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Uric Acid as a Target of Therapy in CKD

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Abstract

The prevalence of chronic kidney disease (CKD) has risen and will continue to rise in the United States and worldwide. This is alarming considering that CKD remains an irreversible condition and patients who progress to chronic kidney failure suffer reduced quality of life and high mortality rates. As such, it is imperative to identify modifiable risk factors to develop strategies to slow CKD progression. One such factor is hyperuricemia. Recent observational studies have associated hyperuricemia with kidney disease. In addition, hyperuricemia is largely prevalent in patients with CKD. Data from experimental studies have revealed several potential mechanisms by which hyperuricemia may contribute to the development and progression of CKD. In this manuscript we offer a critical review of the experimental evidence linking hyperuricemia to CKD, we highlight the gaps in our knowledge on the topic as it stands today, and we review the observational and interventional studies that have examined the potential nephro-protective effect of lowering uric acid in CKD patients . While uric acid may also be linked to cardiovascular disease and mortality in patients with CKD, this review will focus only on uric acid as a potential therapeutic target to prevent kidney disease onset and progression.

Index words

kidney disease progression; uric acid

In the last few decades, CKD has emerged as a global health problem of epidemic proportions [1]. The prevalence of stage 3 CKD has increased in the United States with current estimates placing it at 11.5% [2]. While in many persons CKD remains an asymptomatic pathologic condition that progresses slowly, for many others, CKD represents a progressive irreversible process that ultimately leads to the requirement for renal replacement therapy [3–5]. In addition to the reduced quality of life, mortality rates among

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patients with ESRD remain extremely high. For example, in the 2011 US Renal Data System (USRDS) report, adjusted mortality rates for maintenance dialysis patients aged 45–64 years and ≥ 65 years were 154 and 313 deaths per 1,000 patient-years at risk, respectively. Both rates are some seven times greater than those seen in their counterparts in the general population[6]. Hence, and in the absence of curative therapy for patients with progressive CKD, it is important to pursue therapeutic interventions that may effectively slow CKD progression.

Carl Scheele, a Swedish pharmacist, discovered uric acid in 1776 in a bladder calculus and named it “acid of calculus”. Once the stone was moistened with nitric acid and dried, Scheele noted that the addition of dilute ammonium hydroxide converted it to the purple-red color characteristic of the ammonium salt of purpuric acid [7]. Subsequently, Fourcroy, a French chemist, observed that chlorine water changed uric acid to urea and that distilling uric acid produced hydrocyanic acid, prompting him to name it “acid urique” [8].

Uric acid was thought to play a role in human diseases other than kidney stones as early as 1848 when Garrod, an English physician, discovered that uric acid is present in the blood of individuals suffering an acute gout attack; this observation prompted him to conclude that uric acid plays a role in gout [8]. At the time, skepticism against a role for hyperuricemia in gout was roused by subsequent studies in which injecting uric acid into healthy animals and humans failed to induce gout. The skepticism was further fueled by studies revealing that uric acid was present in the blood of patients with other diseases, such as leukemia, and did not inevitably lead to the development of gout [9]. Today, while we recognize that hyperuricemia alone is insufficient to cause gout and that other factors likely predispose to crystal formation, we also acknowledge that lowering uric acid levels is an effective strategy to prevent gout attacks [10]. In contrast to gout, and even though the association between uric acid, gout, and kidney disease had been noted early on, a role for uric acid—lowering therapies in preventing and slowing kidney disease progression has not been established.

