African Journal of Nephrology
Official publication of the African Association of Nephrology
Volume 25, No 1, 2022, 8-13

REVIEW ARTICLE

Management of asymptomatic hyperuricemia in chronic kidney disease: A proposed stepwise approach

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ABSTRACT

Serum uric acid levels are frequently elevated in patients with chronic kidney disease (CKD). The relatively modest hyperuricaemia in CKD may reflect the reduced efficiency of renal excretion of urate. In the past two decades, basic research has shown that hyperuricaemia plays a causal role in the progression of CKD through direct renal injury. However, clinical studies have reported conflicting results, hence there is much controversy about the scope of treating asymptomatic hyperuricaemia to prevent or reduce the rate of CKD progression. In this review, we highlight the most recent guidelines and clinical trials that tested the use of urate-lowering therapy in the management of asymptomatic hyperuricaemia in CKD patients.

Keywords: Uric acid, hyperuricaemia, chronic kidney disease.

INTRODUCTION

Serum uric acid (SUA) levels are frequently elevated in patients with chronic kidney disease (CKD). The relatively modest hyperuricaemia in CKD may reflect the reduced efficiency of renal excretion of urate [1]. In the past two decades, basic research has shown that hyperuricaemia plays a causal role in the progression of CKD through direct renal injury [2]. Preclinical research has shown that hyperuricaemia-induced renal arteriolopathy involves the renin–angiotensin system, partially dependent on angiotensin II [3]. Moreover, hyperuricaemia was associated with increased renal renin and cyclooxygenase-2 expression in experimental rats, especially in the preglomerular arterial vessels [4]. This indicated that hyperuricaemia could mediate the progression of renal disease through accelerating hypertension and vascular disease.

This progress could help to develop novel therapeutic approaches for alleviating the progression of CKD [5].

The association between hyperuricaemia and CKD may be explained by several possible mechanisms, including the effect of uric acid on renal podocytes [6], free radical generation and subsequent endothelial dysfunction [7], and activation of cytoplasmic phospholipase A2 and inflammatory transcription factor NF-Kb [8]. However, clinical studies have reported conflicting results, hence there is much controversy about the scope of treating asymptomatic hyperuricaemia to prevent or reduce the rate of CKD progression.

Critical appraisal of 13 randomized control trials (RCTs) advised against the use of allopurinol in the treatment of asymptomatic hyperuricaemia, except in the presence of persistent elevation of serum uric acid above 13 mg/dL in men or 10 mg/dL in women, in the case of high urinary excretion of uric acid or in patients in radiotherapy or chemotherapy [9].

Other studies suggest the recognition of the presence of urate crystals in urine and the presence of signs of articular damage on musculo-skeletal ultrasound as indicators to start urate-lowering therapy (ULT) in cases of asymptomatic hyperuricaemia [10]. In this

Received 29 March 2021; accepted 12 July 2021; published 04 March 2022.
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review, we highlight the most recent guidelines and clinical trials testing the use of ULT in the management of asymptomatic hyperuricaemia in CKD patients.

GUIDELINE SUGGESTIONS / RECOMMENDATIONS FOR THE USE OF ULT IN TREATMENT OF ASYMPTOMATIC HYPERURICAEMIA IN CKD PATIENTS

Most available guidelines advise against the use of ULT to treat asymptomatic hyperuricaemia in CKD patients. The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease highlighted the lack of sufficient evidence to support or refute the use of ULT to lower serum uric acid concentrations in people with CKD and with either symptomatic or asymptomatic hyperuricaemia, in order to delay progression of CKD [11]. Recently, the 2020 American College of Rheumatology Guideline for the Management of Gout conditionally recommended against initiating any pharmacological ULT for patients with asymptomatic hyperuricemia [12]. Also, the 2020 recommendations of the French Society of Rheumatology for the management of gout did not endorse the use of ULT in asymptomatic patients [13].

