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MICROVASCULAR COMPLICATIONS—NEPHROPATHY (M AFKARIAN AND B ROSHANRAVAN, SECTION EDITORS)

Does Altered Uric Acid Metabolism Contribute to Diabetic Kidney Disease Pathophysiology?

Ambreen Gul[1] · Philip Zager[1,2]

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Abstract

Purpose of Review Multiple experimental and clinical studies have identified pathways by which uric acid may facilitate the development and progression of chronic kidney disease (CKD) in people with diabetes. However, it remains uncertain if the association of uric acid with CKD represents a pathogenic effect or merely reflects renal impairment.

Recent Findings In contrast to many published reports, a recent Mendelian randomization study did not identify a causal link between uric acid and CKD in people with type 1 diabetes. Two recent multicenter randomized control trials, Preventing Early Renal Function Loss in Diabetes (PERL) and FEbuxostat versus placebo rAndomized controlled Trial regarding reduced renal function in patients with Hyperuricemia complicated by chRonic kidney disease stage 3 (FEATHER), were recently designed to assess if uric acid lowering slows progression of CKD.

Summary We review the evidence supporting a role for uric acid in the pathogenesis of CKD in people with diabetes and the putative benefits of uric acid lowering.

Keywords Uric acid · Hyperuricemia · Diabetic nephropathy · Kidney disease · Type 1 diabetes · Type 2 diabetes

Introduction

Many studies have demonstrated an association between uric acid and kidney disease in patients with diabetes [1–5]. Some investigators have reported a positive correlation between uric acid and the rate of decline in estimated glomerular filtration rate (eGFR), while others have observed only an association with proteinuria. Whether uric acid plays a role in the pathogenesis of chronic kidney disease (CKD) or is simply a marker of metabolic abnormalities remains controversial. This review examines the evidence supporting a role for uric acid in the onset and progression of CKD and the effects of therapeutic lowering of uric acid.

Major Aberrant Metabolic Pathways Leading to Uric Acid Generation in People With Diabetes

In humans, uric acid is the end product of endogenous and exogenous purine metabolism [6•]. Fructose metabolism also generates uric acid [7]. After ingestion, fructose is absorbed into cells and phosphorylated b fructokinase with subsequent depletion of adenosine triphosphate. This leads to increased production of adenosine monophosphate and a rise in serum uric acid [8, 9]. Increases in fructose ingestion may lead to an increase in serum uric acid [10–12]. In people with diabetes, uric acid generation from fructose takes on added importance since fructose may be generated endogenously via the polyol pathway [13•].

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✉ Philip Zager
pzag@unm.edu; pgzager@gmail.com

Ambreen Gul
ambreen.gul@dciinc.org

[1] Dialysis Clinic, Inc., Quality Management, 1500 Indian School Rd. NE, Albuquerque, NM 87102, USA

[2] University of New Mexico, Albuquerque, NM, USA

Why Is Uric Acid Potentially Clinically Relevant?

The serum uric acid level is determined by a balance of uric acid generation, reabsorption, and excretion in the kidney, which is influenced by hydration status and diuretic use [14]. Elevated levels of serum uric acid have been independently associated with cardiovascular disease [15–19], hypertension [18–22], diabetes [23–25], metabolic syndrome [24, 26–29], and CKD [15, 30, 31].

In Vitro Studies: Effects of Uric Acid on Cultured Endothelial Cells Uric acid impairs basal and vascular endothelial growth factor-induced nitric oxide production in cultured endothelial cells, which reflects induction of inflammatory cascades through the expression of chemokines including monocyte chemoattractant protein-1 and cyclooxygenase-2 [31]. Verzola et al. demonstrated that uric acid increases apoptosis in human proximal tubular cells by triggering a pathway involving nicotinamide adenine dinucleotide phosphate oxidase signaling and urate transporter 1 (URAT1) transport [32].

Effects of Uric Acid on Animal Models In animal models, uric acid has a plethora of biologic effects including endothelial dysfunction, oxidative stress, vascular smooth muscle cell proliferation, inflammation, activation of phospholipase A2, and increases in TGF-α and TGF-$ß_1$. These changes may lead to tubulointerstitial injury, hypertension, proteinuria, and decreased renal function [31, 33, 34]. Endothelial dysfunction leading to impaired nitric oxide production is mediated, in part, by reactive oxygen species (ROS) [35, 36].

