

# Management of Chronic Kidney Disease: The Relationship Between Serum Uric Acid and Development of Nephropathy

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## ABSTRACT

Chronic kidney disease (CKD) is increasingly recognized as a global health problem, and new and effective strategies are needed for the management of this condition. Recently, there has been renewed interest in the relationship between serum uric acid (SUA) levels and CKD, and several recent trials have demonstrated a possible link between SUA and the development and/or progression of CKD in patients with and without diabetes. The identification of key urate transporters such as urate transporter 1 and glucose transporter 9 has provided not only insights into the pathophysiology of hyperuricemia, but also possible links to other processes, such as glucose homeostasis. The renewed interest in the role of SUA in CKD has coincided with the development of sodium glucose co-transporter 2 inhibitors for the treatment of diabetes. In addition to

improving glycemic control, these agents, acting via the kidneys in an insulin-independent manner, have also been shown to reduce SUA levels and potentially improve some measures of renal function. This review will discuss the role of uric acid in CKD treatment, and how SUA-lowering therapies may prevent or delay the progression of CKD.

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**Keywords:** Chronic kidney disease; Diabetes; Diabetic nephropathy; Nephrology; Renoprotection; Serum uric acid; Sodium glucose co-transporter 2 (SGLT 2) inhibitors

## INTRODUCTION

Chronic kidney disease (CKD) is a key determinant of poor health outcomes in major non-communicable diseases such as cardiovascular (CV) disease and diabetes, and it is increasingly recognized as a global public health problem [1, 2]. The burden of CKD includes not only progression to end-stage renal disease (ESRD), but also complications related to renal impairment and increased risk

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of CV disease [2]. The increased morbidity and mortality related to CKD may be reduced with early detection and effective management to prevent or delay further progression of renal dysfunction and its associated complications [1, 2].

Interest in the relationship between serum uric acid (SUA) and CKD has been renewed recently, due in part to new experimental and clinical data [3, 4]. The debate continues regarding whether SUA plays a causal role in CKD or is simply a marker of renal dysfunction [3]. Emerging evidence continues to support a pathogenic role for SUA in CKD [5–9]. Notably, this renewed interest has coincided with the development of sodium glucose co-transporter 2 (SGLT2) inhibitors for type 2 diabetes mellitus (T2DM); these agents, acting via the kidneys in an insulin-independent manner, reduce SUA and potentially improve renal outcomes [10–13]. In this review, we will discuss the currently available evidence on the relationship between SUA and CKD, and how the uric acid-lowering effects of SGLT2 inhibitors may contribute to renoprotection. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by the author.

## URIC ACID AND HYPERURICEMIA

Uric acid is a weak organic acid that under physiologic conditions exists mainly as monosodium urate [14]; therefore, uric acid and urate, although chemically different, are generally interchangeable terms. In higher primates, uric acid is the end product of the metabolism of unwanted purine nucleotides [4, 10, 15]. Unlike other mammals, higher primates lack the enzyme uricase that converts uric acid to allantoin [15–17]. Beneficial effects of uric acid, such as its ability to scavenge harmful

radicals, may have been evolutionarily advantageous [15, 16]. However, increased SUA levels can lead to urate crystallization and associated complications, such as kidney stones and gout. There is also increasing evidence that increased SUA levels may negatively affect CV and renal health in a crystal-independent manner [18].

About two-thirds of uric acid is produced endogenously, primarily in the liver, muscle, and intestine, and one-third is derived from dietary sources, including fructose, alcohol, and purine-rich foods like certain meats and seafood [4]. Uric acid is produced from fructose via an endogenous pathway as well as from dietary sources (e.g., corn syrup), and a high fructose intake can cause intracellular adenosine triphosphate depletion and nucleotide turnover, with uric acid formation [19]. In diabetes, fructose is generated endogenously via the polyol pathway; blocking the metabolism of fructose in a diabetic mouse model has been found to mitigate the development of tubulointerstitial injury through blocking the production of tubular uric acid [20].

