR +3.9 improved	Not reported
Saag	parallel, double-blind placebo RCT	Febuxostat vs placebo	12	ΔeGFR -2.05	ΔeGFR +0.33	ΔeGFR +2.38 improved	NS
Kao	parallel RCT	Allo vs placebo	9	ΔeGFR +0.2	ΔeGFR +0.2	ΔeGFR 0 no change	NS
Beddhu	parallel, double-blind placebo RCT	Febuxostat vs placebo	6	ΔeGFR -3	ΔeGFR -3	ΔeGFR 0 no change	NS
Shi	parallel RCT	Allo vs usual Tx	6	ΔeGFR +5.3	ΔeGFR +3.7	ΔeGFR -1.6 worse	NS
Tanaka	parallel open label RCT	Febuxostat vs non-Tx	3	eGFR -0.4	ΔeGFR -1.3	ΔeGFR 0.9 worse	NS
Momeni	parallel placebo RCT	Allo vs placebo	4	ΔsCr +0.00	ΔsCr +0.10	ΔsCr +0.1 worse	NS

Figure 8

The first study, called the PERL,[36] evaluated whether administering allopurinol could reduce the progression of CKD in type 1 diabetes patients. Patients were randomized to placebo or allopurinol over three years. There was a two-month washout period, and the researchers measured GFR by iothalamate, a very sensitive and accurate assay. The study did not show any benefits of allopurinol on iothalamate GFR in type 1 diabetes patients. See (Figure 9).

What were the reasons for this outcome? The study was beautifully designed, and the control group did progress over three years, so it would have fit our original criteria. However, we believe there was a major problem in the patient selection. For one thing, type 1 diabetes is usually associated with low uric acid levels, as diabetes increases urate excretion as a consequence of glycosuria. As a result, hyperuricemia is rare in type 1 diabetes. While there is still a gradient with high normal uric acid levels being associated with progression of kidney disease in type 1 diabetes, the study design allowed subjects even with low normal uric acid levels (4.0 mg/dL or more) to enter the trial. The hypothesis, however, was not that lowering uric acid is protective, but rather that treating hyperuricemia is protective in CKD. This would be similar to giving an anti-hypertensive agent to see if it protects against heart failure to subjects with normal blood pressure.