The reaction of xanthine oxidase with xanthine generates superoxide anion and uric acid leading to endothelial dysfunction and hypertension. Khosla et al. demonstrated that induction of mild hyperuricemia by oxonic acid in Sprague Dawley rats induces endothelial dysfunction and a trend toward higher systolic blood pressure by inhibiting nitric oxide production [35]. These investigators also demonstrated that uric acid inhibited nitric oxide production in cultured endothelial cells. The decrease in nitric oxide production induced by uric acid reflects a decrease in serum nitrites and nitrates which is reversed by allopurinol administration [35–37]. These data are consistent with hypothesis that hyperuricemia induces endothelial dysfunction.

Since uric acid is a product of xanthine oxidase activity, which generates ROS, it may be a marker of oxidative stress [38]. Therefore, the beneficial effects of allopurinol may be mediated by its active metabolite, oxypurinol, which inhibits production of oxidants by xanthine oxidase. Allopurinol inhibits xanthine oxidase which may reduce formation of ROS and thus have beneficial effects unrelated to serum uric acid levels [14, 38, 39].

In rat models, hyperuricemia is associated with renal hypertrophy, glomerulosclerosis, interstitial fibrosis, activation of the renin angiotensin system (RAS), and arteriolopathy of the preglomerular renal vasculature [31, 35, 37]. The arteriolopathy may be blunted by administration of allopurinol or the iodine-containing uricosuric agent, benziodarone. Hyperuricemia aggravates kidney injury in diabetes by recruitment of IL-1ß-secreting macrophages, activating nucleotide-binding oligomerization domain protein 3 inflammasomes in macrophages, and promoting chemokine secretion in proximal tubular cells [40]. Hyperuricemia also decreases E-cadherin expression, which may induce an epithelial-to-mesenchymal transition of renal tubular cells [41], the process of differentiation of tubular epithelial cells to myofibroblasts which facilitates the pathogenesis of tubular fibrosis in CKD [42].

Renal Effects of Uric Acid Lowering Allopurinol administration to mouse models of type 2 diabetes mellitus (KK-A^y/Ta and db/db mice) may blunt proteinuria, tubulointerstitial damage, and decreases in TGF-$ß_1$ [34, 43]. Allopurinol may also partially reverse endothelial dysfunction by reducing intracellular adhesion molecule-1 expression by tubular epithelial cells and blunt hyperuricemia induced changes in E-cadherin and renal fibrosis [43]. Treatment with febuxostat and blocking the metabolism of fructose has been shown to mitigate uric acid-induced pathological changes [44, 45].

Uric Acid and Kidney Disease

Results from cohort studies in the USA, Japan, and Italy provide epidemiologic evidence supporting the hypothesis that uric acid is involved in pathogenesis of kidney disease. Hsu et al. reported results of a cohort study with 5,275,957 person-years of follow-up conducted in patients enrolled in Kaiser Permanente of Northern California. Serum uric acid was an independent risk factor for end-stage renal disease (ESRD) (HR 2.14, 95% CI 1.65–2.77) [30]. Weiner et al. pooled data from 13,338 patients with normal kidney function in two community-based cohorts [46]. Median follow-up was 8.5 ± 0.9 years. Baseline serum uric acid concentrations were higher in the 712 (5.6%) people who developed kidney disease versus those who did not ($p < 0.0001$). During the study, 712 (5.6%) developed kidney disease defined by an eGFR decrease ≥ 15 mL/min/1.73 m^2 with final eGFR < 60 mL/min/1.73 m^2, while 302 (2.3%) individuals developed kidney disease defined by creatinine increase (≥ 0.4 mg/dL with final serum creatinine > 1.4 mg/dL in men and 1.2 mg/dL in women). Ohno et al. conducted a 2-year prospective observational study of 2853 healthy Japanese adults aged ≤ 50 years [47]. Changes in serum uric acid levels, even within the normal range, were a sensitive predictor of changes in eGFR