Overall, the SUA level is determined primarily by a balance of uric acid generation, reabsorption, and excretion in the kidney, but it can also be influenced by other factors, like dietary purine intake, hydration status, and use of diuretics [4, 15]. Volume depletion will reduce uric acid excretion independently of urine flow [21], while a comparison of mannitol- and glucose-associated osmotic diuresis showed that, for each osmolar unit, glucosuric diuresis had a threefold greater uricosuric effect [22].

Uric acid is excreted primarily via the kidneys; therefore, the kidneys play an important role in regulating SUA levels [4, 23]. In the kidneys, urate reabsorption and secretion

are regulated by multiple urate transporters. For example, urate transporter 1 (URAT1) is expressed in the apical membrane of proximal tubule cells and is responsible for urate reabsorption [15, 24]. In addition, two isoforms of the urate transporter SLC2A9 (glucose transporter 9 [GLUT9]) are known, one expressed at the baso-lateral side of the proximal tubule and the other on the apical membranes in the collecting duct. Normally, no glucose will reach the collecting ducts, but in diabetes (and especially with SGLT2 inhibition) large amounts of glucose can be excreted: GLUT9 is now exchanging glucose and fructose for uric acid, and therefore plays an important role in regulating urate homeostasis [23, 25–29]. Only a small fraction of uric acid (8–10%) is excreted (net urinary urate excretion is 250–750 mg/day), as about 90% of filtered urate is reabsorbed [4]. Obesity, insulin resistance, hypertension, and diuretic use have been associated with increased urate reabsorption in renal tubules and hyperuricemia [4]. It is currently not known how tubuloglomerular feedback or fructose-induced uric acid formation can affect uricosuria in the setting of SGLT2 inhibition.

The definition of hyperuricemia in adults is not universally agreed upon, but commonly used thresholds are in the range of 6–7 mg/dL (350–400  $\mu$ M/L), and are usually higher for men than for women [23]. The presence of hyperuricemia has been associated with a number of disorders including CV and renal disease, metabolic syndrome, diabetes, and hypertension [30]. In patients with T2DM, hyperuricemia is associated with an increased risk of developing gout, kidney stones, vascular complications [31, 32], and death [32].

Establishing the exact relationship between SUA level and diabetes has been complicated by the fact that both hypouricemia and

hyperuricemia have been linked to diabetes [33]. SUA levels may be low in patients with recently diagnosed diabetes due to increased urate excretion [34]. Hyperuricemia, on the other hand, has been associated with the development of diabetes, especially in the context of insulin resistance and impaired glucose tolerance [35]. In a large population-based study, increased SUA levels were shown to be an independent risk factor for developing T2DM, and one-quarter of diabetes cases could be attributed to high SUA levels [36]. These findings may have a strong public health impact, as lowering SUA may decrease the incidence of diabetes, if the relationship is causal [37].

## CHRONIC KIDNEY DISEASE

CKD is defined as abnormalities of kidney structure or function that persist for more than 3 months with health implications [37, 38]. Abnormalities include decreased glomerular filtration rate (GFR;  $<60$  mL/min/ $1.73$  m<sup>2</sup>) or evidence of one or more markers of kidney damage (albuminuria, urine sediment abnormalities, electrolyte abnormalities, abnormalities detected by histology or imaging, or history of kidney transplantation [37]). CKD is becoming increasingly recognized as a worldwide public health problem that may be more common in developing countries and in disadvantaged and minority populations [1]. In the USA, CKD is present in over 13% of the population, making it more prevalent than diabetes [38, 39]. Using an updated Kidney Disease: Improving Global Outcomes (KDIGO) classification system for CKD to include the level of both renal function and urinary albumin excretion, recent estimates suggest that the prevalence of CKD among patients

with diabetes is 43.5%, and the prevalence of mildly decreased renal function or worse [estimated GFR (eGFR) <60 mL/min/1.73 m<sup>2</sup>] is 22.0% [40]. Diabetic kidney disease is the single strongest predictor of mortality in patients with diabetes [41, 42]. Furthermore, CKD is associated with an eight- to tenfold increase in CV mortality, and its presence is a negative risk factor in patients with diabetes and hypertension [1]. In developed countries like the USA, diabetic kidney disease is the leading cause of ESRD [41].