Uric acid homeostasis

Uric acid is an end- product of purine metabolism that is produced mainly by the liver and the intestines but also by other peripheral tissues, such as muscles, the endothelium, and the kidney. Under normal conditions, two thirds of the produced uric acid is eliminated in the urine and one third is removed by the biliary tree. Although uric acid occurs predominantly as a urate anion under physiological pH, more uric acid than urate is present in the urine (pH 5–6) [11]. In the kidney, urate is readily filtered by the glomerulus and subsequently reabsorbed by the proximal tubular cells of the kidney; the normal fractional excretion of uric acid is approximately 10% [12]. The cell membrane is impermeable to the urate anion in the absence of specific transporters. Although urate transport is a complex and incompletely understood process [11], the efficiency with which the human kidney reabsorbs urate may contribute to the higher levels of serum uric acid in humans as compared to other species; this in addition to an uricase mutation preventing further uric acid degradation in humans[13]. It is generally accepted that the human urate transporter, URAT1 (encoded by the *SLC22A12* gene), facilitates uric acid reabsorption in the proximal convoluted tubule [14]. More recently, GLUT9 (encoded by *SLC2A9*), a member of the glucose transporter family, has been proposed to be a major regulator of uric acid homeostasis [15]. In humans, it is mainly expressed in the proximal convoluted tubule on the basolateral membrane [11]. Hyperuricemia is defined as the accumulation of serum uric acid beyond its solubility point in water (6.8 mg/dL), and develops due to uric acid over-production, under-secretion, or both [12]. Uric acid homeostasis and main factors that lead to increased serum uric acid levels in CKD are schematically shown in Figure 1.

A Plausible Role for uric acid in kidney disease

Traditionally, hyperuricemia associated with hyperuricosuria has been postulated to cause kidney disease by depositing intra-luminal crystal in the collecting duct of the nephron in a manner reminiscent of gouty arthropathy [16–17]. Individuals with increased serum uric acid levels secondary to high dietary purine intake may also have a lower than normal urinary pH, favoring even more uric acid in the urine than urate. Considering that uric acid is less soluble than urate, this milieu would favor uric acid crystal formation [18]. Uric acid crystals have the capacity to adhere to the surface of renal epithelial cells [19] and to induce an acute inflammatory response in such cell lines [20]. In addition to an increased risk of kidney stone formation, such effects have also been shown to reduce glomerular filtration rate (GFR) [17].

Contrary to the role of uric acid crystals in kidney disease, the non-crystal effects of uric acid remain contentious as, under physiological concentrations, urate is a powerful antioxidant that can scavenge superoxide, hydroxyl radicals, and singlet oxygen [21]. Nevertheless, recent data may implicate mild hyperuricemia in kidney disease onset and progression. Experimentally induced hyperuricemia in rats leads to reduced urinary nitrites and to systemic and glomerular hypertension [22–23]. The latter two can be prevented with the supplementation of L-arginine, suggesting that uric acid may cause endothelial dysfunction. This conclusion, while controversial, is supported by *in vitro* experimental studies showing that uric acid decreases nitric oxide (NO) production [24] and may also lead to NO depletion [25]. In addition to a potential role in endothelial dysfunction, experimental hyperuricemia has been reported to cause an afferent renal arteriolopathy and tubulo-interstitial fibrosis in the kidney by activating the renin-angiotensin-aldosterone system (RAAS) [26]. Uric acid has also been shown to activate the cytoplasmic phospholipase A_2 and the inflammatory transcription factor nuclear factor κ B (NF-κB), leading to the inhibition of proximal tubular cellular proliferation *in vitro* [27]. Other reported sequelae of raising serum uric acid levels include systemic cytokine production such as tumor necrosis factor α (TNF-α) [28] and the local expression of chemokines such as monocyte chemotactic protein 1 (MCP-1) in the kidney [29–30], and cyclooxygenase 2 (COX-2) in the blood vessels [30]. Consistent with such experimental data, further animal studies suggest that lowering uric acid may slow CKD progression. Notably, lowering uric acid has been reported to reduce tubulointerstitial fibrosis both in the 5/6th nephrectomy model [31] and in diabetic nephropathy [32]. Additionally, in humans, withdrawing uric acid—lowering therapy was found to increase urinary transforming growth factor β-1 in a group of hyperuricemic patients with CKD [33]. The putative mechanisms by which increased serum uric acid may contribute to CKD onset and progression are illustrated in Figure 2.

