The kidney in hyperuricemia and gout

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Purpose of review
Gout is a painful inflammatory arthritis associated with hyperuricemia, with a prevalence of almost 10 million in the USA. Reduced renal excretion of urate is the underlying hyperuricemic mechanism in the vast majority of gout patients; most of the genes that affect serum urate level (SUA) encode urate transporters or associated regulatory proteins. Acquired influences can also modulate SUA and renal urate excretion, sometimes precipitating acute gout. Coincidentally, the prevalence of renal comorbidities in gout – hypertension, chronic kidney disease (CKD), and nephrolithiasis – is very high.

Recent findings
Recent advances in genetics and molecular physiology have greatly enhanced the understanding of renal reabsorption and secretion of filtered urate. Moreover, baseline SUA appears to be set by the net balance of absorption and secretion across epithelial cells in the kidney and intestine. There have also been substantial advances in the management of gout in patients with CKD.

Summary
The stage is set for an increasingly molecular understanding of baseline and regulated urate transport by the kidney and intestine. The increasing prevalence of gout with CKD will be balanced by an expanding spectrum of therapeutic options for this important disease.

Keywords
allopurinol, colchicine, febuxostat, gout, transporter, uric acid

INTRODUCTION

Hyperuricemia is both causative and protective in disease. The causative link between hyperuricemia and disease is clearest for gout, a painful inflammatory arthritis. The prevalence of gout is substantial, affecting 8.3 million Americans [1▪]. The burden of the major comorbidities of gout [hypertension, chronic kidney disease (CKD), etc.] is also considerable [2▪▪]. Hyperuricemia has also been linked to the pathogenesis of several gout-associated comorbidities, particularly hypertension [3] and diabetic renal disease [4]. Hyperuricemia can be seen in metabolic syndrome and there is a high prevalence of metabolic syndrome in patients with gout [5].

In contrast to gout and associated diseases, hyperuricemia has an evident protective effect in neurodegenerative disease, including Parkinson's disease, multiple sclerosis [6], and Alzheimer's disease/dementia [7]. Higher uric acid levels reduce the risk of Parkinson's disease and reduce the risk of disease progression [8]. Although the underlying mechanisms are likely heterogeneous, most theories incorporate some role for the antioxidant effect of uric acid [9]. Similar mechanisms may account for the apparent protective effect of hyperuricemia in end-stage renal disease patients on hemodialysis, as observed in the Dialysis Outcomes and Practice Patterns Study; higher SUA was associated with lower risk of all-cause and cardiovascular mortality [10▪▪].

Recent advances in the molecular genetics of hyperuricemia and the molecular physiology of urate homeostasis have underlined the key role of the kidney in determining the level of SUA. In addition, patients with gout have a high prevalence of CKD [2▪▪], with new opportunities for nephrology involvement in its management.

MOLECULAR PHYSIOLOGY OF URATE HOMEOSTASIS

In most mammals, uric acid generated from purine metabolism undergoes oxidative degradation via the uricase enzyme, generating allantoin.

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KEY POINTS

- Serum uric acid is determined by the balance in activity between secretory and absorptive urate transporters in the kidney and intestine.
- Genome-wide association studies and molecular physiology studies have established a molecular framework for urate secretion and absorption, mediated by separate, opposing groups of transporters.
- Most of the genes that contribute to variation in uric acid level encode urate transporters or associated regulatory proteins.
- Neurohumoral influence on urate homeostasis includes insulin, angiotensin-II, sympathetic tone, and parathyroid hormone.
- A substantial portion of patients with gout have chronic kidney disease, with a significant opportunity for greater involvement of clinical nephrologists in gout management.

In humans, the uricase gene is crippled by two mutations that introduce premature stop codons. The absence of uricase, combined with extensive reabsorption of filtered urate, results in urate levels in human plasma that are approximately 10 times that of most other mammals. Whereas primates such as the chimpanzee share the same truncating mutations in uricase, independent loss-of-function mutations in gibbon apes suggest that this gene was subject to significant negative pressure during the evolution of hominids [11]. There are several speculative evolutionary advantages conferred by the relative hyperuricemia in humans. The clinical risk of hyperuricemia in humans is in turn mitigated by relative repression of the human xanthine oxidoreductase (*XOR*) gene [12], which encodes the enzyme that mediates the last two steps of purine metabolism to produce urate.