No Benefit of Allopurinol on Iothalamate GFR

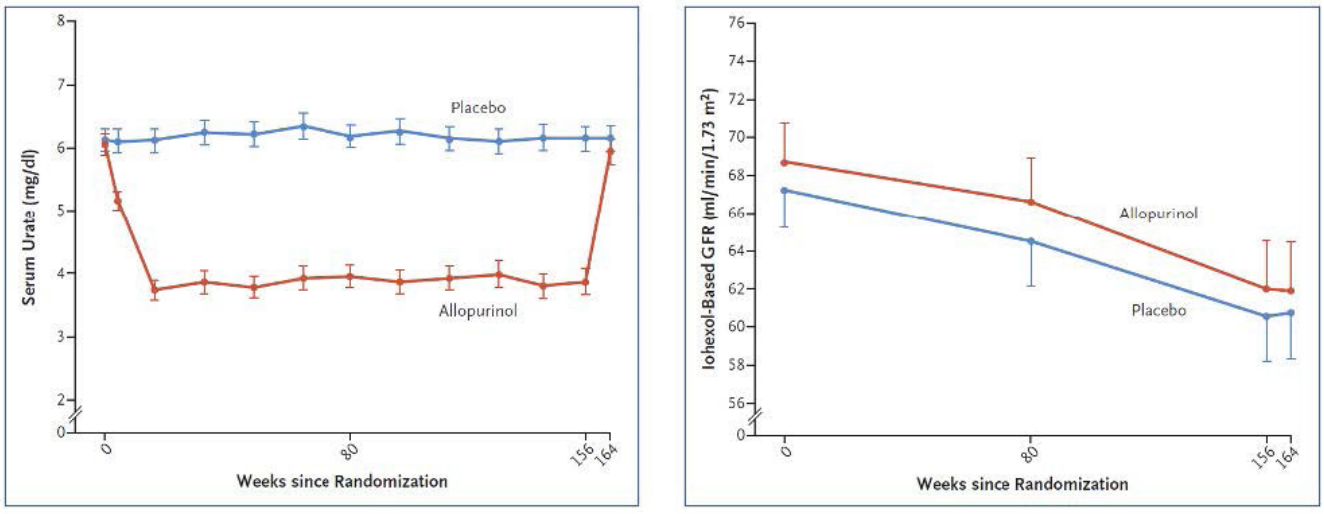


Figure 9

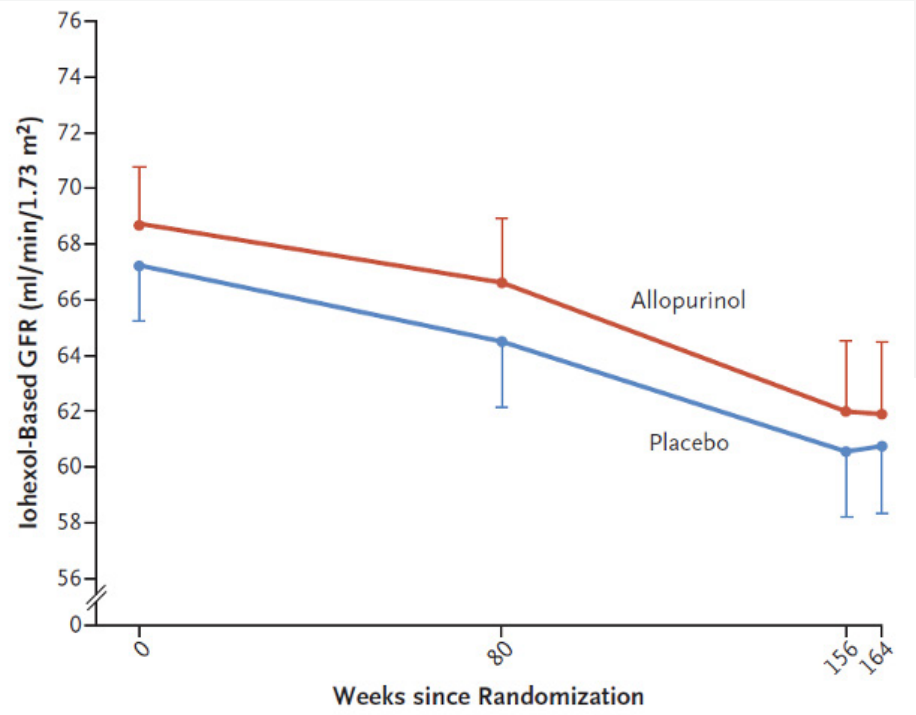
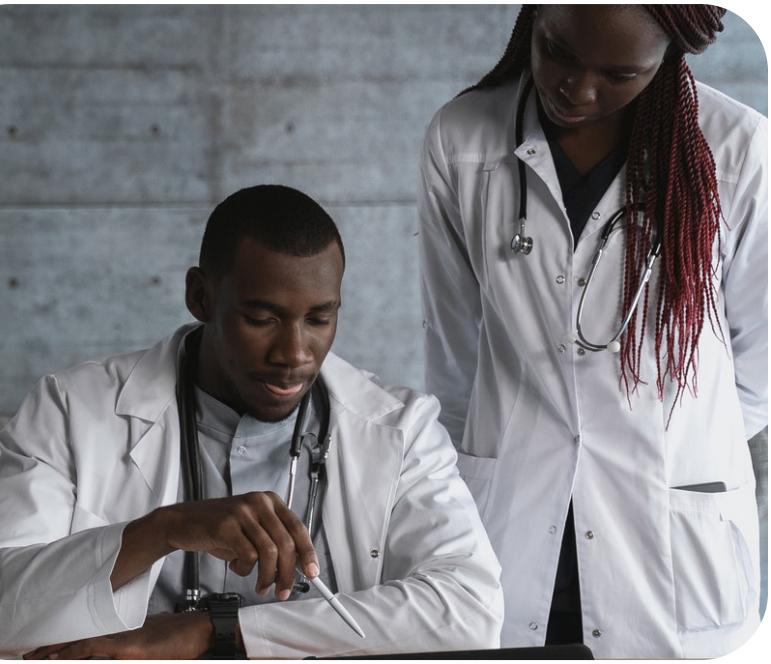


Figure 10

The second study was called the CKD-FIX,[37] and it was also a negative study that was published in the New England Journal of Medicine. The CKD-FIX trial determined whether lowering uric acid with allopurinol could slow progression of CKD. This was a randomized, controlled trial of adults with stage 3 or 4 CKD who had a urinary albumin-to-creatinine ratio of 265 or higher (with albumin measured in milligrams and creatinine in grams) or an eGFR decrease of at least 3.0 ml per minute per 1.73 m^2 of body-surface area in the preceding year. The subjects received either allopurinol (100 to 300 mg daily) or placebo. The primary outcome was the change in eGFR from randomization at two years, calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation. See (Figure 10).

Enrollment was stopped because of slow recruitment after 369 of 620 intended patients were randomly assigned to receive allopurinol (185 patients) or a placebo (184 patients). Three patients per group withdrew immediately after randomization. The remaining 363 patients (mean eGFR 31.7 ml per minute per 1.73 m^2; median urine albumin-to-creatinine ratio 716.9; mean serum urate level 8.2 mg/dL) were included in the assessment of the primary outcome. The change in eGFR did not differ significantly between the allopurinol group and the placebo group (−3.33 ml per minute per 1.73 m^2 per year [95% confidence interval {CI}, −4.11 to −2.55] and −3.23 ml per minute per 1.73 m^2 per year [95% CI, −3.98 to −2.47], respectively; mean difference, −0.10 ml per minute per 1.73 m^2 per year [95% CI, −1.18 to 0.97]; P=0.85). Serious adverse events were reported in 84 of 182 patients (46%) in the allopurinol group and in 79 of 181 patients (44%) in the placebo group. This study did show progression of CKD in the placebo group, and the treatment group also showed a significant decrease in uric acid levels. However, no benefit was



Yet again, the main problem was in patient selection. An elevated sUA level was not a criterion for entry, nor was treatment targeted to lower uric acid levels. Moreover, subjects with a history of gout were excluded. While subjects with active gout on treatment should be excluded, there are many subjects with gout who are not on treatment. Some studies show that 30–40% of subjects with CKD have gout, of which two-thirds are not on treatment and hyperuricemia. Thus, the patients most likely to benefit were excluded, and many subjects who were predicted not to benefit were included. There was also a very large dropout rate, which complicated interpretation because these subjects were included in the outcome analysis since this was an intention-to-treat trial.

