ADVANCES IN NEPHROLOGY

Reconsidering Urate-Lowering Therapy in Chronic Kidney Disease- Guideline Driven Perspectives on the Management of Asymptomatic Hyperuricaemia

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Abstract

Hyperuricaemia is highly prevalent in patients with chronic kidney disease (CKD), primarily due to reduced renal urate excretion. Elevated serum uric acid (SUA) levels have been linked with CKD progression, cardiovascular disease, and mortality. However, association does not imply causation. Over the last decade, multiple studies have failed to demonstrate a renoprotective or cardiovascular benefit of urate-lowering therapy (ULT) in patients with asymptomatic hyperuricaemia. Consequently, major international societies, including Kidney Disease: Improving Global Outcomes (KDIGO), the American College of Rheumatology (ACR), and the European Alliance of Associations for Rheumatology (EULAR), recommend against pharmacologic treatment of asymptomatic hyperuricaemia, including in patients with CKD. This review synthesizes current guideline recommendations, randomized clinical trial evidence, and practical clinical considerations to delineate scenarios in which ULT should not be initiated in patients with chronic kidney disease, while highlighting the importance of supportive and non-pharmacologic management strategies.

Keywords: Hyperuricaemia, Chronic kidney disease, Asymptomatic hyperuricaemia, Urate-lowering therapy, Allopurinol, Febuxostat, Gout

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Introduction

Hyperuricaemia is a frequent biochemical finding in CKD, with prevalence increasing progressively as glomerular filtration rate (GFR) declines. Hyperuricaemia affects 40-60% of patients with CKD stages 1 to stage 3, and 70% of patients with CKD stage 4 or stage 5.[1-3] Reduced renal excretion accounts for > 90% cases of elevated SUA levels in CKD, although increased production may also contribute to selected patients.[3,4] Hyperuricaemia has been implicated as a potential mediator of kidney injury through mechanisms such as endothelial dysfunction, oxidative stress, activation of the renin–angiotensin system, and renal microvascular disease.[5] The clinical relevance of asymptomatic hyperuricaemia, defined as elevated SUA in the absence of gout, tophi, or uric acid nephrolithiasis, remains controversial. The temptation to treat hyperuricaemia in CKD stems largely from observational data suggesting worse renal and cardiovascular outcomes at higher SUA levels.[6] However, contemporary randomized evidence and updated international guidelines increasingly caution against this practice. This review critically appraises the evidence and guideline positions to delineate clinical circumstances where ULT is unwarranted in CKD.

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Hyperuricaemia in CKD: Definitions and Clinical Spectrum

Hyperuricaemia is defined as an elevated SUA level, usually greater than 6 mg/dL in women and 7 mg/dL in men.[7] Clinically, it may be categorized as:

- **Asymptomatic hyperuricaemia:** Elevated SUA without gout flares, tophi, or uric acid stones
- **Symptomatic hyperuricaemia:** Gout, chronic tophaceous disease, or uric acid nephrolithiasis

In patients with CKD, asymptomatic hyperuricaemia is far more common than overt gout.[8] Table 1 depicts the various causes of elevated SUA in patients with CKD.[7]

Guideline Positions

KDIGO- The KDIGO 2024 Clinical Practice Guideline suggests not using pharmacologic agents to lower serum uric acid in individuals with CKD and asymptomatic hyperuricaemia for the purpose of delaying kidney disease progression (Grade 2D).[9] This recommendation reflects the Work Group's assessment that randomized controlled trials and systematic reviews have not demonstrated a clear renoprotective benefit, while treatment adds pill burden and potential adverse effects without proven clinical advantage.[9]

ACR- The ACR adopts a similarly conservative stance toward

Table-1: Causes of Hyperuricaemia in Patients with Chronic Kidney Disease.

