Gout and Hyperuricemia in Chronic Kidney Disease

WHAT IS CLINICALLY SIGNIFICANT?

National Kidney Foundation®

BACKGROUND

In chronic kidney disease (CKD), gout is a concomitant illness that increases health risk and treatment burden. The direct clinical impact of gout is also amplified by the comorbidities it shares with CKD — hypertension, diabetes, and features of the metabolic syndrome. Ironically, CKD may often lead to gout, as observational studies have found CKD to be the third most common independent risk factor for gout after obesity and hypertension.[1,2] CKD is associated with decreased excretion of uric acid and resultant hyperuricemia, a major risk factor for gout. Other mechanisms may be implicated in CKD since variations in serum uric acid do not account for most of the risk for developing gout.[1,3]

Conversely, there is evidence that gout and associated hyperuricemia may independently impair kidney function.[4,5] Hyperuricemia in the presence of gout, as well as the use of gout medications that are potentially harmful to the kidneys, are initiation factors for developing CKD, and progression factors for worsening CKD.[6]

Observational data also suggest that hyperuricemia, even in the absence of gout, may independently worsen CKD,[7,8] possibly via a pathogenic role in hypertension (Figure 1), and diabetic nephropathy, the two leading causes of CKD.[9,10] This bulletin highlights the clinical significance of both gout and hyperuricemia by discussing their etiologies, epidemiology, and relationship to CKD.
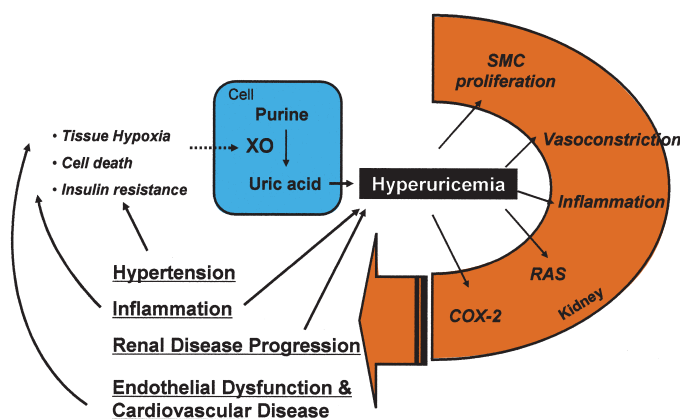

Figure 1. The potential interrelationships of uric acid, xanthine oxidase activity, and clinical endpoints of cardiovascular and renal disease

Adapted from: Kang DH, Nakagawa T. Uric acid and chronic renal disease: possible implication of hyperuricemia on progression of renal disease. *Semin Nephrol* 2005;25:43-9.

ETIOLOGIES OF HYPERURICEMIA AND GOUT

Because humans lack uricase, they cannot convert the uric acid generated during purine metabolism into a soluble form. This can lead to an increased risk for hyperuricemia and monosodium uric acid crystallization in joints and tissues, a hallmark of gout. Hyperuricemia can be caused by the overproduction of uric acid, but is more often the result of insufficient kidney uric acid excretion. Because a family history is often seen in primary gout, much research is focused on genes that cause hyperuricemia, notably those that regulate renal uric acid transport, such as human urate transporter 1 (URAT1).[11] Genetic polymorphisms in anion transporters such as URAT-1 and SLC2A9, which encodes for GLUT9, can cause hyperuricemia by decreasing proximal tubular uric acid clearance.[12-14] Other non-modifiable risk factors for gout include male gender, increasing age, and menopause.[11,15]

Approximately 15% of uric acid clearance occurs via the gastrointestinal tract, and therefore small bowel disease can contribute to increased serum uric acid.[16] A variety of medications can increase serum uric acid, including loop and thiazide diuretics. High intake of meat, shellfish, alcohol, and fructose also can cause hyperuricemia,[17,18] while obesity increases the risk for its development by three-fold.[19] For many people, these causes of hyperuricemia will not lead to gout, but for those who are susceptible, these factors may trigger gout attacks.[18]