Mendelian Randomization

There is additional data challenging the uric acid hypothesis. This involves an analysis called Mendelian randomization,[38] which is a method of using measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease. Specifically, genetic polymorphisms that can raise uric acid levels are weighted and applied in observational studies, to determine if those with a higher genetic score for elevated uric acid are at risk for developing CKD. One analysis used a large, genome-wide association database of over 100,000 people to study genetics for higher preponderance for developing hyperuricemia. Theoretically, there should have been a causal relationship between elevated sUA levels and CKD, but the analysis showed that uric acid had no causal effect on eGFR or CKD risk, though it did increase the risk for gout.

Mendelian randomization studies are relatively strong, and they would suggest that an elevated sUA may not be directly linked with CKD. Nevertheless, when one is lowering sUA, one is also lowering the urate pool, which includes extracellular uric acid crystals and intracellular uric acid levels. Thus, the ultimate proof would be a clinical trial of subjects with hyperuricemia and/or gout.

Insights and Questions

1 While pilot studies found the benefit of lowering uric acid in CKD paitients, two recent trials failed to show protection, although they may have not selected the best patient population for the studies.

2 In particular, the PERL and CKD-FIX both excluded people with gout, which is extremely common in CKD patients. They included subjects with normal UA levels, though data suggests that the risk factor for CKD is hyperuricemia.

3 What would be the ideal population to study? While hyperuricemic subjects might be an ideal group, it is also possible that it is not the hyperuricemia itself, but whether there is associated crystal deposition. Recently, it has been recognized that subjects with gout frequently have crystals in other sites besides joints and tophi, and this can include the blood vessels, heart and kidney. A Kidney International paper [39] notes echogenicity of the renal medulla correlation with the deposition of crystals, present in about one-third of gout subjects. These crystals can be identified by special imaging tests such as the DECT scan. It is possible that the benefit on cardiac and kidney disease may be related to preventing or reducing crystal deposition See (Figure 11).

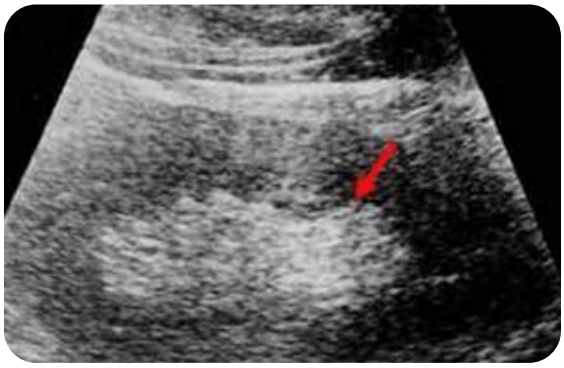


Figure 11

It is also possible that not all subjects with hyperuricemia carry the same risk. Some subjects with hyperuricemia have the elevated uric acid levels driven by increased production (usually associated with high xanthine oxidase activity) and others with hyperuricemia from decreased elimination. Experimental studies suggest the former are at greater risk for metabolic complications. It may be that treating the former group might provide better protection from worsening of CKD. This might account for the lack of evidence from Mendelian randomization studies, as the genetic score for uric acid is almost completely based on elimination and not production.

4 Studies suggest that many patients with CKD have a history of gout but are not currently receiving urate-lowering therapy. Could acute or chronic deterioration in these patients be linked to crystals, and if doctors avoid treating patients with gout, are they avoiding treating the patients who are having the problems with their kidney disease?

5 Is there a causal link between uric acid and vascular calcification? More and more data shows urate crystal deposits in the kidney and in other sites like the vasculature. A JAMA Cardiology paper [40] showed that calcification in the blood vessels often correlates with sites where urate is deposited, and that many patients with gout have urate crystals occurring both in their kidneys and in their blood vessels. There is a real danger in patients with kidney disease having crystal deposition in their vessels and in their kidneys
See (Figure 12).