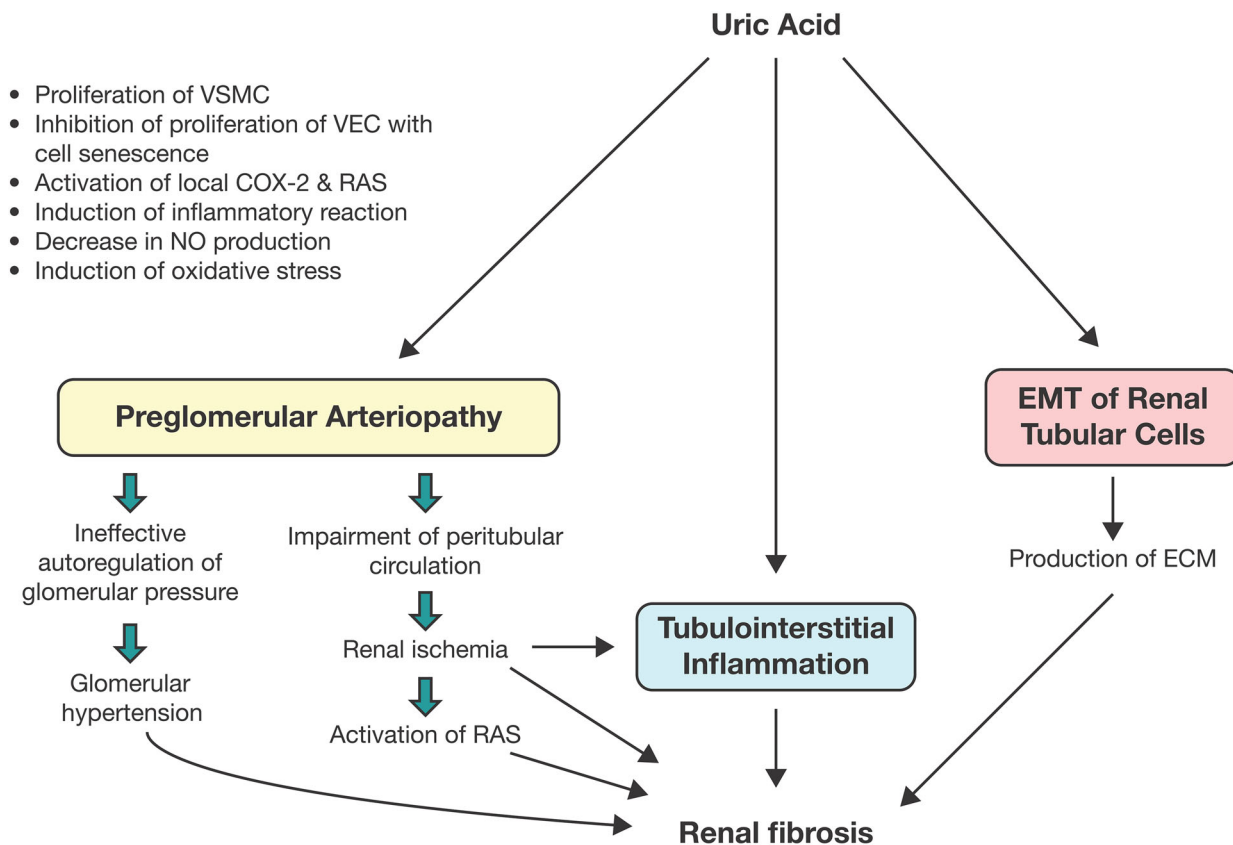
Prognosis is determined primarily by GFR and albuminuria category (albumin excretion rate <30 [A1], 30–300 [A2], or >300 [A3] mg/24 h for normal, microalbuminuria, or macroalbuminuria [clinical proteinuria], respectively) [43], but other factors, such as the cause of CKD and presence of comorbidities, may also be taken into account. Progression of CKD, as defined by a decline in category (e.g., from CKD stage 3 to 4) or a loss of 5 mL eGFR or more per year, can potentially lead to ESRD. It has been suggested that early detection and management of CKD, when patients are typically seen by general internists, can slow or prevent progression of the disease using simple and relatively inexpensive interventions, including control of blood pressure and, in diabetes, blood glucose level [1, 44]. However, while glycemic control has been shown to reduce the initial development of micro- and macroalbuminuria, there are limited data on its effects on GFR [45, 46]. Control of CV risk factors, such as hyperlipidemia, plays also an important role in the management of patients with diabetic kidney disease [38]. Despite evidence of significant reductions in CV events with statin therapy in patients with and without albuminuria, no significant effect on slowing CKD progression was found with statin use [45,