($p < 0.001$). However, the change in serum uric acid levels (β value of − 0.279) was not sufficient to completely explain the change in eGFR indicating the presence of confounding factors. Moreover, the changes in eGFR and other variables over 2 years were small and could be within expected biologic variation. In a prospective Italian cohort of 900 healthy blood donors followed for 5 years, higher serum uric acid levels were associated with a greater likelihood of eGFR (calculated using the 4-variable Modification of Diet in Renal Disease [MDRD] study equation) decline (HR, 1.13, 95% CI 1.04–1.39) each 1 mg/dL increase in uric acid [48]. Consistent findings have been reported by some but not all studies [49–54]. In the MDRD study, the highest tertile of serum uric acid was associated with increased all-cause mortality (HR 1.57, 95% CI 1.07–2.32) but not with kidney failure (HR, 1.20, 95% CI 0.95–1.51) [52]. Sturm et al. reported on a prospective study of 177 Caucasian non-diabetic individuals with CKD and 7 years of follow-up, uric acid was not established as an independent predictor of progression [55]. These discrepant results may reflect differences in study design, definitions of CKD, and criteria for decrease in eGFR.

Uric Acid and Kidney Disease in Patients With Diabetes Mellitus

Renal uric acid handling may be altered in people with diabetes and may differ according to the type of diabetes [13•]. Therefore, we discuss the relationship of uric acid to kidney disease in type 1 and type 2 diabetes individually.

Uric Acid and Kidney Disease in Patients With Type 1 Diabetes Mellitus

Multiple prospective cohort studies in patients with type 1 diabetes mellitus have demonstrated strong associations between baseline uric acid and incidence of albuminuria. Hovind et al. conducted a prospective observational study of 263 patients followed from the onset of type 1 diabetes [2]. Median follow-up was 18 years. The cumulative incidence of persistent micro- and macroalbuminuria was 32.2% (95% CI 25.7–38.7%) and 12.6% (95% CI 7.3–17.9%), respectively. Serum uric acid was independently associated with subsequent development of persistent macroalbuminuria (HR 2.37, 95% CI 1.04–5.37) per 1.68 mg/dL increase in serum uric acid level ($p = 0.04$), but was not associated with persistent microalbuminuria.

In the Coronary Artery Calcification in Type 1 Diabetes trial (CACTI), a prospective follow-up study, every 1 mg/dL increase in serum uric acid was associated with an independent risk of developing albuminuria (OR 1.8, 95% Cl 1.2–2.8) [3]. Similarly, in the Second Joslin Kidney Study of type 1 diabetes mellitus, serum uric acid levels in the upper portion of the normal range were independently associated with a decreased eGFR [56]. Subsequently, when a subset of patients ($n = 355$) with albuminuria was followed for 4 to 6 years, there was a dose-response relationship between serum uric acid and risk for an early decrease in eGFR [57].

Mendelian Randomization Studies in Type 1 Diabetes Mellitus

The findings from a recent Mendelian randomization (MR) study cast doubt on the causal relationship of uric acid and progression of kidney disease among patients with type 1 diabetes mellitus while underscoring potential confounding by obesity. The Finnish Diabetic Nephropathy Study group found that baseline serum uric acid was strongly associated with the single nucleotide polymorphisms score but not with any stage of nephropathy based on albuminuria or eGFR. The investigators concluded that there was no evidence of a causal link between serum uric acid and progression of kidney disease [58••]. Whether these results, from a predominantly white population, are generalizable to other ethnicities is uncertain [59]. Furthermore, results from a population-based study of 6184 Caucasians using a bidirectional MR approach suggest that elevated serum uric acid levels may be a consequence of obesity [60]. Another MR study demonstrated that a 1 kg/m^2 higher BMI conferred a 28% increased risk in macroalbuminuria, a 43% increased risk of ESRD, and a 33% increased risk of diabetic kidney disease [61]. Therefore, a direct causal link between type 1 diabetes mellitus and uric acid may not exist but rather hyperuricemia may, in part, be a consequence of obesity.

Uric Acid and Kidney Disease in Patients With Type 2 Diabetes Mellitus

Hyperuricemia has been independently associated with incident CKD in patients with type 2 diabetes mellitus [1]. In a 5-year Italian prospective observational study of 1449 participants with normal kidney function at baseline, hyperuricemia was an independent predictor of CKD [5]. In another Italian prospective cohort study of patients with type 2 diabetes mellitus ($n = 13{,}964$) with eGFR ≥ 60 mL/min/1.73 m^2 and normal urinary albumin excretion rate (UAER), the risk for developing a 10% decrease in eGFR increased linearly across serum uric acid quintiles [1]. Each 1 mg/dL increase in baseline serum uric acid was associated with a 10% increase in risk for developing a decrease in eGFR. In a meta-analysis of nine articles including 20,981 patients with type 2 diabetes, an elevated serum uric acid was associated with an increased risk for kidney disease (OR 1.91, 95% CI 1.07–3.42) [4].