Approximately one-third of urate elimination in humans occurs in the gastrointestinal tract, with the remainder excreted in the urine [13]. In plasma, uric acid exists primarily as Na^+-urate and is freely filtered at the glomerulus. Urate can only permeate tubular cell membranes through facilitated mechanisms predominantly in the proximal tubule. For many years, the accepted human model of renal urate handling consisted of four components: glomerular filtration, reabsorption from the glomerular ultrafiltrate, subsequent secretion, and then postsecretory reabsorption [13]. This model was based entirely on an interpretation of the pharmacological interactions of antiuricosuric and uricosuric agents. The antituberculosis agent pyrazinamide causes significant hyperuricemia and a marked decrease in the fractional excretion of urate. This effect was attributed to an inhibition of urate secretion by the active metabolite, pyrazinoate (PZA). However, direct inhibition of proximal tubular urate secretion by PZA has never been demonstrated, and Guggino and Aronson [14] utilized brush-border membrane vesicles (BBMVs) from canine kidney to demonstrate that PZA activated the reabsorption of urate, via indirect stimulation of apical urate exchange. Thus, PZA and related anions do not inhibit secretion, but rather activate urate reabsorption (see also Figs. 1 and 2 and below).

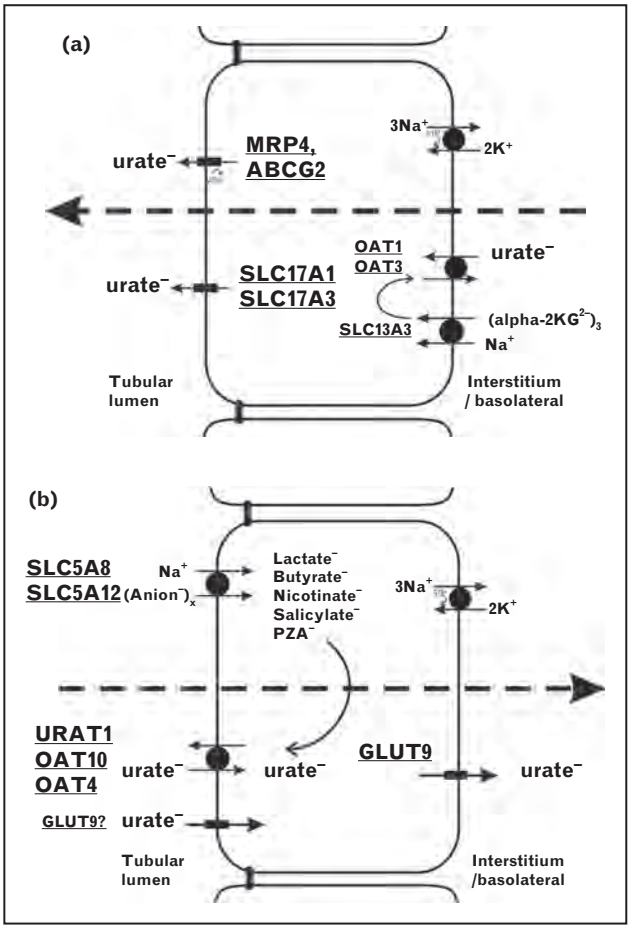

FIGURE 1. Proximal tubular urate transport. (a) Urate secretion. Urate enters the cell at the basolateral membrane via exchange with alpha-ketoglutarate, mediated by OAT1 and OAT3. At the apical membrane, urate is secreted via MRP4, ABCG2, NPT1, and NPT4. (b) Urate reabsorption. Sodium-dependent anion transport by SLC5A8 and SLC5A12 increases the intracellular concentrations of anions that exchange with luminal urate (URAT1/OAT10; OAT4 has a different mechanism, see text). GLUT9 is the presumptive exit pathway for urate at the basolateral membrane, but may also traffic to the apical membrane.