Uric acid as a predictor of human kidney disease

In the last two decades, a large number of observational studies have examined the potential link between increased serum uric acid levels and CKD [34–51]. These studies (summarized in Table 1) have shown conflicted results in some instances. For example, an analysis of the Cardiovascular Health Study (CHS), [45] which involved 5,808 participants with 5 years of follow-up, showed no significant association between serum uric acid levels and incident CKD, and yet there was a significant relationship between increased serum uric acid and CKD progression even after adjustment for age, sex, race, serum creatinine, body mass index, waist circumference, blood pressure, use of anti-hypertensive drugs, use of allopurinol, blood glucose, lipids, ankle-arm index, carotid intima-media thickness, major electrocardiogram abnormalities, hemoglobin, C-reactive protein, and albumin levels. However, the older age of this population may have precluded the identification of serum uric acid as a predictor of incident CKD. Consistent with this, serum uric acid was found to be an independent risk factor for incident CKD in a pooled analysis of the Atherosclerosis

Risks in Communities (ARIC) study and the CHS. This analysis involved 13,338 participants with intact kidney function at baseline who were followed for a mean period of 8.5 years [35]. Similar findings were reported from the Vienna Health Screening Project, where an analysis of 21,475 healthy participants followed for 7 years indicated that elevated baseline uric acid levels were associated with an increased risk of incident CKD (defined as GFR <60 ml/min/1.73 m^2), independently of age, sex, waist circumference, plasma lipids, fasting plasma glucose, estimated GFR, blood pressure, and use of anti-hypertensive drugs [36]. Such an independent association between serum uric acid and incident CKD also has been corroborated by many other studies in Asian populations [34, 37–39]. In addition, elevated levels of serum uric acid appear to be associated with an increased risk of diabetic nephropathy in both type 1 and type 2 diabetes [41–43].

Several epidemiological studies have examined whether higher serum uric acid levels predict an increased risk of CKD progression. Hsu *et al.* evaluated this in a cohort of 177,570 participants and found that increased serum uric acid was associated with an increased risk of ESRD over a 25 year follow-up period, independently of age, race, sex, body mass index, educational level, blood pressure, diabetes status, serum creatinine, hemoglobin, and proteinuria[47]. This association between increased serum uric acid and CKD progression has been supported further by some other studies [45–46] but not all [50–51]. For example, an analysis of 840 individuals with stage 3–4 CKD participating in the Modification of Diet in Renal Disease (MDRD) Study did not find uric acid levels to be an independent risk factor for progression to chronic kidney failure despite a 10-year follow-up [51]. A potential explanation for these conflicted results may lie in the fact that uric acid clearance is impaired in CKD [52] and as such serum uric acid is increased even early on in kidney disease [53]. The MDRD Study adjusted for measured GFR, and perhaps that adjustment may account for its negative findings. In other words, it is possible that uric acid is a sensitive indicator of compromised kidney function and that adjustment for accurate measurement of GFR would offset a potential association.

Another issue that is commonly raised when reviewing the results of prospective observational studies on uric acid is that xanthine oxidase, the enzyme that produces uric acid, also produces reactive oxidative species. As such, serum uric acid might be simply a marker of oxidative stress rather than a mediator of disease per se. Unfortunately, such observational studies are naturally incapable of addressing these concerns. To the skeptics, the significant association between uric acid levels and CKD may be explained by such confounders, i.e., the renal clearance of uric acid and the xanthine oxidase system. The believers, however, may contend that if high uric acid decreases kidney function early on in the disease process, thus increasing the risk of CKD progression, then adjusting for baseline GFR would be expected to attenuate any relation between serum uric acid and chronic kidney failure and that does not exclude a contributing role for hyperuricemia in CKD.

Uric acid and xanthine oxidase

As indicated above, a major challenge in understanding the potential role of uric acid in CKD is that it is a product of xanthine oxidase in conjunction with reactive oxidative species. Xanthine oxidoreductase (XOR) exists in two forms, xanthine dehydrogenase (XDH) and xanthine oxidase (XO). When grouped together, the dehydrogenase and oxidase forms catalyze the final step in purine metabolism by converting hypoxanthine to xanthine and xanthine to urate/uric acid. XOR plays an important role in survival and development, as XOR knockout mice die within the first month of their birth secondary to severe renal dysplasia [54]. This seems counterintuitive, but these findings can be explained by impaired COX-2 expression [54] and the accumulation of triglyceride-rich substances, xanthine, and hypoxanthine in the renal tubules, which lead to interstitial fibrosis during early