Hyperuricemia may increase progression of CKD. Altemtam et al. conducted a retrospective cohort study of 270 patients with type 2 diabetes and stage 3 and 4 CKD followed at the Sheffield Kidney Institute in the UK from 2000 to 2008 [62]. Mean follow-up was 5.2 ± 1.8 years. The mean rate of decline in eGFR was 1.46 mL/min/1.73 m^2/year. Progressive disease was observed in 34.8% patients in whom the mean decline in eGFR was 3.57 ± 1.45 mL/min/1.73 m^2/year. Baseline serum uric acid was higher in patients with more rapidly progressive CKD (9.94 ± 1.74 mg/dL) versus those with slower progression (7.63 ± 1.7 mg/dL) (p = 0.004). More recently, Bartakova et al. reported on a prospective cohort of 422 individuals with type 2 diabetes mellitus in the Czech Republic. The median duration of type 2 diabetes was 15 years and median follow-up was 43 months [63]. At baseline, 68% of patients had hyperuricemia, which was associated with an increased rate of CKD progression, independent of the baseline stage of CKD ($p < 0.0001$).

Kim et al. conducted a retrospective observational longitudinal study of 512 patients with type 2 diabetes in Korea with normal serum uric acid levels and preserved kidney function (eGFR ≥ 60 mL/min/1.73 m^2) for a mean follow-up of 3 years. Interestingly, participants with baseline serum uric acid levels in the upper portion of the normal range were at increased risk for developing CKD stage ≥ 3 (HR 2.97, 95% CI 1.15–7.71; $p = 0.025$) and increased albuminuria (HR 5.52, 95% CI 2.47–12.36; $p < 0.001$) [64]. Other investigators have reported that high normal serum uric acid levels may be a risk factor for declining renal function in patients with type 2 diabetes mellitus [65, 66].

Serum uric acid may modulate the risk for albuminuria. A Japanese study of 343 men with type 2 diabetes found that serum uric acid concentration was an independent determinant of logarithm of UAER ($p < 0.0001$) [67]. Similarly, a cross-sectional study of 60 patients in Iran found a positive association of serum uric acid level with proteinuria ($p < 0.001$) [68]. In addition, a more recent Japanese cohort study of 1802 patients with type 2 diabetes mellitus with normoalbuminuria and eGFR ≥ 60 mL/min/1.73 m^2 found that elevated serum uric acid levels were associated with an increased risk for albuminuria but not a decrease in eGFR [69].

Interaction of Insulin and Glucose With Renal Handling of Uric Acid

Renal handling of uric acid is complex. Genome-wide association studies have identified multiple loci, most of which are uric acid transporters [70]. Uric acid is freely filtered across the glomerulus. This is followed by reabsorption and secretion, which coexist along the proximal tubule [70–72]. The fractional excretion of uric acid is 8 to 10% [7]. The identification and characterization of these genetically determined uric acid transporters may facilitate the development of novel therapies for lowering serum uric acid.

Insulin facilitates uric acid reabsorption and, not surprisingly, uric acid clearance is inversely correlated with insulin resistance [73]. Administration of sodium glucose cotransporter 2 (SGLT2) inhibitors increase uric acid excretion indirectly enhancing glycosuria, which in turn interacts with GLUT9 isoform 2 along the proximal tubule and possibly in the collecting duct [74].

Multiple factors may explain the association of serum uric acid with eGFR decline and albuminuria in patients with diabetes. Hyperuricemia may be an early manifestation, rather than a risk factor for kidney disease. Obesity is common among patients with diabetes and therefore may be a potential confounder in the observed association of hyperuricemia with kidney disease. Hyperuricemia is a risk factor for hypertension, which in turn increases the risk for kidney disease [22, 75]. Feig et al. suggested that treating hyperuricemia in adolescents with newly diagnosed hypertension was effective at lowering blood pressure [76].