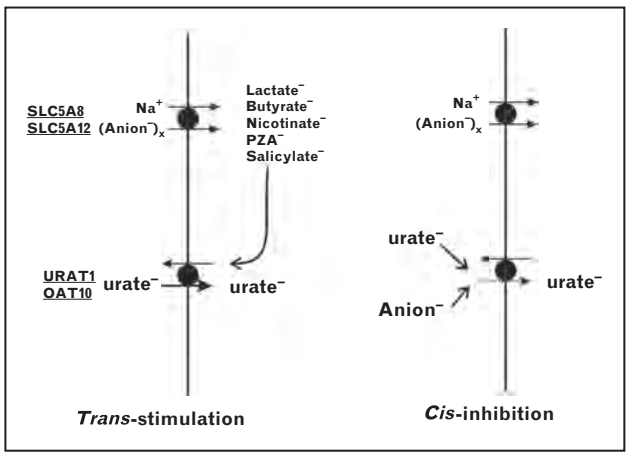

FIGURE 2. Trans-activation versus *cis*-inhibition. Anions that share transport via urate exchangers (URAT1 and OAT10) at the apical membrane of the proximal tubular can either activate urate absorption via trans-activation or can inhibit uptake via *cis*-inhibition. Increases in the circulating concentrations of the substrates for SLC5A8/A12 results in increased glomerular filtration of the anions, increased uptake at the apical membrane, a secondary increase in apical urate–anion exchange because of trans-activation, and hyperuricemia. However, at higher concentrations, these same anions can *cis*-inhibit urate uptake, because of competition with urate for urate–anion exchanger, leading to reduced reabsorption of filtered urate, uricosuria, and a reduction in serum urate level.

Renal urate transport (Fig. 1) is central to the pathogenesis of gout, in that reduced renal excretion of urate is the underlying hyperuricemic mechanism in the vast majority of patients [15]. Not surprisingly, most of the genes that affect serum urate level (SUA) and risk of gout encode urate transporters or associated regulatory proteins [16,17,18▪▪]. A major insight from these genetic studies is that SUA level reflects the net sum of proximal tubular reabsorption and secretion (see Fig. 1). For example, the complete genetic inactivation of proximal tubular reabsorption (renal hypouricemia caused by loss-of-function mutations in *SLC2A9*) is associated with a fractional excretion of urate that exceeds 100% [19], because of unopposed urate secretion.

RENAL URATE REABSORPTION

The reabsorption of filtered urate by the proximal tubule involves the coordinated activity of several transport pathways (Fig. 1b). Sodium-dependent absorption of lactate and other monocarboxylate anions 'primes' the cell for apical urate transport, by increasing the intracellular concentration of anions that exchange with luminal urate. The apical Na^+-dependent monocarboxylate transporters SLC5A8 (solute carrier gene family 5, 8th member) and SLC5A12 (solute carrier transporter gene family 5, 12th member) that mediate this transport are sequentially coexpressed with urate transporters at the apical membrane of proximal tubule cells. Urate–anion exchange is in turn mediated by OAT10, URAT1, and OAT4 (Fig. 1b). Increases in the circulating concentrations of the substrates for SLC5A8/A12 (lactate, ketones, nicotinate, and pyrazinoate) result in hyperuricemia, because of increased glomerular filtration of the anions, increased uptake at the apical membrane, and a secondary increase in apical urate–anion exchange [20]. This physiology effectively disproves the four-component model of renal urate transport. In addition, Na^+-dependent loading of these anions at the apical membrane serves to bypass uptake via the apical urate exchangers, which would lead to competitive '*cis*-inhibition' of urate transport (see Fig. 2). Notably, however, at higher concentrations the Na^+-dependent uptake via SLC5A8/A12 is overwhelmed such that these anions can become 'paradoxically' uricosuric, because of this *cis*-inhibition of urate uptake via apical urate exchangers [20].

URAT1, encoded by the *SLC22A12* (solute carrier gene family 22, 12th member) gene, is the dominant apical urate exchanger in humans; loss-of-function mutations in *SLC22A12* are associated with varying degrees of hypouricemia and hyperuricosuria, in the syndrome renal hypouricemia [21]. More recently, the 'orphan' OAT 'ORCTL3' (OAT10) was shown to mediate urate–nicotinate exchange [22]. OAT10 also functions as a urate–PZA exchanger and shares many of the same substrates transported by URAT1. Human OAT4 reportedly functions as a urate transporter [23]. However, it differs mechanistically from URAT1 and OAT10, with no evident urate–PZA exchange and evidence of asymmetrical urate transport (absence of trans-stimulation of other OAT4 substrates). Genetic influence on SUA has been reported in genome-wide association studies (GWAS) for the *SLC22A11* gene encoding OAT4 and the immediately adjacent *SLC22A12* gene encoding URAT1 [17]. Additionally, SUA is affected by variation in the gene encoding the subapical apical scaffolding protein PDZK1 (PDZ-containing kidney protein 1), one of several PDZ domain proteins that tether and regulate the apical complex of reabsorptive and secretory urate transporters [17].