EPIDEMIOLOGY AND PATHOGENIC RELATIONSHIPS
GOUT AND CKD

Gout has been steadily increasing worldwide, and is now the most common type of inflammatory arthropathy.[11] In the United States alone, its prevalence more than doubled between the 1960s and the 1990s,[20,21] and it is now estimated at 3.9% of U.S. adults (8.3 million adults — 6.1 million men and 2.2 million women).[20,22] Hyperuricemia is also common, with a prevalence of 6-8% in healthy adults, and a prevalence of 1 in 3 adults who have uncontrolled hypertension and several cardiovascular risk factors.[23] Concomitantly, the prevalence of CKD has been increasing, with estimates at 14% of adults in the United States,[24] and 8-16% globally.[25] The parallel rise in gout and CKD (Figure 2) has led to investigations to study their relationship, including a retrospective cohort study based on 54 years of follow-up data from the Framingham Heart Study, which found that the risk of developing gout in CKD doubled compared to subjects not having CKD and gout at baseline (HR=2.09; 95% CI 1.41 to 3.08). This difference remained significant after adjusting for other known gout risk factors.[1,26]
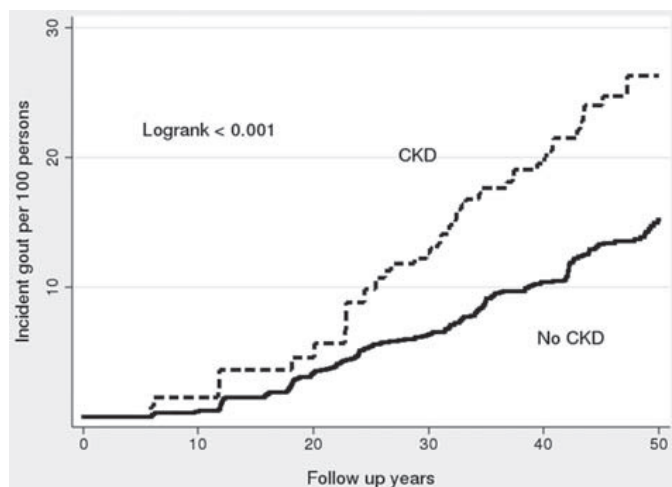
Figure 2. Kaplan-Meier failure estimates for incident chronic kidney disease (CKD) to incident gout among participants who developed incident CKD after the baseline visit and those who never developed CKD in the original Framingham Heart Study cohort.

Adapted from: Wang W, Bhole VM, Krishnan E. Chronic kidney disease as a risk factor for incident gout among men and women: retrospective cohort study using data from the Framingham Heart Study. *BMJ Open*. 2015;5:e006843.
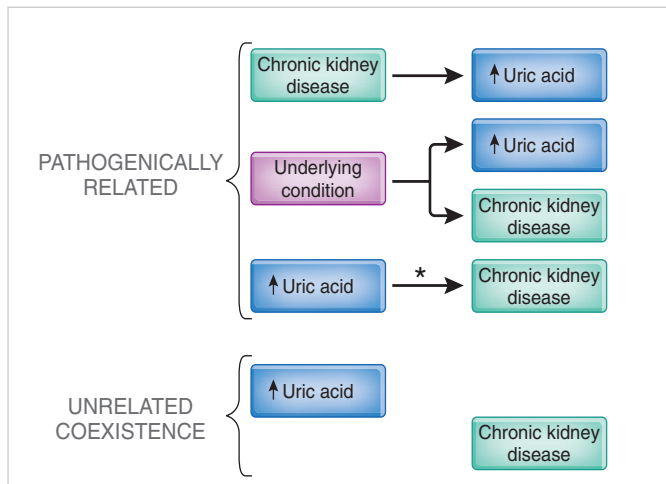

Figure 3. Possible relationships between hyperuricemia and chronic kidney disease

Adapted from: Moe OW. Posing the question again: does chronic uric acid nephropathy exist? *J Am Soc Nephrol* 2010; 21:395-397.

*True causality

HYPERURICEMIA AND CKD

Epidemiologic studies have also addressed the association of hyperuricemia and prevalent or worsening CKD. The largest study included 177,570 patients in the US Renal Data System (USRDS) database followed over 25 years. Subjects within the highest quartile of serum uric acid had a hazard ratio of 2.14 for CKD, a level of risk that ranked third after proteinuria and severe obesity.[27] However, causality cannot be established solely from observational studies, especially because the temporal relationship between the onset of CKD and hyperuricemia is unclear. Accordingly, serum uric acid levels have not always been found to be an independent risk factor for CKD progression, especially when baseline kidney damage is considered.[28]

Observational studies and animal models suggest that hyperuricemia itself is directly nephrotoxic, even before the clinical syndrome of gout develops, and may be a mechanism in the pathogenesis of hypertension, cardiovascular disease, and CKD. But studies are conflicting and establishing how hyperuricemia, hypertension, and CKD are connected is difficult because of 1) the direct effect kidney function itself has on uric acid levels, and 2) the association of hyperuricemia with other causes of CKD, notably hypertension, confounding the interpretation of direction or mechanism of the association.[28] The possible pathogenic relationships between hyperuricemia and CKD are represented in Figure 3.