The only available guideline supporting the use of ULT in asymptomatic hyperuricaemic CKD patients comes from the Japanese Society of Gout and Uric & Nucleic Acids 2019 Guidelines for Management of Hyperuricemia and Gout (3rd edition). They suggest the use of ULT in asymptomatic hyperuricaemic CKD patients if serum uric acid is ⩾8 mg/dL [14]. Five RCT papers were recognised in this guideline [15-19]. The weight of the results of Goicoechea et al. [15] was the highest at 77 %, followed by Hosoya et al. [16] at 13%. The difference in the amount of change in eGFR in the drug intervention group was 4.12 mL/min /1.73 m^2 (95% confidence interval 3.7–4.6), indicating a better result than the control group and a statistically significant difference ($P < 0.001$). The observation period ranged from 22 weeks to 3 years and the more heavily weighted investigation by Goicoechea et al. [20] lasted 2 years, so it had a comparatively high weight of evidence.

CLINICAL TRIALS FOR THE USE OF ULT IN TREATMENT OF ASYMPTOMATIC HYPERURICAEMIA IN NON-HAEMODIALYSIS CKD PATIENTS

Available evidence for treating asymptomatic hyperuricaemia in CKD is inconsistent and contradictory. A number of observational studies [21-25], a randomized control trial [26] and a meta-analysis [27] did not show improved kidney outcomes from the use of ULT. However, other observational studies [28-34], randomized control trials [15,20,37] and meta-analyses [38-40] detected a benefit from the use of ULT in CKD patients. The results of these studies should be interpreted with caution, as many factors seem to have affected their outcomes such as the heterogeneity of patients, baseline glomerular filtration rate (GFR) and risk factors. Unmeasured and unadjusted confounding factors may have also affected their results, including variation of outcome definitions and follow-up time in most of the studies [41].

Recently, the Preventing Early Renal Loss in Diabetes trial (PERL RCT) [42] failed to show any benefits of serum urate reduction with allopurinol as compared with placebo on kidney outcomes among type 1 diabetes patients with early-to-moderate diabetic kidney disease and with no history of gout or xanthinuria or other indication for ULT. Can the results of the PERL study be generalized to all type 1 diabetic CKD patients who have asymptomatic hyperuricaemia? The answer is no, because there are several issues related to this study. First, patients with normal serum urate were included in the study. Second, the study enrolled only patients of middle to old age (51.1 ± 10.9 years). Finally, they excluded patients who had hepatic diseases, anaemia and congestive or pulmonary insufficiency, which are relatively common in CKD patients.

Moreover, the recent CKD-FIX RCT [43] concluded that ULT with allopurinol did not slow the decline in eGFR as compared with placebo in patients with chronic kidney disease and a high risk of progression or albuminuria ≥265 mg/g. Also, the CKD-FIX study result cannot be generalized to all CKD patients with albuminuria or high risk of progression, for several reasons. First, the study also included patients with normal serum urate. Second, the study enrolled older patients (62.4 ± 12.7 years). Third, they included only moderate CKD stages and, as is well known, halting progression may be easier at earlier stages of CKD because of limited fibrosis than at late stages 3 or 4 of CKD. Fourth, in contrast to the CKD-FIX trial, there is evidence [44] that in patients with progressing CKD, empiric allopurinol may be appropriate. However, several issues have been raised including questions about the quality and biases of these studies [45]. Fifth, related to the CKD-FIX study, the enrollment of patients was stopped because of the slow recruitment after 369 of 620 intended patients. That means there was insufficient power in the study as a result of the difficulty of recruiting patients who met the criteria for eligibility, and this possibly limits generalizability of the results. Finally, in the CKD-FIX study about 30% of patients in the allopurinol group and 25% in the placebo group discontinued the assigned medication for different reasons, though there was still a

sustained mean reduction of 35% in the serum level in the allopurinol group A summary of the most important clinical trials tested the use of ULT in asymptomatic CKD patients are summarized in Table 1.