Multiple GWAS of SUA variation have implicated genetic variability in the *SLC2A9* (solute carrier gene family 2, member 9) gene [24]. *SLC2A9* encodes a urate transporter known as GLUT9

(glucose transporter 9). Despite the ever-increasing list of hyperuricemic genes, variation in *SLC2A9* remains the major single genetic determinant of SUA [24,25], followed closely by the *ABCG2* (ATP-binding cassette sub-family G, member 2) gene (see below). Notably, the causal variant(s) within *SLC2A9* has not been identified, although progress has been made in fine-mapping of the GWAS signal [26▪▪].

GLUT9 protein is the exit mechanism for urate at the basolateral membrane, functioning in transepithelial urate reabsorption [24,25]; the identity of this pathway had been something of a mystery, given that the basolateral urate transporters OAT1 and OAT3 function in urate secretion (see below). As is the case for URAT1, loss-of-function mutations in GLUT9 cause renal hypouricemia, but with much higher fractional urate excretion than in URAT1 deficiency (>100% [19]), suggesting that GLUT9 is the exclusive exit pathway for urate in the proximal tubule. Loss-of-function in canine GLUT9 is also associated with hyperuricosuria and hyperuricemia, primarily in Dalmatian dogs [27]; notably, however, in addition to a renal effect, the inactivation of canine GLUT9 constrains liver uricase by restricting the uptake of urate by hepatocytes.

Coding sequence variation in *SLC2A9* is considerable, with at least 24 annotated nonsynonymous variants. Unfortunately, other than functional studies of mutants associated with familial hypouricemia, there has been no systematic characterization of the transport phenotypes of rare and common coding variants in GLUT9. The overall contribution of coding sequence variation to the genetic effect of *SLC2A9* on urate homeostasis is also unclear, owing to population heterogeneity and linkage disequilibrium. For example, the R265H variant has been linked to hyperuricemia [28] and severity of gout [29▪▪], but not in all populations [30]. Coding variants may also modulate the quantitative impact of the 'causative' variation in *SLC2A9* detected in GWAS.

RENAL URATE SECRETION

The basolateral urate transporters, OAT1 and OAT3, function in urate secretion [31] by the proximal tubule, transporting the anion into the cell in exchange for α-ketoglutarate (Fig. 1a). Urate secretion thus begins with the basolateral transport of urate via urate–anion exchange on OAT1 and OAT3, followed by secretion via ATP-driven efflux pumps (MRP4 [32] or ABCG2 [33]) and electrogenic apical urate transporters (SLC17A1 and SLC17A3, also known as NPT1/Oatv1 [34,35] and NTP4 [36]) (Fig. 1a).

Again, as in the reabsorptive transporters, many of the genes encoding secretory urate transporters are implicated in the genetic risk for hyperuricemia and gout [36]. Thus, loss-of-function or reduction-of-function mutations in *NPT4* [36] and *ABCG2* [33] are associated with hyperuricemia and gout. Superficially, these mutations serve to reduce renal urate secretion, leading to unopposed renal tubular urate reabsorption. However, a landmark study has recently established that ABCG2 dysfunction is in fact associated with increased renal urate excretion, because of decreased intestinal secretion [37▪▪]; intestinal secretion contributes significantly to urate homeostasis [13]. This heretofore unappreciated hyperuricemic subtype of 'extra-renal urate underexcretion' may explain the pathophysiology in the majority of patients with hyperuricemia and increased urinary urate excretion – previously attributed to 'urate overproduction' [37▪▪].

ACQUIRED INFLUENCES ON SERUM URATE LEVEL

There is considerable evidence for regulated homeostasis of urate. In bacteria, transcriptional regulation of urate occurs via repression of uricase expression by urate-binding transcription factors [38]; this and related operons are hypothesized to affect the ability of bacteria to respond to oxidative stress [38]. In humans, oxidative stress induced by exposure to high altitude increases serum urate [39], indicating the ability to modulate urate production and excretion in response to changes in oxidative stress and other stimuli. Nigam and colleagues have argued that tight regulation of ABC transporters and SLC22 transporters plays a key role in regulating urate acid homeostasis, such that this transporter network coordinates to regulate circulating urate concentration [40].