47, 48]; these findings highlight the need for more effective strategies for managing CKD.

## RELATIONSHIP BETWEEN HYPERURICEMIA AND CKD

SUA levels are usually increased in patients with CKD, but whether SUA plays a causal role in CKD remains a topic of debate [3, 4]. A recent renal biopsy study of 167 Japanese patients with CKD (eGFR <60 mL/min/1.73 m<sup>2</sup>) found that, after adjusting for age, sex, hypertension, diabetes, and eGFR, an SUA level above 7.2 mg/dL was associated with renal arterial wall thickening and hyalinosis consistent with renal arteriolopathy [49]. The suggestion that hyperuricemia is a risk factor for CKD is supported by many studies. Preclinical data suggest that hyperuricemia induces renal injury through multiple crystal-independent mechanisms involving renal vasoconstriction mediated by endothelial dysfunction, inflammation, and activation of the renin–angiotensin system (Fig. 1) [8, 17, 18, 50–53]. Hyperuricemia has also been associated with afferent renal arteriolopathy, tubulointerstitial fibrosis, and renal inflammation [54].

Data from most epidemiological studies suggest that uric acid is a major independent risk factor for the development and progression of renal disease in patients both with [9, 55–57] and without diabetes [56, 58–68]. In a recent meta-analysis of 13 observational trials involving over 190,000 patients [56], the presence of hyperuricemia was an independent predictor of new-onset CKD development. The effect was seen in subsets of patients with and without diabetes, and the magnitude of the effect was comparable in both subsets. Possibly reflecting dietary differences, this effect was



**Fig. 1** Potential mechanisms of uric acid-induced kidney disease [4]. *COX-2* Cyclooxygenase-2, *ECM* extracellular matrix, *EMT* epithelial-to-mesenchymal transition, *NO* nitric oxide, *RAS* renin–angiotensin system, *VEC* vascular endothelial cells, *VSMC* vascular smooth muscle cells.

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more pronounced in Western populations than in Asian populations [56]. Notably, in patients with increased SUA levels, the risk of developing new-onset CKD increased as the duration of follow-up increased, suggesting that hyperuricemia may play a role in the long-term progression of chronic renal dysfunction [56]. In a recent cross-sectional study enrolling 3212 Chinese patients with T2DM, the prevalence of diabetic kidney disease was significantly elevated in hyperuricemia subjects and increased with increasing uric acid levels [55]. The presence of a mutation in the urate transporter GLUT9 strongly predicted progression of CKD in a

cohort of 755 patients with CKD [69]. Lastly, in a study of 4233 women, increased SUA during pregnancy was associated with a higher risk of subsequent hospitalization for significant atherosclerotic-related events, including renal failure, diabetic ketoacidosis, hypertensive crisis, and CV events [70].