KIDNEY MANIFESTATIONS OF GOUT
URIC ACID NEPHROLITHIASIS

Although gout patients have a higher risk for uric acid stone formation than people without gout, the primary metabolic abnormality that promotes uric acid lithiasis is excessive urinary acidity, since urine pH is the major determinant of uric acid crystallization.[28] Acidic urine is present in people with gout, even in the absence of kidney stones, but is worse in stone formers,[29] and this is associated with decreased ammonium excretion.[30] Although hyperuricosuria is an important factor in causing uric acid stones in some patient groups, this is not the case for most people with uric acid nephrolithiasis.[29] Likewise, the association between uric acid nephrolithiasis and the metabolic syndrome is not so much related to hyperuricemia, but rather to excessive urinary acidity. Urinary pH and ammonium excretion are directly correlated with the number of metabolic syndrome features, with a greater urinary acidity and lower ammonium excretion correlated to more features. In fact, clinical studies have demonstrated that insulin resistance is associated with excessive urinary acidity.[28,31]

KIDNEY MANIFESTATIONS OF HYPERURICEMIA

URATE NEPHROPATHY

Urate nephropathy is defined as urate crystal deposition in the physiologic pH of the renal medulla, rather than the tubular lumen obstruction caused by uric acid lithiasis in tumor lysis syndrome or uricase knockout mice. Pathological features observed in the kidneys of gout patients are those mainly associated with hypertensive kidney disease: advanced arteriosclerosis, glomerulosclerosis, and interstitial fibrosis. (Figure 4) Urate crystal deposition is present, but the focal nature of that feature appears inconsistent with the diffuse nature of the kidney disease.[32] And possibly analogous to the fact that most people with hyperuricemia do not develop gout, 86% of postmortem cases with renal medullary urate deposits had not developed gout in life.[28,33]
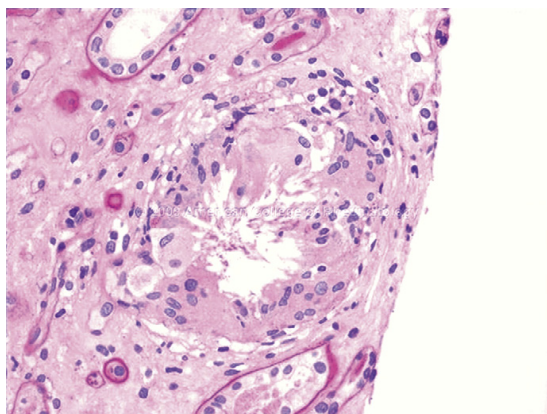

Figure 4 Urate nephropathy. There is chronic tubulointerstitial nephritis. Note the tubule distended by a collection of needle-like spaces, originally containing urate deposits, associated with multinucleated giant cells (PAS stain, magnification ×40). *(© 2011 American College of Rheumatology. Available online at Rheumatology Image Bank: http://images.rheumatology.org/viewphoto.php?albumId=75676&;imageId=2862276.)*

Figure 4. Urate nephropathy

Adapted from: Taylor WJ, Grainger R. In: Terkeltaub R, ed. *Gout and Other Crystal Arthropathies*: 1st ed. Philadelphia, PA: Elsevier Saunders; 2012:105-120.

OTHER DISEASES

Less common kidney manifestations of hyperuricemia include: familial juvenile hyperuricemic nephropathy (FJHN), an autosomal dominant disease leading to end-stage renal disease (ESRD) at an early age, reduced fractional excretion of uric acid, renal interstitial uric acid deposits, and sporadic gouty arthritis; complete or partial hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency (Lesch-Nyhan and Kelley-Seegmiller syndromes, respectively); acute uric acid-related nephropathy, a condition that is not usually associated with gout, but with a sudden, massive uric acid load caused by chemotherapy-induced tumor lysis.[28]