development [55]. Xanthine, albeit rarely, can crystallize in supersaturated urine leading to stone formation [56]. In contrast, in older rats, an increase in xanthine oxidase activity may contribute to tubulointerstitial injury in experimental hyperlipidemia [57]. While these detrimental effects of xanthine oxidase may be merely due to increased oxidative stress, preliminary evidence suggests that uric acid is a mediator of xanthine oxidase effects. For example, the renal dysplasia phenotype found in XOR knockout animals is identical to that seen in COX-2 deficiency. Considering that uric acid ingestion has been shown to stimulate COX-2 expression both *in vivo* and *in vitro* [54], it is logical to conclude that uric acid may be at least a partial mediator of XOR effects. Unfortunately, little is known about XOR activity in models of kidney disease; we identified only one study in our review where xanthine oxidase activity is reportedly reduced in the 5/6th nephrectomy model [58]. Although the findings of this experimental model suggest that the increase in uric acid seen in CKD may be related to reduced renal clearance as opposed to increased XOR activity, virtually no studies have examined XOR activity in human CKD.

Treatment of hyperuricemia in CKD

In general, xanthine oxidase inhibitors such as allopurinol or febuxostat are the preferred agents to lower uric acid due to their effectiveness in both “over-producers” and “under-secretors” of uric acid. Allopurinol is metabolized by xanthine oxidase to oxypurinol, and both substrates act to inhibit xanthine oxidase [59]. Patients with CKD may be at increased risk of toxicity with allopurinol (e.g., rash, gastrointestinal intolerance, leukopenia, and severe hypersensitivity reaction), as oxypurinol is cleared by the kidney[60]. In addition, some investigators have suggested that insufficient dosing of allopurinol in CKD patients with gout leads to undertreatment[61]. Thus, it is widely recommended to start with low dosages of allopurinol in CKD patients and to slowly titrate it to an effective dose. Febuxostat, a non-purine selective xanthine oxidase inhibitor, has been shown to be safe and effective for lowering serum uric acid levels [62] and represents a pharmacological alternative to allopurinol in hyperuricemic patients who are unable to tolerate allopurinol Other agents that can be used to lower uric acid levels include uricosuric agents such as probenecid and benzbromarone (the latter is unavailable in the US) in addition to losartan and fenofibrates (both drugs exert mild uricosuric effects).

The use of an uricosuric agent such as probenecid is generally lauded as a better approach than xanthine oxidase inhibition to evaluate the potential role of uric acid in disease states, given that such treatment would eliminate the confounding effect of xanthine oxidase inhibition. However, this may differ in CKD. Uricosuric agents would obviously increase urinary uric acid excretion, and this increase of uric acid on the luminal side of the nephron may be associated with the same deleterious effects. In addition, increased urinary uric acid excretion may increase the risk of crystallization, thus leading to further inflammation and a higher risk of kidney stones.

In any event, the potential benefit of lowering uric acid on CKD progression has been evaluated in only a handful of studies. In a small randomized trial by Siu *et al.* [63], 54 hyperuricemic patients with mild-to-moderate CKD were assigned to allopurinol (100–300 mg/day with the goal of normalizing serum uric acid levels) *versus* no therapy (control) and followed for 12 months. At the end of follow-up period, a significantly larger number of participants in the control group (16% *vs.* 46%; P =0.015) achieved the combined endpoint of a serum creatinine increase of 40% or more, dialysis, or death.. More recently, a larger study conducted by Goicoechea *et al.* included 113 hyperuricemic patients with CKD randomized either to allopurinol (100 mg/day) or to a control group (no therapy). [64] At the end of the 2 year follow-up period, estimated GFR decreased by 3.3 ± 1.2 ml/min / 1.73 m^2 in the control group compared to the allopurinol group, where estimated GFR increased by

1.3 ± 1.3 ml/min / 1.73 m^2 (P=0.018). The major limitations of both of these interventional studies are the relatively small number of patients and the absence of a placebo arm. One recent open label randomized controlled trial conducted by Shi Y *et al* evaluated allopurinol treatment in 40 patients with IgA nephropathy [65]. After 6 months of treatment, allopurinol did not significantly alter kidney disease progression or proteinuria, although it did significantly improve blood pressure in these patients. In addition to the open label design and the small number of participants, the short duration of follow-up is a major limitation of this study. The only double blinded randomized placebo controlled trial that examined the effect of lowering uric acid on diabetic nephropathy [66] included 40 patients with type 2 diabetes followed the participants for a period of 4 months, and evaluated proteinuria as an outcome. The small number of participants, short duration of follow-up, and lack of assessment of kidney function are notable limitations of this study, although it did show a significant reduction in proteinuria with allopurinol treatment, which appeared to be complementary to RAAS blockade.