Some epidemiological studies, however, have reported no significant relationship between hyperuricemia and progression of kidney disease and development of kidney failure [71, 72]. In a prospective analysis of the Mild to Moderate Kidney Disease study, 177 patients with non-diabetic primary CKD and various stages of renal impairment were

followed for 7 years [71]. Increased SUA levels predicted CKD progression only when patients receiving uric acid-lowering drugs were excluded from the analysis. After adjusting for baseline GFR and proteinuria, hyperuricemia was no longer an independent predictor of CKD progression [71]. Similarly, in the Modification of Diet in Renal Disease study, 838 patients with stage 3–4 CKD were followed for median of 10 years [72]. In continuous analyses, each 1 mg/dL increase in SUA level was associated with an increased risk of all-cause mortality and CV disease-related mortality, but not with progression to kidney failure [72].

### Diabetes

In patients with diabetes, a multifactorial treatment approach with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) is needed to control hypertension, i.e., reducing blood pressure below 140/90 mmHg, and to lower albuminuria. Tight glucose control and correction of hyperlipidemia have been shown to reduce CV risks, but currently no data exist to show that such interventions can slow down the progression of CKD [50, 73]. In patients with type 1 diabetes mellitus, elevated SUA levels at baseline were shown to predict the development of CKD in several trials [5–7, 57]. A recent multiple regression analysis performed on 1108 patients with type 1 diabetes identified SUA as the third most important risk factor after tumor necrosis factor receptor 1 and albuminuria, associated with early progressive renal decline [74]. Similar results have been reported in patients with T2DM. For example, in a study of 1449 patients with T2DM, normal kidney function, and no proteinuria, subjects were followed for 5 years to assess the occurrence of new-onset CKD [9]. During the

5-year period, the cumulative incidence of CKD was significantly higher in patients with baseline hyperuricemia (>7.0 mg/dL) compared with those without hyperuricemia (29.5% vs. 11.4%). A multivariate analysis in this population of patients with T2DM confirmed that hyperuricemia, together with older age, use of antihypertensive drugs, and lower eGFR and higher albuminuria at baseline, was an independent risk factor for the development of CKD [9].

### IgA Nephropathy

IgA nephropathy (IgAN) is the most common type of primary glomerular disease characterized by variable tubulointerstitial lesions, and it can progress to ESRD over time [75]. In patients with IgAN, SUA levels have been shown to correlate with renal damage [76, 77] and progression of IgAN [58, 78, 79]. In a recent study of 93 patients with IgAN, baseline SUA levels significantly predicted the change in eGFR over a 6-month period after adjusting for multiple factors, including baseline GFR and albumin level [58]. In a long-term study (mean follow-up 5 years) of 348 consecutive cases of IgAN, patients with high SUA levels at baseline were significantly more likely to experience a decline in GFR (41% vs. 16%) and develop ESRD (65% vs. 35%) compared with patients with SUA levels within the normal range [78].

### Acute Kidney Injury

Lastly, little is known about the relationship between SUA and acute kidney injury (AKI). Data from Atherosclerosis Risk in Communities, a population-based study of over 11,000 participants followed for an average of 12 years, indicated that increased plasma urate (>5.0 mg/dL) was independently associated

with the risk of hospitalization for AKI [80]. For each 1 mg/dL increase in plasma urate beyond 5.0 mg/dL, the risk of AKI increased 16%. However, a causal role of urate in AKI could not be established.

## EFFECTS OF LOWERING SUA LEVELS

SUA levels are an important risk factor for progression of renal dysfunction, hypertension, and lifestyle-related diseases such as metabolic syndrome or T2DM. Lowering SUA levels may represent a new therapeutic approach, but large clinical trials are warranted to evaluate the associated benefits and risks before implementation in clinical practice.