SPECIAL CKD SUBGROUPS

There is little evidence that some groups of CKD patients may derive benefit from treatment of asymptomatic hyperuricaemia. In a subanalysis of the FEATHER trial, the decline in eGFR was significantly reduced by the use of febuxostat in the subgroup of patients with no proteinuria and serum creatinine level below the median [24]. Another subgroup that may obtain benefit from treatment of asymptomatic hyperuricemia is CKD patients with mild to moderate renal impairment, whose kidney function improved by ULT [39]. Interestingly, young CKD patients were excluded in almost all trials that tested the effect of the treatment of asymptomatic hyperuricaemia. Also, patients with a single kidney were not involved in any of these trials. There is evidence for the relation between serum uric acid and GFR deterioration in populations with a solitary kidney. Higher predonation SUA levels (>4.5 mg/dL) in females were associated with lower 6-month and 1-year eGFR and a higher percentage of donors with 1-year eGFR <60 mL/min/1.73 m^2 compared with female donors in the lower SUA (≤4.5 mg/dL) range [13]. More randomized control trials are needed in these different patients' subgroups to detect the effect of treatment of asymptomatic hyperuricaemia.

PROPOSED APPROACH FOR MANAGEMENT OF ASYMPTOMATIC HYPERURICAEMIA IN CKD PATIENTS

According to the available evidence, we propose a stepwise approach for the management of asymptomatic hyperuricaemia in CKD patients (Figure 1). First, drugs that may affect serum uric acid level should be discontinued or switched to alternatives, if possible. Drugs commonly used in CKD can increase serum uric acid, such as aspirin and immunosuppressive agents such as cyclosporine and tacrolimus [46]. Also, diuretics, ß blockers, angiotensin-