Uric acid may also have direct toxicity increasing the risk for acute kidney injury. Uric acid may induce renal vasoconstriction by inhibiting release of nitric oxide [35, 77]. Although results from animal experiments [35, 37, 78] and observational studies in humans [79] have suggested that uric acid may activate the renin angiotensin system (RAS), a recent randomized controlled trial found that uric acid lowering had no effect on kidney or systemic RAS [80]. Uric acid may also damage the kidney by stimulating an inflammatory response [81, 82]. Urate has both antioxidant and pro-oxidant properties, and although it may be beneficial in scavenging free radicals, it can also impair endothelial function [83].

Effect of Uric Acid Lowering on Kidney Function

Observational studies of the association between uric acid lowering and improved renal outcomes underscore a biologically plausible causative role for uric acid in diabetic kidney disease and identify therapeutic strategies to improve renal outcomes. Multiple studies have assessed the effects of allopurinol on renal disease [84–86]. Levy et al. conducted a large, population-based retrospective cohort study (n = 16,186) to assess the effects of serum uric acid lowering on rate of eGFR decline [87]. Patients who achieved serum uric acid < 6 mg/dL had a 37% reduction in outcome events (30% reduction in eGFR or eGFR ≤ 15 mL/min/1.73 m^2) (HR 0.63, 95% CI 0.5–0.78; $p < 0.0001$). Goicoechea et al. conducted a prospective study in which hyperuricemic participants with an eGFR < 60 mL/min/1.73 m^2 were randomized to receive allopurinol (100 mg/day) or usual treatment [88]. Mean follow-up was 23.4 ± 7.8 months. At study end, the eGFR had

increased minimally in those receiving allopurinol (1.3 ± 1.3 mL/min/1.73 m^2; NS) but decreased in the control arm (3.3 ± 1.2 mL/min/1.73 m^2; $p = 0.018$). Allopurinol also reduced the risk for cardiovascular events and all-cause hospitalization.

Similar results were observed in an open parallel study in China where 176 participants with type 2 diabetes were randomized to allopurinol or standard treatment [89••]. After 3 years, the decline in eGFR in the allopurinol group was 0.8 ± 3.9 mL/min/1.73 m^2 versus 4.9 ± 5 mL/min/1.73 m^2 in the conventional group ($p < 0.001$). The decrease in albuminuria was greater in the allopurinol group ($p < 0.01$).

Results of a meta-analysis of eight randomized controlled trials (RCTs) with a total of 476 participants suggested that the effects of allopurinol on proteinuria, eGFR, and progression to ESRD are inconclusive [90]. In five trials, there were no significant differences in the changes in eGFR between the allopurinol and control arms (mean difference 3.1 mL/min/1.73 m^2; $p = 0.1$). In contrast, in three trials, the changes in serum creatinine from baseline favored allopurinol (mean difference 0.4 mg/dL; $p = 0.03$). In another meta-analysis of 19 RCTs with 992 participants, the pooled estimate of eGFR (mean difference 3.2 mL/min/1.73 m^2; $p = 0.04$) favored allopurinol, while the changes in proteinuria were similar across arms ($p = 0.58$) [39]. In an Iranian RCT with 40 participants with type 2 diabetes, low-dose allopurinol treatment for 4 months reduced proteinuria from 1756 mg/24 h to 1011 mg/24 h ($p = 0.049$) [91].

Recent Studies That Assessed the Effects of Serum Uric Acid Lowering

Two recent multicenter RCTs were designed to assess the renal protection afforded by uric acid lowering. The Preventing Early Renal Function Loss in Diabetes (PERL) trial is an ongoing multicenter, double-blind, placebo-controlled RCT that is comparing the effects of allopurinol versus placebo on decline in eGFR to determine if uric acid lowering slows progression of CKD in participants with type 1 diabetes mellitus (ClinicalTrials.gov Identifier NCT02017171) [92, 93]. Eligibility criteria are an increased UAER (30–5000 mg/24 h if not on RAS blocking agent or 18–5000 mg/24 h if on RAS blocking agent) or a decreasing eGFR (≥ 3 mL/min/1.73m^2/year). Estimated GFR was chosen as the primary outcome since it may decline in the absence of microalbuminuria [94, 95]. The majority of the patients with microalbuminuria may regress to normoalbuminuria but early eGFR loss usually progresses to CKD and ESRD [95, 96]. The study is important because there is clinical equipoise and the risk of significant adverse reactions is low [97].