### Allopurinol

Several small studies have explored the impact of treatment with the xanthine oxidase inhibitor allopurinol on renal outcomes [81–85]. Recent meta-analyses have produced variable results. In an analysis of randomized trials of patients with or without CKD at baseline, uric acid-lowering therapy with allopurinol had no effect on GFR compared with controls in five trials ( $n = 346$ ) but abrogated increases in serum creatinine in three trials ( $n = 130$ ) [85, 86]. In a separate analysis of 19 randomized trials involving a total of 992 patients with stage 3–5 CKD, treatment with allopurinol was associated with significant reductions in SUA levels and blood pressure and more favorable eGFR compared with controls [87]. Both meta-analyses reported significant heterogeneity among the trials of allopurinol in terms of design, duration of follow-up, and comparators used. It has been suggested that the potential renoprotective

effect observed in one study of allopurinol may have been caused by lowering SUA levels from slightly above to slightly below the uric acid saturation point (6.8 mg/dL); mean SUA levels over the 7-year observation period were 7.2 mg/dL in the control group and 6.5 mg/dL in the allopurinol-treated group. Reducing the SUA level as low as possible may be less important than simply maintaining the level below the saturation point, in terms of preventing renal damage [84, 85]. Interpretation of results obtained with allopurinol can also be complicated by a secondary effect related to xanthine oxidase. Xanthine oxidase, which is inhibited by allopurinol, produces reactive oxygen species (ROS); inhibition of this ROS formation with allopurinol may have beneficial effects unrelated to SUA levels [4, 54, 87]. Two ongoing trials sponsored by the US government are evaluating the effects of allopurinol on the progression of IgAN [88] and diabetic nephropathy in patients with type 1 diabetes mellitus [89, 90].

### Febuxostat and Topiroxostat

Febuxostat is a non-purine selective inhibitor of xanthine oxidase approved by the US FDA for the treatment of adult hyperuricemia with gout (not for hyperuricemia alone), and can be used in stage 3 CKD (eGFR 30–60 mL/min/1.73 m<sup>2</sup>). A 108-week prospective, double-blind, placebo-controlled study (FEATHER; UMIN identifier, UMIN000008343) is currently ongoing, investigating the effect of febuxostat on eGFR in 400 adult Japanese patients with stage 3 CKD and hyperuricemia (SUA 7.1–10.0 mg/dL) without gouty arthritis [91]. Topiroxostat is another selective xanthine oxidase inhibitor, approved for use in Japan. A recent 22-week double-blind study in 123

patients with stage 3 CKD and hyperuricemia with or without gout showed that treatment with topiroxostat significantly reduced SUA by about 45% and lowered the albumin to creatinine ratio by almost 30%, compared with placebo [92].

### Losartan

Losartan is an ARB that has renoprotective effects in patients with diabetic nephropathy [93]. This effect is attributed primarily to its ability to reduce blood pressure and proteinuria [93], but evidence indicates that, unlike other ARBs, losartan also reduces SUA levels [94], possibly by inhibition of URAT1, leading to reduced urate reabsorption in the proximal tubule [95]. To determine the effect of SUA reduction on renal outcomes in patients with T2DM and nephropathy treated with losartan, a post hoc analysis was conducted using data from the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Trial (ClinicalTrials.gov identifier, NCT00308347) [96]. In 1342 patients, losartan treatment significantly reduced SUA levels over a 6-month period. Moreover, for every 0.5 mg/dL decrement in SUA, the risk of adverse renal outcomes (a doubling of serum creatinine or development of ESRD) decreased by 6% [96]. Excluding the effects of SUA on renal outcomes reduced the renoprotective effect of losartan from 22% to 17%, suggesting that the SUA-lowering effect of losartan accounts for approximately one-fifth of the agent's renoprotective effects [96]. Results of this post hoc analysis provide evidence that strategies to reduce SUA levels may reduce renal risk.