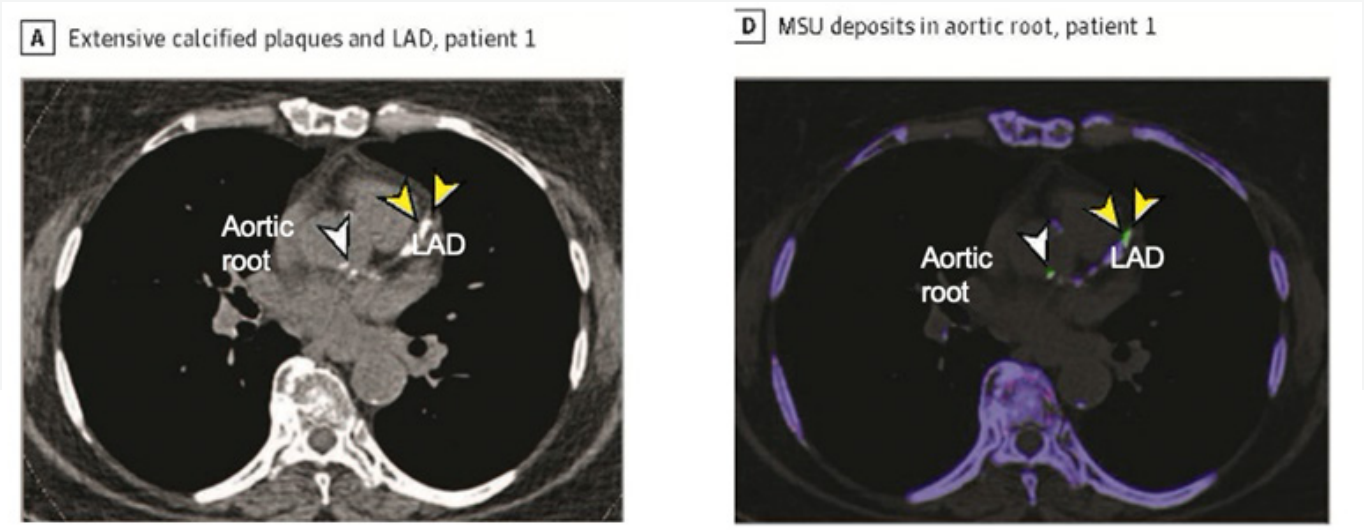


Figure 12

Conclusion

Serum uric acid predicts the development of CKD, suggesting its role in kidney disease. Experimental studies and pilot clinical studies also suggest that it has a contributory role. Though two major New England Journal of Medicine studies had negative results (PERL and CKD-FIX), both excluded patients with gout and included patients with normal uric acid. They also both had high dropout rates, which makes it hard to interpret the data.

Though it has been best-practice protocol not to treat if a patient has a normal sUA level, there is also a need for more studies to understand whether a certain subset might benefit from treatment, such as those who have gout, tophi and crystals. Those who are hyperuricemic, or have evidence of high uric acid production such as high xanthine oxidase activity, could explain why high sUA levels predict the development of kidney disease.

Gout & Renal Health: Treatment Guidelines and Patient Adherence

While many treatments for gout have been developed, there is not complete consensus around treating gout patients, including those with CKD. Over the past 17 years, there have been 18 practice guidelines and eight consensus papers on the subject from around the globe.

There are two guidelines to focus on in terms of CKD in gout patients:

2020 ACR Guidelines [41]

These guidelines strongly recommend including allopurinol as first-line therapy for those with moderate to severe CKD stage 3 or greater and advocate using a low starting dose. They also note that indications for urate-lowering therapy (ULT) include patients with CKD stage 3 or greater and sUA levels greater than 9.0 mg/dL with their first flare. (Most guidelines do not mention initiating ULT until after two flares within a 12-month period, but it's been shown to be important to recognize that gout will worsen in these types of patients.) If needed, it is safe to go above 300 mg/day of allopurinol to treat these patients to an sUA target of preferably less than 6.0 mg/dL (and less than 5.0 mg/dL in a lot of guidelines).

2016 EULAR Guidelines [42]

In contrast, these guidelines recommend allopurinol in normal kidney function starting at 100 mg per day and increasing by 100 mg every two to four weeks. In those with renal impairment, the guidelines do not suggest a specific max dose for allopurinol, but hint toward a maximum dose that should be adjusted to the patient's creatinine clearance specifically. (The ACR guidelines don't mention a creatinine clearance; they only mention to try to use allopurinol safely to reach target.) The EULAR Guidelines also suggest (in those with renal impairment), if the goal is not reached, changing to febuxostat or benzbromarone (not available in the U.S.), with or without allopurinol in eGFR of greater than 30 mL/min.

Controversy with Allopurinol [43-44]

Many in the medical community believe that oxypurinol is responsible for most of the inhibition of xanthine oxidase by allopurinol and believe it comes with a lot of toxicities, allopurinol hypersensitivity syndrome (AHS) or severe cutaneous reactions. The half-life of oxypurinol is about 18 to 36 hours, and allopurinol's half-life is about one to two hours.

A Randomized Controlled Trial of the Efficacy and Safety of Allopurinol Dose Escalation in Gout [45]

Lisa Stamp, MBChB, FRACP, Ph.D., a rheumatologist at Christchurch Public Hospital and University of Otago in New Zealand, and colleagues evaluated the efficacy and safety of allopurinol dose escalation using a treat-to-target serum urate approach. It followed 183 patients (93 control, 90 dose escalation) for 12 months, and showed that a target sUA level of less than 6.0 was achieved in about 75% of serum samples with plasma oxypurinol levels greater than 100 µmol/L. It is acknowledged that it's not highly sensitive or specific to one patient or another and does not guarantee reaching these oxypurinol levels. The study also found that increasing the allopurinol dose resulted in increased plasma oxypurinol at reduced serum urate concentrations, which was expected.

Low-Dose Allopurinol Promotes Greater Serum Urate Lowering in Gout Patients with CKD [46]

A New York University study looked at CKD patients, examining 83 patients taking 100 mg of allopurinol and 97 subjects taking 300 mg of allopurinol. It found a significant trend for serum urate-lowering with the 100 mg dose with increasing CKD stages, with each additional stage associated with an additional mean decrement in serum rate of around 0.6 mg (the worse the CKD got in the 3 to 4 range, the lower the dose of allopurinol needed to bring down the serum urate). There was no significant trend for the 300 mg dose, but it highlighted the question of whether there was a ceiling effect that allopurinol and subsequently oxypurinol may have in CKD patients.