The FEATHER trial (FEbuxostat versus placebo rAndomized controlled Trial regarding reduced renal function in patients with Hyperuricemia complicated by chRonic kidney disease stage 3) is being conducted in asymptomatic hyperuricemic Japanese patients with CKD stage 3 (UMIN Clinical Trials Registry, Unique trial number UMIN000008343). It was designed to assess the effects of febuxostat in moderately controlled diabetes ($HgbA_{1C} < 8\%$) and participants without diabetes [98, 99]. In comparison to allopurinol, febuxostat provides more selective and potent inhibition of xanthine oxidase with greater hypouricemic activity [100]. Febuxostat is excreted primarily through the liver, whereas allopurinol is excreted by the kidney. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Comorbidities (CARES) trial is the first randomized, controlled clinical trial that evaluated the long-term safety of xanthine oxidase inhibitors in gout patients with a history of prior CV events or disease (ClinicalTrials.gov Identifier NCT01101035). Although the trial has been completed, the results have not yet been published. However, the United States Food and Drug Administration has issued a preliminary warning of increased risk of cardiovascular and all-cause mortality with the use of febuxostat compared to allopurinol [101••, 102, 103].

A post hoc analysis of the Febuxostat Open-Label Clinical Trial of Urate-Lowering Efficacy and Safety Study (FOCUS) with 116 hyperuricemic patients treated with febuxostat for 5 years found an inverse correlation between uric acid and eGFR and projected an improvement in eGFR of 1 mL/min/1.73 m^2 for every 1 mg/dL decrease in serum uric acid [104]. In a placebo controlled RCT, conducted in Eastern India, patients with stage 3 and 4 CKD and asymptomatic hyperuricemia were randomized to febuxostat ($n = 45$) versus placebo ($n = 48$) for 6 months [105]. Estimated GFR decreased in the placebo group (32.6 ± 11.6 to 28.2 ± 11.5 mL/min/1.73 m^2; $p = 0.003$) but not in the febuxostat group (31.5 ± 13.6 to 33.7 ± 16.6 mL/min/1.73 m^2; NS). The percentage of participants who experienced ≥ 10% decrease was greater in the placebo (54%) versus the febuxostat group (38%).

SGLT2 inhibitors have been shown to lower uric acid levels. Zinman et al. conducted a RCT using the SGLT2 inhibitor empagliflozin or placebo in 7020 patients for a median duration of 3.1 years and found lower rates of death from cardiovascular causes, hospitalization from any cause and all-cause mortality. It was also associated with reduction in diastolic and systolic blood pressure, hemoglobin A1C, and serum uric acid levels [106]. In a meta-analysis of 62 studies consisting of 34,951 participants, SGLT2 inhibitors decreased serum uric acid by a range of 17.4 mmol/L (0.29 mg/dL) to 45.8 mmol/L (0.77 mg/dL) with a weighted mean difference of 37.73 mmol/L (0.63 mg/dL). However, the decline in serum uric acid was blunted in patients with longer duration of diabetes, higher hemoglobin A1C, and patients with eGFR < 60 mL/min/1.73m^2. These small reductions in serum uric acid are unlikely to explain the cardiovascular benefits seen with the use of these drugs [107].

A post hoc analysis of 1342 participants with type 2 diabetes and nephropathy who participated in the Reduction of End Points in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) trial (1342 participants with diabetic nephropathy, median follow-up 3.4 years) found that the risk of adverse renal outcomes was decreased by 6% for every 0.5 mg/dL decrease in serum uric acid levels during the first 6 months of treatment with losartan [108]. This effect accounted for about 20% of the renoprotective effect of losartan.

Conclusion

There is substantial evidence from observational studies that supports a significant association between higher serum uric acid levels and the risk for CKD among people with diabetes mellitus. Surprisingly however, the results of clinical trials to date have not conclusively demonstrated a beneficial effect of serum uric acid lowering. Despite the current availability of conclusive trial data, Barkatoba et al. have recommended 10 to 15% lower serum uric acid cutoff values for people with diabetes mellitus (6.35 mg/dL for men and 5.2 mg/dL for women) to confer protection against kidney disease [63]. Results from the PERL and FEATHER trials may better define the potential benefit of lowering serum uric acid [93, 98, 99].

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Compliance with Ethical Standards

Conflict of Interest Ambreen Gul is an employee of Dialysis Clinic, Inc. Philip Zager is an employee of the University of New Mexico and Dialysis Clinic, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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