LOWERING SERUM URIC ACID TO TREAT GOUT IN THE SETTING OF CKD

The 2012 American College of Rheumatology (ACR) Guidelines emphasizes both non-pharmacologic and pharmacologic approaches for managing gout and lowering serum uric acid levels. The recommended serum uric acid level should be low enough to effectively improve and maintain the signs and symptoms of gout, a goal most often associated with a level of <6 mg/dL. The two first-line options for urate lowering therapy (ULT) are the xanthine oxidase inhibitors, febuxostat and allopurinol. Febuxostat does not require renal dose adjustment in mild to moderate CKD. Because insufficient evidence exists on its safety in CKD stage 4 or worse (eGFR of 0-29 mL/min/1.73 m^2), no recommendation was issued for febuxostat in this setting. In CKD, the starting dose for allopurinol should not be more than 100 mg/day in moderate to severe CKD, followed by gradual upward titration of the maintenance dose, which can exceed 300 mg/day. Anti-inflammatory prophylaxis of acute gouty arthritis also involves the continuation of established pharmacologic ULT, without interruption, during an acute gout attack.[17]

The ACR recommends prophylaxis when initiating ULT because the rapid decrease in serum urate can often trigger gout flares. First line options include low-dose colchicine (0.6 mg orally once or twice daily, with lower doses for moderate-to-severe CKD (eGFR of 15-59 mL/min/1.73 m^2) and potential drug-drug interactions). Although low-dose non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen, 250 mg orally twice daily is recommended by the ACR. NSAIDs should generally be avoided in CKD. A stronger level of evidence exists for using colchicine.[34]

LOWERING SERUM URIC ACID TO TREAT CKD

In view of the pathogenic connection between CKD and hyperuricemia, researchers have been evaluating how lowering serum uric acid levels might reduce the progression of CKD. Data is based mostly on observational studies and small clinical trials,[35-37] and a significant problem with comparing their data, aside from methodology and confounding disease states and treatments, is the lack of uniformity in defining hyperuricemia. Levy, et al conducted a large retrospective review of 111,992 patients defined as having hyperuricemia at a level of > 7 mg/dL, and found that patients treated with uric acid lowering therapy (one of the following: allopurinol, febuxostat, or probenecid), who achieved a serum uric acid < 6 mg/dL, showed a 37% reduction in outcome events.[38] In a recent small prospective, randomized, open-label study with 21 patients receiving febuxostat and 19 receiving conventional treatment, the authors reported renoprotective effects from febuxostat in hyperuricemic patients with CKD.[39]

At a single center, post hoc analysis of 113 patients who had completed a 2-year, single-blind, randomized controlled trial of allopurinol (56 patients received allopurinol and 57 were in the control group), showed improved estimated glomerular filtration rate and reduced cardiovascular risk.[40]

The larger Preventing Early Renal Function Loss (PERL) Allopurinol study, an international, multi-center, stratified, double-blind, placebo-controlled, parallel-group randomized clinical trial, is currently investigating the effect of allopurinol in delaying the progression of CKD in type 1 diabetes. The reason for creating this trial stems from growing evidence that hyperuricemia may have a role in the pathogenesis of diabetic nephropathy and the progression of CKD observed in type 1 diabetes. This evidence includes epidemiologic data,[41] and prospective data from trials such as Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL), in which lowering serum uric acid through the use of losartan accounted for 20% of the renoprotection provided by this drug.[41,42] Mounting evidence over the last decade provides increasing support for the hypothesis that hyperuricemia leads to vasoconstriction and vascular remodeling that results in hypertension and contributes to the progression of CKD in at risk individuals.[10]

CONCLUSION

Gout and hyperuricemia are clinically significant in the setting of CKD, especially when drugs used for their management can further impair kidney function. The established role of CKD as an independent risk factor for gout may therefore warrant screening for CKD when gout is first diagnosed.[23] The role of hyperuricemia as an independent risk factor for CKD, however, is still being debated. Large randomized controlled trials can provide definitive answers about its relationship to CKD, and how its treatment might forestall CKD progression in populations such as those with hypertension and diabetic nephropathy.

Until the completion of large randomized controlled trials that support safety and efficacy, the ACR does not recommend serum uric acid lowering therapy for asymptomatic hyperuricemia.[17] The dangers of inappropriately treating asymptomatic hyperuricemia are well documented,[43-45] especially in the elderly.[41]

As emphasized by both the ACR and the National Kidney Foundation, lifestyle and dietary modifications that ameliorate the features of gout and hyperuricemia, along with appropriate pharmacologic treatments for gout and uric acid nephrolithiasis, are the proven strategies for reducing the risk of developing or worsening CKD.[17,46]

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