Addressing Concerns with Allopurinol and Kidney Disease

As far back as 1984, an article in the Green Journal [47] showed correlation between a higher dose of allopurinol and greater likelihood of developing AHS, especially in patients with kidney disease in general.

Starting Dose Is a Risk Factor for Allopurinol Hypersensitivity Syndrome

In 2012, a study [48] published by Nicola Dalbeth, MCHhB, MD, FRACP, FRANZ, professor at The University of Auckland, New Zealand, and Dr. Lisa Stamp looked at the relationship between allopurinol dosing and AHS, a rare but potentially fatal adverse event. Allopurinol is the most commonly used urate-lowering therapy in gout and associated with this health risk. Dosing guidelines based on creatinine clearance have been proposed based on the recognition that dosages of ≥300 mg/day may be associated with AHS, particularly in patients with renal impairment. However, the relationship between the allopurinol starting dose and AHS had not been evaluated.

This retrospective case-control study looked at patients with gout who developed AHS between January 1998 and September 2010. For each case, three controls with gout who were receiving allopurinol but did not develop AHS were identified. Controls were matched with cases for gender, diuretic use at the time of initiating allopurinol, age (±10 years) and eGFR. Starting dose and dose at the time of the reaction in cases were compared between cases and controls.

Percentage of Patients Who Develop AHS for Allopurinol Starting Dose Relative to eGFR

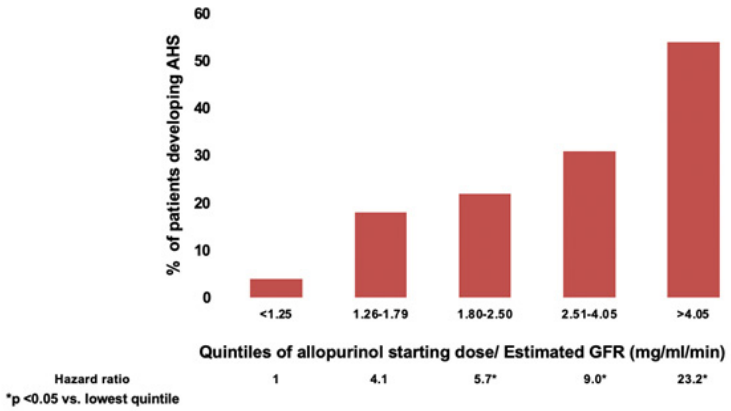


Figure 13

Fifty-four AHS cases and 157 controls were identified. The result found that it wasn't so much the maximum dose of allopurinol that was associated with AHS, but the starting dose that was more associated with the likelihood of having a severe subcutaneous reaction or AHS. A table from this study showed that as the starting dose of allopurinol increased (and also the estimated eGFR), so did the risk of developing AHS (Figure 13).

Proposed Starting Dose of Allopurinol Based on 1.5mg per eGFR

eGFR	Allopurinol starting dose
<5	50 mg/week
5-15	50 mg twice weekly
16-30	50 mg every two days
31-45	50 mg daily
46-60	50/100 mg alternate days
61-90	100 mg daily
91-130	150 mg daily
>130	200 mg daily

Figure 14

Effects of Heart Disease, Kidney Disease and Initial Allopurinol Dosing on Sever Allopurinol Hypersensitivity

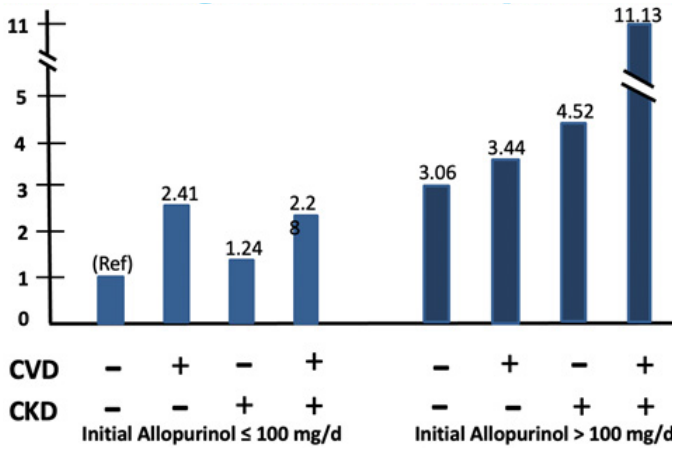


Figure 15

Considering that every patient is different, if they have an eGFR less than 5, their allopurinol starting dose would be 50 mg/week. Consideration should also be given to even lower starting doses in high-risk patients, such as those with HLA-B*5801 (Figure 14).

The University of British Columbia

A 2019 study [49] examined a large database of patients in British Columbia. It looked at all patients who were admitted for some type of severe subcutaneous reaction to allopurinol (like AHS). It showed that patients who had both CVD and CKD had a significantly higher risk of developing AHS, and that there was more than CKD involved. The study pointed to a discovery that a combination of kidney and heart dysfunction may contribute to an increased risk of AHS (Figure 15).

Prophylactic Colchicine Can Be Dosed Appropriately for CKD and Estimated GFR [50–51]

Monitoring is needed for creatine kinase (CK) and complete blood count (CBC) levels; drug interactions are possible since gout patients have multiple comorbidities and are often taking multiple medications. Noting strong inhibitors of P4503A4 and p-glycoprotein before initiating or using colchicine is important.