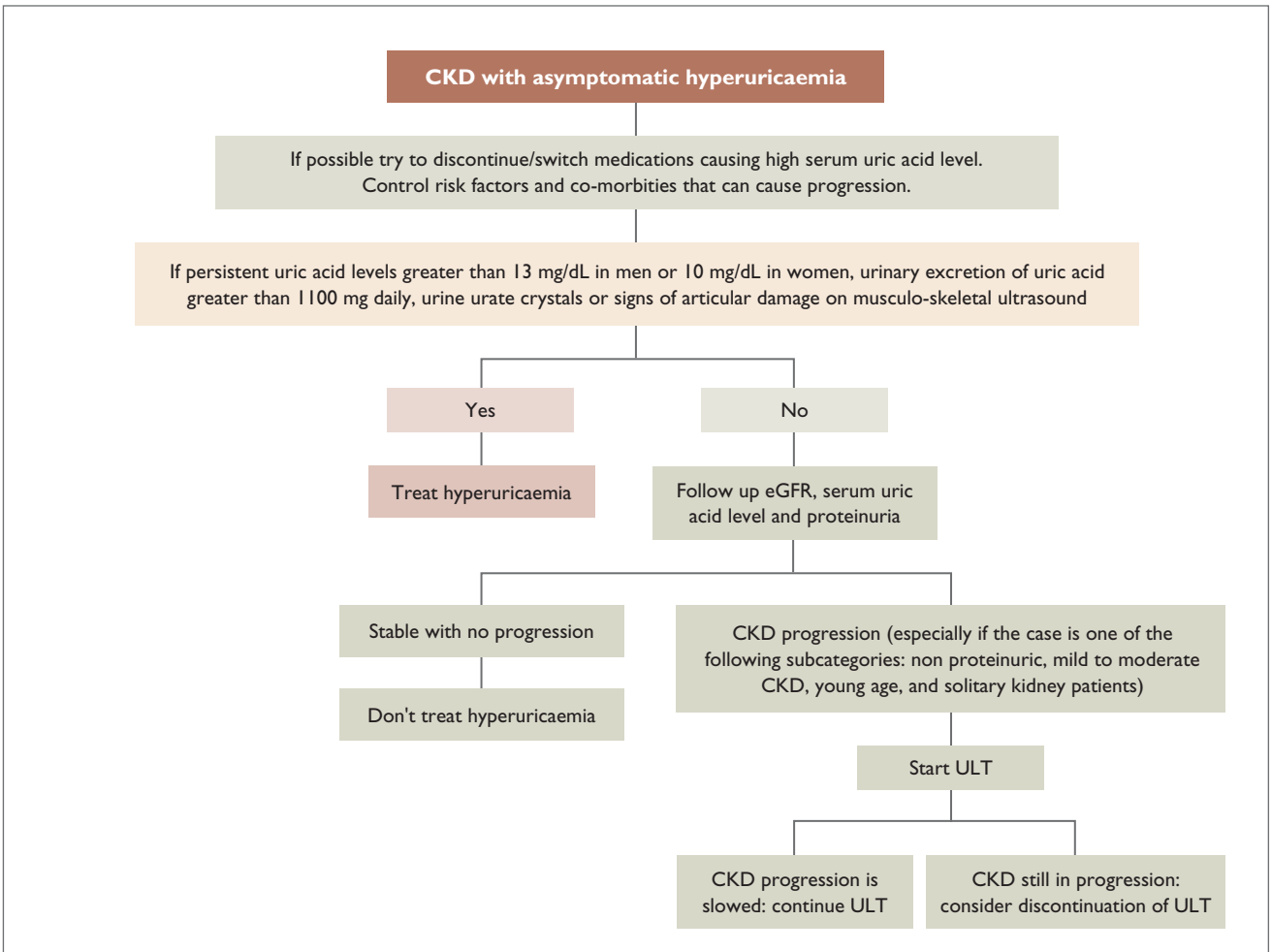

Figure 1. Proposed stepwise approach for the management of asymptomatic hyperuricaemia in CKD patients.
Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ULT, urate-lowering therapy

Table 1. Summary of clinical trials using ULT in treatment of asymptomatic hyperuricemia in CKD patients not on hemodialysis.

Study	Design	Population	Medication	Main outcome
FEATHER study, 2018 [26]	Randomized, double-blind, placebo-controlled trial.	467 patients with stage 3 CKD and asymptomatic hyperuricemia.	Febuxostat for 108 weeks	1: No significant difference in mean eGFR slope between the febuxostat and placebo. 2: Significant benefit from febuxostat in patients without proteinuria and for whom serum creatinine concentration was lower than the median. 3: The incidence of low incidence of gouty arthritis in the febuxostat group. 4: Adverse events specific to febuxostat were not observed.
Goicoechea et al., 2010 [15]	Randomized, double-blind, placebo-controlled trial.	113 patients with estimated GFR (eGFR) <60 ml/min.	Allopurinol	1: Significant reduction of serum uric acid and C-reactive protein levels. 2: Slow decline of eGFR in the allopurinol group after 24 months. 3: 71% reduction of risk of cardiovascular events in allopurinol group.
FREED study, 2019 [37]	Multicentre, prospective, randomized open-label, blinded endpoint study.	1070 patients were included in the intention-to-treat population.	Febuxostat for 36 months	Primary composite event rate (cerebral, cardiovascular, and renal events and all deaths) was significantly lower in the febuxostat group.
PERL study 2020 [42]	Randomized, double-blind, placebo-controlled trial.	530 patients with type 1 diabetes.	Allopurinol for 3 years	No evidence of clinically meaningful benefits of serum urate reduction with allopurinol on kidney outcomes among patients with type 1 diabetes and early-to-moderate diabetic kidney disease.
CKD-FIX study, 2020 [43]	Randomized, double-blind, placebo-controlled trial.	363 patients with CKD stage 3 or 4.	Allopurinol for 104 weeks	Allopurinol failed to slow the decline in eGFR as compared with placebo.

converting enzyme inhibitors and non-losartan angiotensin II receptor blockers are associated with an increased risk of gout [47].

Some medical conditions common in CKD patients, such as hyperparathyroidism [48], hypothyroidism [49] and vitamin B12 deficiency [50], can increase the SUA level. Successful treatment of these medical conditions can reduce the SUA level without the need of ULT.

The main idea of the stepwise approach is to follow up eGFR, serum uric acid level, and proteinuria while controlling blood pressure, glycaemic control and other known risk factors of progression. If there is progression of the case in spite of the control of other risk factors, then starting ULT may be considered. Some patients, such as cases of non-proteinuric or mild to moderate CKD, a young age, and those with a solitary kidney may need closer attention.

CONCLUSIONS

The evidence for the treatment of asymptomatic hyperuricaemia in CKD patients remains controversial and, where it exists, cannot be extrapolated to all CKD patients. We suggest that management should be individualized according to the rate of CKD progression and depending on the ability to control other associated risk factors. Finally, well-designed RCTs are needed especially for subgroups with mild to moderate CKD, a young age, and patients with a single kidney.

Conflict of interest

The authors have no conflict of interest to declare.

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