Category	Specific Cause	Mechanism
Reduced Renal Excretion (Most common in CKD)	Declining GFR	Reduced filtration and impaired tubular secretion of urate
	Volume depletion	Enhanced proximal tubular urate reabsorption
	Metabolic acidosis	Increased urate reabsorption via organic anion transporters
	Insulin resistance/ metabolic syndrome	Reduced renal urate clearance
	Hyperparathyroidism	Alters tubular handling of urate
Drug-Induced Hyperuricaemia	Thiazide and loop diuretics	Volume contraction & increased proximal urate reabsorption
	Calcineurin inhibitors	Reduced tubular secretion
	Low-dose aspirin	Competes with urate for tubular secretion
	Pyrazinamide, ethambutol	Decrease urate excretion
	Niacin	Reduces renal urate clearance
	Non-losartan RAAS blockers, beta blockers	May promote urate retention
Increased Uric Acid Production	High purine intake	Increased substrate for urate generation
	Alcohol (especially beer and spirits)	ATP degradation and lactate generation reduce urate excretion
	Fructose-rich beverages	Accelerates hepatic ATP breakdown
	Obesity	Increased purine turnover and insulin resistance
High Cell Turnover States	Haematologic malignancies	Rapid nucleic acid breakdown
	Severe psoriasis or haemolysis	Increased cellular turnover
Genetic / Metabolic Disorders	PRPP synthetase overactivity	Excess purine synthesis
	HGPRT deficiency (Lesch–Nyhan spectrum)	Impaired purine salvage
Other Secondary Causes	Lead nephropathy	Tubulointerstitial damage & impaired excretion
	Hypothyroidism	Reduced renal plasma flow
	Ketoacidosis / lactic acidosis	Competition for tubular transporters

CKD- chronic kidney disease, GFR- glomerular filtration rate, ATP- adenosine triphosphate, RAAS- renin–angiotensin–aldosterone system, PRPP- phosphoribosyl pyrophosphate, HGPRT- hypoxanthine-guanine phosphoribosyltransferase

asymptomatic hyperuricaemia. The 2020 ACR Guideline for the Management of Gout conditionally recommends against initiating pharmacologic ULT in individuals with elevated SUA who have no prior gout flares or subcutaneous tophi.[10] This recommendation is based on moderate-certainty evidence indicating that the absolute risk of progression to symptomatic gout is relatively low for most patients, while long-term pharmacotherapy introduces potential adverse effects, treatment burden, and cost without clearly demonstrated clinical benefit. The ACR further emphasizes that treatment decisions should be guided primarily by clinical manifestations rather than biochemical thresholds alone, reinforcing that hyperuricaemia in isolation does not constitute a sufficient indication for lifelong ULT.[10]

EULAR- The EULAR likewise discourages pharmacologic treatment in the absence of clinical disease.[11] It states that asymptomatic hyperuricaemia does not warrant ULT, underscoring that treatment should be reserved for patients with established gout manifestations or crystal-related complications. This position reflects the limited evidence supporting preventive pharmacotherapy and aligns with broader international guidance emphasizing lifestyle optimization and management of comorbidities rather than routine drug initiation for isolated biochemical hyperuricaemia.[11]

Evidence from Randomized Controlled Trials

Over the past decade, several RCTs have evaluated whether pharmacologic urate lowering can slow kidney disease progression in patients with CKD or those at high renal risk. Collectively, these trials have provided largely neutral results, challenging earlier observational associations between hyperuricaemia and kidney function decline.[12-15] The CKD-FIX (Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase) trial was a multicenter, placebo-controlled study that enrolled 369 adults with stage 3–4 CKD who were considered at risk for progression.[12] Participants were randomized to receive allopurinol or placebo for approximately two years. The study demonstrated that ULT did not significantly slow the decline in eGFR compared with placebo.[12]

Similarly, the PERL (Preventing Early Renal Loss in Diabetes) trial examined whether allopurinol could preserve kidney function in individuals with type 1 diabetes and mild-to-moderate diabetic kidney disease.[13] This RCT found no clinically meaningful benefit of SUA reduction on kidney outcomes.[13] The FEATHER trial, which evaluated febuxostat in patients with stage 3 CKD, also failed to demonstrate improvement in GFR compared with placebo.[14] Investigators noted that the relatively modest decline in kidney function among participants may have limited the ability to detect treatment effects.[14] However, when interpreted alongside PERL and CKD-FIX, the findings contribute to a growing body of evidence suggesting that pharmacologic urate lowering is not indicated solely to slow CKD progression. Secondary analyses and reviews further reinforce this perspective, highlighting that both PERL and CKD-FIX revealed no significant advantage of allopurinol over placebo in preventing CKD progression15.

When Hyperuricaemia Should Not Be Treated in CKD

Elevated SUA alone, regardless of CKD stage or the presence of comorbidities such as hypertension, diabetes, or cardiovascular disease, does not constitute a sufficient indication for pharmacologic therapy, as current evidence does not support a benefit in slowing kidney disease progression or improving cardiovascular outcomes.[9-15] We suggest the evidence-based scenarios where ULT is not indicated in CKD, as showcased in Table 2. A conservative strategy is particularly appropriate in such patients, where the potential risks of therapy may outweigh uncertain benefits. Instead, management should focus on

Table-2: Evidence-Based Scenarios Where ULT Is Not Indicated in CKD.