Single-Dose, Open-Label Study of the Differences in Pharmacokinetics of Colchicine in Subjects with Renal Impairment, Including End-Stage Renal Disease [52]

A 2014 study conducted by Dr. Mount looked at open-label single dose (0.6 mg) colchicine. There were eight subjects in five different groups who received one single dose: patients with normal renal function; patients with mild, moderate and severe CKD; and patients with ESRD (exception: received the dose before and after hemodialysis). The study found that colchicine exposure was similar for the patients with normal and mild impairment, as well as for the ESRD patients on dialysis. But in the moderate to severe groups that had twofold higher exposure to colchicine, a small amount of the colchicine dose was recovered in dialysate.

Colchicine Toxicity in End-Stage Renal Disease Patients: A Case-Control Study [53]

A 2014 retrospective cohort study with ESRD patients on hemodialysis taking colchicine (for any reason) looked at 22 patients using half a tablet a day, 14 patients using 1 mg per day, and four using 1.5 mg per day. There was no evidence of toxicity by signs, symptoms, CBC or myoglobin.

British Society of Rheumatology Guidelines for the Management of Acute Flares [54]

Although there is limited evidence from clinical trials for dosing colchicine in patients with kidney disease, guidelines have been published. The British Society of Rheumatology recommends a dose reduction in patients with an eGFR between 10 and 50 mL per minute and contraindicated in those with less than 10 mL per minute. Their recommendations for prophylactic colchicine were 0.5 mg (a standard dose in Europe, whereas it's 0.6 mg in the U.S.) twice a day in stage 1/2 kidney disease; 0.5 mg every other day if a patient's eGFR is between 30 and 60 mL/min; 0.5 mg every two to three days if their eGFR is between 10 and 30 mL/min; and avoid it in patients with eGFR less than 10 mL/min.

Treatment Gaps and Nonadherence

Patients with chronic conditions typically have low adherence rates in general. With gout so extremely painful during a flare, such poor patient adherence is surprising. The medication possession ratio (MPR) is defined as the day's supply of the drug dispensed during the follow-up year divided by the number of days in the year (Figure 16):

- Nearly 25% of gout patients had achieved adherence rates up to 19%.
- Almost 16% of gout patients had achieved adherence rates up to 39%.
- 12.3% of gout patients achieved adherence rates up to 59%.
- 10.8% of gout patients achieved adherence rates up to 79%.
- 36.8% of gout patients achieved adherence rates from 80–100%.

Low Adherence Rates Common Among Chronic Conditions

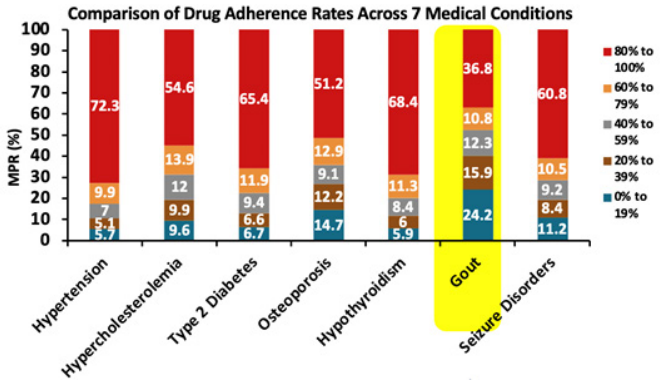


Figure 16

Inverting the Treatment Pyramid for Gout

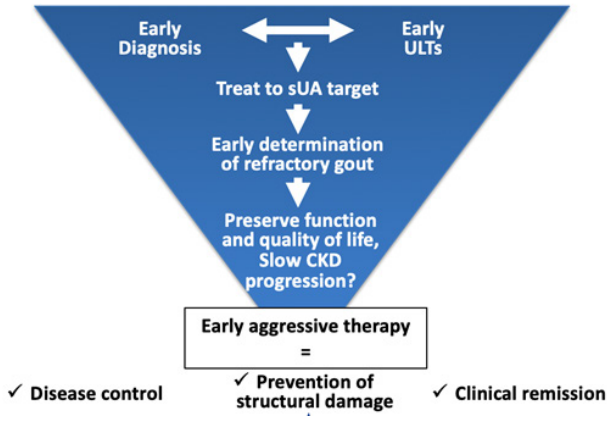


Figure 17

Patient Knowledge

Are patients receiving adequate, even necessary education from their treatment medical providers? Is this lack of knowledge contributing to poor patient adherence?

- In 2012, a survey of 240 gout patients [56] showed that only 25% of patients who received ULT were aware that the medication had to be used chronically.
- Only 12% knew that the initiation of ULT could worsen symptoms in the short term.

Inverting the treatment pyramid for gout and starting with diagnosing patients early means recognizing the disease early and treating aggressively with early use of ULT (Figure 17).

- Treat to less than 6.0 mg/dL and, ideally, 5.0 mg/dL.
- Early treatment will mitigate chronic NSAID use and kidney damage if patients haven't been on NSAIDs daily for 10-plus years.
- Better tools are needed for clinical care to help with the providers' education of patients.