### SGLT2 Inhibitors

The kidney plays a key role in glucose homeostasis by contributing to endogenous glucose production via gluconeogenesis and by reabsorbing filtered glucose [97]. SGLT2 is a high-capacity, low-affinity glucose transporter that is found primarily in the proximal tubule of the kidney and is responsible for 90% of glucose reabsorption [98]. Inhibition of SGLT2 increases urinary glucose excretion, thereby improving glycemic control in an insulin-independent manner in patients with T2DM [99]. As a class, SGLT2 inhibitors have shown multiple beneficial effects in patients with T2DM, including reduction in HbA1C, decreased blood pressure, and weight loss [11–13, 98, 99]. They may also have some beneficial renal-related effects, including a reduction in intraglomerular pressure and amelioration of albuminuria [100, 101]. In addition, SGLT2 inhibitors also reduce SUA levels, possibly through mediating the GLUT9 urate transporter via induction of glycosuria: higher levels of glucose in the urine due to SGLT2 inhibition result in a higher level of exchange of uric acid across the apical membrane of tubular cells, so more uric acid is released from blood into the urine, ultimately reducing SUA levels [10, 102, 103]. In a pooled analysis of data from four phase 3 trials, canagliflozin was shown to reduce SUA levels compared with placebo [10]. In a subgroup with hyperuricemia at baseline, 20–30% of patients with hyperuricemia achieved normal SUA levels after 26 weeks of treatment with canagliflozin [10]. Similarly, in a meta-analysis of small, randomized, placebo-controlled trials, treatment with dapagliflozin at doses  $\leq 20$  mg significantly reduced SUA levels [13]. Results



from individual phase 2 trials of the SGLT2 inhibitor empagliflozin have reported reductions in SUA [11, 12]. The uricosuric effect seen in phase 3 trials of all three FDA-approved SGLT2 inhibitors has not been associated with an increase in uric acid nephrolithiasis.

The beneficial effects of SGLT2 inhibition on renal parameters must be weighed against potential side effects [98]. As a class, SGLT2 inhibitors have been associated with an increased risk of genitourinary infections, both bacterial and fungal [11–13, 104]. For example, in clinical trials, canagliflozin was associated with increased risk of genital mycotic infections as well as events related to osmotic diuresis [104]. Renal-related adverse events were uncommon. Small, transient reductions in eGFR have been observed with SGLT2 inhibitors during the initial weeks of treatment [12, 104], but longer-term studies (104 weeks) have confirmed that eGFR remains stable after this initial reduction [101, 105]. Since the efficacy of SGLT2 inhibitors is dependent on renal function, it is not surprising that the HbA1C-lowering effects of SGLT2 inhibitors are reduced in patients with renal impairment [106–108]. In the USA, initiation of available SGLT2 inhibitors requires an eGFR  $>45$  mL/min/1.73 m<sup>2</sup> for empagliflozin and canagliflozin (100 mg), and  $>60$  mL/min/1.73 m<sup>2</sup> for dapagliflozin. Ongoing trials may provide further insight into the effects of SGLT2 inhibitors on SUA and renal outcomes. The CREDENCE trial (ClinicalTrials.gov identifier, NCT02065791), for example, is a phase 3 trial evaluating canagliflozin in patients with T2DM, stage 2 or 3 CKD (eGFR 60–89 and 45–59 mL/min/1.73 m<sup>2</sup>, respectively), and macroalbuminuria (albumin excretion  $>300$  mg/24 h) [109]. The trial will assess whether canagliflozin has renal

and vascular protective effects in this population. The ongoing phase 4 CANVAS-R trial (ClinicalTrials.gov identifier, NCT01989754) [110] will also study the effects of canagliflozin on renal endpoints.

## CONCLUSIONS

The burden of CKD is increasingly recognized as a global health problem, underscoring the need for new and effective disease-management strategies. Renewed interest in the relationship between uric acid and CKD has led to new data that, on the whole, suggest that SUA may be a modifiable risk factor for CKD. Ongoing research continues to explore the exact relationship between hyperuricemia and CKD, and how SUA-lowering therapies may influence renal outcomes. Preliminary data suggest that SGLT2 inhibitors can reduce SUA levels, which may in turn contribute to a potential renoprotective effect. Ongoing clinical studies are prospectively evaluating the effect of SGLT2 inhibitors on SUA levels and renal parameters and outcomes in patients with CKD.

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