Clinical Scenario	CKD Context	Recommendation	Rationale
Asymptomatic hyperuricaemia	Any CKD stage	Do not treat	No evidence of renal or CV benefit; potential drug toxicity
Elevated SUA without gout or stones	CKD stages 1–5	Do not treat	Hyperuricaemia reflects reduced excretion, not causal injury
CKD with hypertension or diabetes	Common comorbidity	Do not treat solely for SUA	RCTs show no slowing of CKD progression
CKD with cardiovascular disease	High CV risk	Do not treat	No proven CV outcome benefit of ULT
Elderly CKD patients	Frailty/ polypharmacy	Avoid ULT	Higher risk of adverse drug reactions
Mild–moderate urate elevation (<8–9 mg/dL) without symptoms	Stable renal function	No pharmacologic therapy	Low absolute risk of gout; high NNT

SUA- serum uric acid, ULT- urate-lowering therapy, CV- cardiovascular, NNT- number needed to treat.

optimization of CKD risk factors, lifestyle modification, and periodic clinical monitoring.[15]

Risks of Unnecessary ULT in CKD

Initiating ULT in patients with CKD without clear clinical indications may expose them to avoidable risks without established benefit. Reduced renal clearance can alter drug metabolism and increase susceptibility to adverse effects, particularly with xanthine oxidase inhibitors.[16] Allopurinol, although generally well tolerated, carries a rare but potentially life-threatening risk of allopurinol hypersensitivity syndrome, the likelihood of which is higher in individuals with impaired kidney function.[17] Febuxostat has been associated with concerns regarding cardiovascular safety in selected populations, necessitating cautious patient selection.[18] Beyond drug-specific toxicities, unnecessary therapy contributes to polypharmacy, increases treatment burden, and may negatively affect adherence to medications with proven renoprotective benefit. There is need for drug audit of such cases to reduce polypharmacy and unnecessary ULT initiation.

Recommended Non-Pharmacologic Approach

In patients with CKD and asymptomatic hyperuricaemia, management should prioritize a careful clinical evaluation before considering any therapeutic intervention.[19] A detailed history and medication review are essential to identify reversible contributors, particularly drug-induced hyperuricaemia from agents such as thiazide and loop diuretics, low-dose aspirin, calcineurin inhibitors, or certain cytotoxic drugs.[7] Clinicians should also assess for secondary causes including high alcohol intake, fructose-rich diets, obesity, metabolic syndrome, psoriasis, and high cellular turnover states. Addressing these modifiable factors may reduce serum urate without exposing patients to unnecessary pharmacotherapy.[7]

Beyond etiologic assessment, treatment should focus on established renoprotective strategies, optimization of blood pressure, glycaemic control, and proteinuria, along with lifestyle measures such as weight management, regular physical activity, adequate hydration, moderation of alcohol consumption, and reduced intake of purine and fructose-rich foods.[19] Losartan is known to reduce SUA by inhibiting the urate transporter 1 in proximal tubules, which prevents the reabsorption of uric acid.[20] SGLT2 inhibitors (SGLT2i) are also known to reduce SUA though the precise outcomes still need to be established.[21] SGLT2i can act as an adjunct therapy in such cases. Reviewing concomitant medications, including drug audits, and substituting urate-elevating drugs where clinically feasible can be particularly impactful. Periodic monitoring of serum uric acid and kidney function is advisable, and patients should be educated about the symptoms of gout to ensure timely evaluation if clinical manifestations arise. Such a structured, conservative approach aligns with current evidence and supports holistic CKD care while avoiding unnecessary treatment burden.[9-11]

Conclusions

Current evidence and international guidelines uniformly support not treating asymptomatic hyperuricaemia in patients with CKD. Despite strong observational associations, randomized trials have failed to demonstrate renoprotective or cardiovascular benefits from ULT in this population. Given the potential for harm, increased pill burden, and lack of efficacy, pharmacologic intervention should be reserved for patients with clear clinical indications such as gout, tophi, or uric acid nephrolithiasis. A conservative, evidence-based approach centered on comprehensive CKD care and lifestyle optimization remains the standard of care.

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