> **There isn't a consensus when it comes to managing CKD in gout patients, but there's more evidence needed to convince colleagues about the impact of hyperuricemia on kidney health and overall morbidity. We need true consensus and need to improve communication and collaboration between everyone—primary care providers, nephrologists, rheumatologists, podiatrists, orthopedists, cardiologists…everyone.** -Robert T. Keenan, MD, MPH, MBA

Group Discussion

After the panelists presented, Dr. Edwards led a short group discussion on barriers to treatment in both rheumatology and nephrology.

Dr. Edwards: How do you think nephrologists view allopurinol? Do they think it's nephrotoxic? Do they think it's something that we should be limiting? David—do you think that nephrologists in general have an issue with the treat-to-target approach for addressing hyperuricemia in gout patients regardless of renal function? Do you think that the misconception of allopurinol being nephrotoxic is still widely held?

Dr. Mount: It's complex. The drug recommendation has been updated to a more nuanced approach to using allopurinol in CKD. Nephrologists are trained to see what medications aren't dosed appropriately, and we as a group have been culprits when telling our patients about urate-lowering therapies.

Another reason: I have a lot of patients at the VA with CKD, and when they get admitted, someone spreads misinformation about high-dose allopurinol, scaring the patient.

Education among rheumatologists is coming over to the nephrology community and the community at large. You can see interstitial nephritis with allopurinol either as part of the allopurinol hypersensitivity or even sometimes granulomatous interstitial nephritis in the absence of systemic hypersensitivity.

Allopurinol is not nephrotoxic in and of itself, and neither is colchicine except in huge overdoses. I use colchicine a lot, and as long as you are very careful to use eGFR-appropriate dosing (0.3 mg a day in stage 4 CKD and worse) and monitor CPK and manage that carefully, I recommend it and prefer to use colchicine over prednisone in patients with CKD.

We have come a long way from the 1980s, when it was taught that we needed to adjust the allopurinol dose depending on renal function. We now know that those older guidelines led to significant under-treatment of hyperuricemia and weren't necessarily a safer approach. The current internationally accepted guidelines would have us start allopurinol at a dose no higher than 100 mg per day in all gout patients and even lower (50 mg per day) in patients with more advanced CKD. From those starting points, the allopurinol should be escalated in a stepwise fashion until the target serum urate level is achieved. There is still a lot of misinformation out there about the use of high-dose (greater than 300 mg/day) allopurinol in CKD patients, and that leads to frequent under-treatment. Allopurinol is not nephrotoxic in and of itself.

Dr. Johnson: If there is a nephrotoxicity with allopurinol, it might be in the CKD patient where allopurinol is started at a high dose. When you first give allopurinol, there's a rise in xanthine, and if that gets too high, the xanthine can precipitate and form crystals similar to uric acid.

If you give an animal with CKD that has high xanthine oxidase levels allopurinol, we've precipitated renal failure with crystals. In studies of animals with CKD given allopurinol, renal failure from crystal precipitation can occur. Humans, however, have lower xanthine oxidase activity, so if you start at a low-level dose, you wouldn't see the rapid rise in xanthine. I believe once you start lowering UA, you can continue to raise the allopurinol slowly without worry of nephrotoxicity.

Dr. Edwards: Do you think rheumatologists still believe that allopurinol is nephrotoxic? Do the cautious guidelines from the 1980s alluded to by David earlier have any relevance in the 21st century? Rob—do you think rheumatologists are still hesitant to adequately escalate the dose of allopurinol because of fear of nephrotoxicity?

Dr. Keenan: I think most rheumatologists don't feel that way anymore, but there are some, unfortunately, that remain a little timid. I've seen too many people switch to febuxostat when it was not really necessary or were sent to me because they're not responding adequately to their allopurinol. Physicians, in general, give up on dose-escalating allopurinol too easily. Some of this reflects the fact that they haven't totally bought into the accepted standard of treat to a target serum urate level. In others, it stems from an uneasiness in using allopurinol in doses greater than 300 mg daily. We do know that 60% of gout patients will need more than 300 mg daily to get to the minimum urate target of less than 6.0 mg/dL. That means that some of our gout patients will need 400, 500 or up to 800 mg daily to be adequately treated. If patients are not able to tolerate higher doses, then switching to febuxostat or pegloticase in some patients to their target serum urate would be appropriate.

Dr. Edwards: We need to look at all of the gout guidelines, that all of them have recommended to start low and go slow on a dose escalation of the xanthine oxidase inhibitors, primarily because of the effects on AHS, but also the frequency of flares by rapidly changing the serum urate levels. It sounds like we all agree that the treat-to-target approach of managing hyperuricemia associated with gout is the way we should proceed in patients with or without CKD. I think we are also in agreement that this can safely be accomplished using allopurinol as long as we start with a low dose and slowly advance until hyperuricemia is controlled.

Advocacy Organization Education

National Kidney Foundation

The National Kidney Foundation (NKF) is dedicated to serve as a lifeline for all people affected by kidney disease. As pioneers of scientific research and innovation, NKF focuses on the whole patient through the lens of kidney health. They are dedicated to the awareness, prevention and treatment of kidney disease.

The Gout & CKD microsite (housed at https://www.kidney.org/atoz/content/gout) compiles all materials in one place, including general information on gout and CKD, information for patients, and information for professionals, available in print and online.