Renal urate transport plays a major role in the acquired factors that influence SUA. Alcohol intake can increase SUA and magnify the risk of gout [41]; transient increases in serum lactate and β-hydroxy butyrate from the metabolism of alcohol cause indirect activation of renal urate reabsorption [42] via trans-activation (Fig. 2). Volume status also influences urate excretion and the risk of acute gout, such that volume-depleted patients become hyperuricemic; this physiology underlies in large part the association between diuretic therapy and acute gout [43]. In humans, there is a direct linkage between proximal tubular salt and urate transport [44]. Short-term and long-term salt restriction in humans causes significant hyperuricemia, which is dramatically reversed by salt loading [45,46]. The magnitude of these differences depends on the degree of salt

restriction or salt loading, with a 1.8–2.0 mg/dl difference in SUA between 29–38 and 258 mEqu/day [46]. These short-term changes in dietary salt affect SUA via changes in renal urate excretion [46]. Potential mediators include angiotensin-II [47] and epinephrine [48]. Insulin-stimulated renal urate retention may in turn play an important role in the associations between the metabolic syndrome, hyperuricemia, and gout [49].

Excessive parathyroid hormone (PTH) also reduces urate excretion, in primary hyperparathyroidism and during pharmacological therapy for osteoporosis [50]; this may be particularly relevant to the association between gout and CKD [2▪▪]. A cross-sectional study of National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2006 reveal that serum PTH levels are independently associated with SUA levels, particularly in patients with renal impairment [51▪▪].

Acquired factors can also reduce SUA and ameliorate hyperuricemia or gout. SUA is thus lower during acute gout flares, owing to cytokine-stimulated uricosuria [52]. Negative dietary influences on SUA include cherries, which are an evolving adjunctive therapy for gout [53,54]. Preliminary reports suggest both a uricosuric effect of cherry intake [53] and an inhibitory, antioxidant effect mediated via XOR inhibition [55]. Increased intake of vitamin C, also found in cherries [53], lowers SUA via uricosuric effects and protects against gout [56]. Many other related natural products found in cherries have uricosuric properties.

CHRONIC KIDNEY DISEASE-SPECIFIC THERAPEUTIC ISSUES IN GOUT

Renal disease is highly prevalent in gout. Zhu *et al.* have thus calculated the national prevalence of major comorbidities in gout, using 2007–2008 data from NHANES. Of the estimated 8.3 million Americans affected [1▪], 71% had hypertension, 71% had CKD greater than stage 2 [glomerular filtration rate (GFR) <60], and 24% had nephrolithiasis [2▪▪]. The estimated prevalence of CKD of at least stage 3 (GFR <30) in gout was 19.9% [2▪▪]. With increasing levels of SUA, there were graded increases in the prevalence of CKD [2▪▪]. Historically, gout was felt to be rare in dialysis patients; however, a more recent study has indicated an incidence of 5% in the first year of dialysis and 15.4% in the first 5 years of dialysis [57]. Overall, there is a substantial burden of CKD in gout and of gout in CKD. Comprehensive guidelines for the management of gout have recently been published [58▪▪,59▪▪], emphasis here being on CKD-specific issues.

In acute gout, CKD generally precludes the use of nonsteroidal anti-inflammatory (NSAID) agents. A major recent advance of relevance to patients with CKD was the re-examination of colchicine therapy for acute gout, as an alternative to prednisone or NSAIDs. If given within 36 h of the onset of symptoms, a 'low-dose' regimen (1.2 mg of oral colchicine followed by another 0.6 mg 1 h later) is equivalent in efficacy to high-dose colchicine (4.8 mg total over 6 h) [60]. Although patients treated with low-dose colchicine had a 23% incidence of diarrhea, none had severe diarrhea – versus 79% with diarrhea in the high-dose group, 19.2% with severe diarrhea [60]. No dosage modification in CKD is required for the use of low-dose colchicine for acute flares; however, a treatment course should not be repeated within 2 weeks.

Reducing SUA to less than 6 mg/dl in gout reduces synovial fluid crystals, reduces acute gout flares, reduces tophi, and reduces NSAID use [61]; the presence or absence of CKD does not alter the need to reach this therapeutic goal in patients with gout. A lower target of less than 5 mg/dl may be appropriate in patients with more advanced disease. Indeed, sustained reduction in SUA to approximately 1 mg/dl, after intravenous therapy with a polyethylene glycol-modified recombinant uricase (pegloticase) [62▪▪], has been reportedly associated with dramatic and rapid reduction of tophi in patients with severe tophaceous gout [9].

At present, most American patients on urate-lowering therapy (ULT) for gout receive a XOR inhibitor, either allopurinol or febuxostat. Either XOR inhibitor is appropriate first-line ULT, with no evidence to prefer one agent over the other [58▪▪]. However, a major issue unique to allopurinol is the associated hypersensitivity syndrome (AHS); there is no equivalent syndrome associated with febuxostat. AHS can encompass rash, Stevens–Johnson syndrome, toxic epidermal necrolysis, eosinophilia, vasculitis, and major end-organ disease. AHS has an incidence of approximately 1 : 1000 to 4 : 1000 of treated patients, with a reported mortality of 20–25%. Risk factors for AHS include recent institution of therapy with allopurinol, diuretic therapy, and renal impairment [63].

The active metabolite of allopurinol, oxypurinol, accumulates in renal insufficiency and has historically been implicated in AHS [63]; this purported mechanism underpins the widely accepted dosage guidelines for allopurinol in CKD [64]. However, there is no direct evidence that GFR-adjusted dose reduction in renal impairment reduces the risk of AHS. Furthermore, in a large, peer-reviewed, case-controlled study of AHS, there was no significant difference in allopurinol dose in

those patients with AHS and those who tolerated allopurinol [65]. Severe AHS thus is variably dose dependent [63,66▪▪] and does not always correlate with oxypurinol levels. AHS is HLA linked [65] and can be avoided by genetic screening in at-risk populations [67▪▪]. Specifically, HLA-B*5801-positive individuals have a very high risk of AHS and thus should not receive allopurinol [58▪▪]. The prevalence of HLA-B*5801 alleles in whites is approximately 2%, hence this pharmacogenetic recommendation chiefly applies for now to patients of Korean, Han Chinese, and Thai descent, who have allele frequencies of 6–8% [58▪▪]. Notably, in genetically uncharacterized patients, there is no increase in adverse reactions to allopurinol in patients receiving higher than recommended GFR-adjusted doses [68,69▪▪].

These issues are critical to successful ULT with allopurinol in patients with CKD. Patients without CKD thus require a median dose of approximately 380 mg/day of allopurinol to reduce SUA to less than 6 mg/dl [70]; not surprisingly, dosage reductions in CKD based on Hande *et al.* [64] result in a rate of attaining this goal of only 19% [71]. Current recommendations are to administer up to more than 300 mg/day of allopurinol, as needed, to attain an SUA of less than 6 mg/dl. To minimize the risk of both AHS and of provoking a gout flare, current recommendations are to start with 50 mg/day of allopurinol in CKD IV or worse and gradually increase the dose to reach the goal of a SUA of less than 6 mg/dl [58▪▪]. Patients need to be educated regarding the risk of AHS, with monitoring for the development of rash and abnormal liver function tests as indicators of evolving AHS. Patients intolerant of allopurinol can be treated with febuxostat, which has a different structure and mechanism of XOR inhibition.

Adjunctive urate-lowering measures in gout include dietary and lifestyle modification, curbing the intake of alcohol and purine-rich foods; notably, however, dietary modification alone is rarely adequate to reduce SUA to goal. Cherries are adjunctive ULT for gout [53,54]. Modest but clinically significant uricosuria has also been reported with several common drugs. In particular, both losartan and fenofibrate inhibit URAT1 [72,73]. In addition, several novel uricosurics drugs are in development, further expanding the therapeutic armamentarium in the management of gout.

Finally, the reduction in SUA with any form of ULT can induce acute gout, but this risk can be reduced with the use of anti-inflammatory flare prophylaxis [59▪▪]. Again, colchicine has an important role to play in flare prophylaxis in CKD. Colchicine therapy, 0.6 mg p.o. b.i.d., coadministered during ULT with XOR inhibitors, reduces the flare risk substantially [74]. Pharmacokinetic data for daily colchicine therapy in CKD is sparse in CKD; current data supports a 50% reduction in CKD stages 3–5 [59▪▪]. The recommendations are to continue coadministered colchicine for more than 6 months, 3 months after achieving SUA less than 6 mg/dl in a patient without tophi, or 6 months after achieving SUA less than 6 mg/dl in a patient with tophi [59▪▪].

CONCLUSION

In summary, there have been dramatic developments over the last few years in the molecular physiology of hyperuricemia. Recent advances notwithstanding, there are major gaps in the understanding of renal [16,17,18▪▪] and intestinal [37▪▪] urate transport. In particular, although insulin [49], angiotensin II [47], epinephrine [48], and PTH [50] stimulate urate retention, the mechanisms involved are uncharacterized.

At the clinical level, significant CKD is a frequent comorbidity of gout, with important implications for therapy. The rapidly evolving therapeutic options for gout in CKD [58▪▪,59▪▪], combined with greater refinement in the target SUA [58▪▪], should encourage increased involvement of clinical nephrology in the management of this important disorder.

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None.

Conflicts of interest

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- ▪▪ of outstanding interest

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