Most recently, NKF launched “Kidney Pathways,” an online, interactive educational platform that uses kidney assessment tools to guide patients along a learning pathway that is based on the stages of CKD and its associated risks and comorbidities.

To enhance public awareness of kidney disease and its risk factors the foundation launched the “Are You the 33%?” campaign. The concept is that 33% of the American population either has CKD or is at risk for CKD, so NKF partnered with the Department of Health and Human Services and the American Society of Nephrology to raise both public and clinician awareness, leading to improved health outcomes.

Working with major laboratories to promote a kidney profile test to standardize some reports, which includes eGFR and urine albumin to creatinine ratio, the NKF worked with the National Committee for Quality Assurance (NCQA) in developing the new Kidney Health Evaluation measure. It was included in the Healthcare Effectiveness Data and Information Set (HEDIS) Measurement Year 2020 and will be in the Measurement Year 2021, too. It is a huge step toward improving the diagnosis of kidney disease.

NKF is also building the first interactive community of kidney disease patients, the NKF Patient Network, a registry that will advance both patient education and kidney disease treatment.

American Kidney Fund

The American Kidney Fund (AKF) fights kidney disease on all fronts as the nation’s leading kidney nonprofit, with programs of prevention, early detection, financial support, disease management, clinical research, innovation and advocacy. No kidney organization impacts more lives than AKF.

AKF's "Goutful" campaign focuses on removing common myths and misconceptions associated with gout, to help humanize the disease. The group will be releasing data from surveys gathered through the campaign on patient opinion data.

The "Kidney Kitchen" (kidneyfund.org/kitchen) is an initiative that has almost 500 recipes, vetted by a dietitian and easily sorted, so patients can find what they need (low sugar, low protein, low potassium, etc.). Patients can also find food guides, cooking tips and videos on the website.

An important endeavor that AKF is known for is providing financial assistance to low-income patients to ensure that they have access to life-saving medical treatment, including dialysis. It has also provided assistance for patients through its Disaster Relief Program and its Coronavirus Emergency Fund—the only program of its kind for kidney patients.

Gout Education Society

The Gout Education Society (GES), which began in September 2005, is dedicated to raising awareness of gout and provides education for both patients and medical professionals. The organization established the official Gout Awareness Day, held annually on May 22, as a day to raise awareness about the disease during National Arthritis Month.

During the week when Gout Awareness Day falls, GES hosts a Twitter chat for patients, medical professionals and organizations to join in on the gout conversation and debunk myths about the disease. GES CEO and Chairman Larry Edwards, MD, MACP, MACR, also regularly participates in Reddit AMAs (Ask Me Anything), allowing both patients and physicians to ask him specific questions directly.

The GES website (GoutEducation.org) includes information and resources for both patients and medical professionals around gout, its treatment and its comorbidities. The Gout Specialists Network (GoutSpecialistsNetwork.org) was formed to develop a database of gout experts who recognize the importance of a treat-to-target approach to gout and will adhere to the ACR guidelines. Patients are then able to access a medical professional locator to find a knowledgeable medical professional who can treat their gout—particularly for those patients in farther away from big cities.

Consensus on Educational Initiatives

After the educational organizations spoke more about their mission and what they're doing to help kidney patients suffering from gout, a group discussion was held. There was a consensus on gout and diet, along with the role that education can play in both gout and renal disease.

Diet

Many patients search for diet information—both for gout and/or CKD. While diet is significant for those with CKD, it's not as significant for people with gout. In fact, diet is often over-prioritized in gout patients and typically only results in decreasing uric acid levels by 1.0 mg/dL. AKF's "Kidney Kitchen" found that most gout patients were searching for low-purine foods, so it made that content minimal and then focused language around understanding more about gout and treatments.

Collaboration and Education

There is a need for education on gout and CKD for patients and nephrologists, and work needs to be done in both parties for there to be effective conversations, while simultaneously trying to destigmatize gout and avoid embarrassing patients.

There were a few key takeaways from the panelists and our moderator, Dr. Edwards:

Dr. Keenan: We need to connect the dots with all specialists—cardiologists, nephrologists, et cetera—to get them to realize they should check uric acid of a CKD patient. If the nephrologist who saw a CKD patient would check for uric acid more frequently, it'd be a huge start having that data from the beginning, especially if that patient just had labs done a couple of weeks ago.

Dr. Edwards: One VA hospital looked at data for patients who were co-managed by rheumatologists, nephrologists and cardiologists, in addition to PCPs or a combination of these groups together. The VA found a step improvement that the more specialists helping one patient, the more it helps to manage all of the diseases better. A more collaborative effort is exactly what needs to be done.

Dr. Johnson: Patients with CKD and gout are more likely to carry tophi, which puts the patient at risk for developing crystal deposition elsewhere, not only in the kidneys, but also in the vasculature. We need to learn more about the role of crystal deposition in patients with CKD, not just in the joints, but also in other sites, and DECT scans should help with this. Nephrologists have many patients with gout, but if their gout isn't active, they may not be treating them, and patients could be getting urate deposition disease in different sites that could be playing a role in their overall morbidity.

Dr. Keenan: Connecting and improving education among all of these medical professionals—like the cardiologist and deposition in the vasculature, and deposition in the kidneys for the nephrologist—will put the pieces together and create a bigger picture, by making it part of their wheelhouse and not just the next doctor's responsibility.

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