The potential nephro-protective effect of lowering uric acid in addition to traditional therapies of CKD is further supported by the findings of a post-hoc analysis of the RENAAL (Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan) Trial [67]. In this study, the risk of renal events was decreased by 6% for every 0.5-mg/dL decrement in serum uric acid during the first 6 months of treatment with losartan. The lower uric acid levels in the losartan group are most likely due to the uricosuric effect of this drug. While such studies suggest that lowering uric acid may slow CKD progression, considering their many limitations, a role for uric acid lowering therapies in CKD cannot be advocated based on their results. Rather, the results of such studies imply that properly designed, randomized, placebo-controlled studies need to be conducted to assess objectively whether uric acid lowering therapies would benefit patients with CKD.

In addition to the aforementioned trials, some recent studies suggest that treating hyperuricemia may prevent or delay the onset of CKD. A randomized double blinded study by Feig *et al*. [68] showed that treating hyperuricemia in adolescents with newly diagnosed hypertension was effective at lowering blood pressure. Similar to the studies mentioned above, allopurinol was used to lower serum uric acid levels and resulted in significant improvement in systolic and diastolic blood pressure when compared to placebo. It remains uncertain if this is an effective anti-hypertensive approach as opposed to the current standard of care, but the results of this small clinical trial raise the possibility that lowering uric acid early on may prevent the onset of kidney disease. In attempt to evaluate if lowering uric acid would prevent kidney disease onset, Kanbay *et al*. [69] conducted a small case controlled study. Here, 59 hyperuricemic individuals with estimated GFR ≥60 ml/min / 1.73 m^2 were treated with 300-mg allopurinol daily over a 3 months period and were noted to have improvements in systolic and diastolic blood pressure as well as a significant increase in estimated GFR (proteinuria was unchanged in this trial). Results of such a study, however, need to be confirmed in larger placebo controlled trials. Whether pharmacological lowering of uric acid is more effective than dietary and life-style modifications prior to CKD onset will also need to be assessed.

Hyperuricemia in Kidney Transplantation

Hyperuricemia is common in patients post kidney transplantation [70]. While increased uric acid levels in this setting may represent reduced graft function, hyperuricemia has been reported even in patients with intact graft function [71]. Several factors contribute to hyperuricemia post transplantion, such as cyclosporine therapy, use of diuretics, and the high prevalence of metabolic syndrome and diabetes in kidney transplant recipients [72]. Although hyperuricemia contributes to cyclosporine- associated nephrotoxicity in animal

models [73], we are unaware of any studies that have evaluated the role of uric acid—lowering therapies in kidney transplant patients, and observational studies evaluating uric acid as a predictor of graft dysfunction have shown conflicted results [71, 74–80]. These studies are summarized in Table 3.

Conclusions

Hyperuricemia is common in CKD. Experimental evidence suggests that uric acid itself may harm CKD patients by contributing to increased inflammation and CKD progression. While controversial, these observations are supported by many large prospective, observational studies that show increased levels of serum uric acid that predict the development and progression of CKD in various populations. Interventional studies, while sparse, suggest that lowering uric acid in hyperuricemic patients with CKD is safe and might slow CKD progression. The currently published studies are promising and suggest that there may be a role for uric acid lowering therapy in patients with CKD. It is important to note, however, that these studies are limited by the small number of participants and the lack of a placebo arm. Considering the significant limitations of the current literature, further studies are needed before we can advocate lowering uric acid in patients with CKD. In addition, the best therapeutic strategy to lower uric acid in this patient population needs to be determined.

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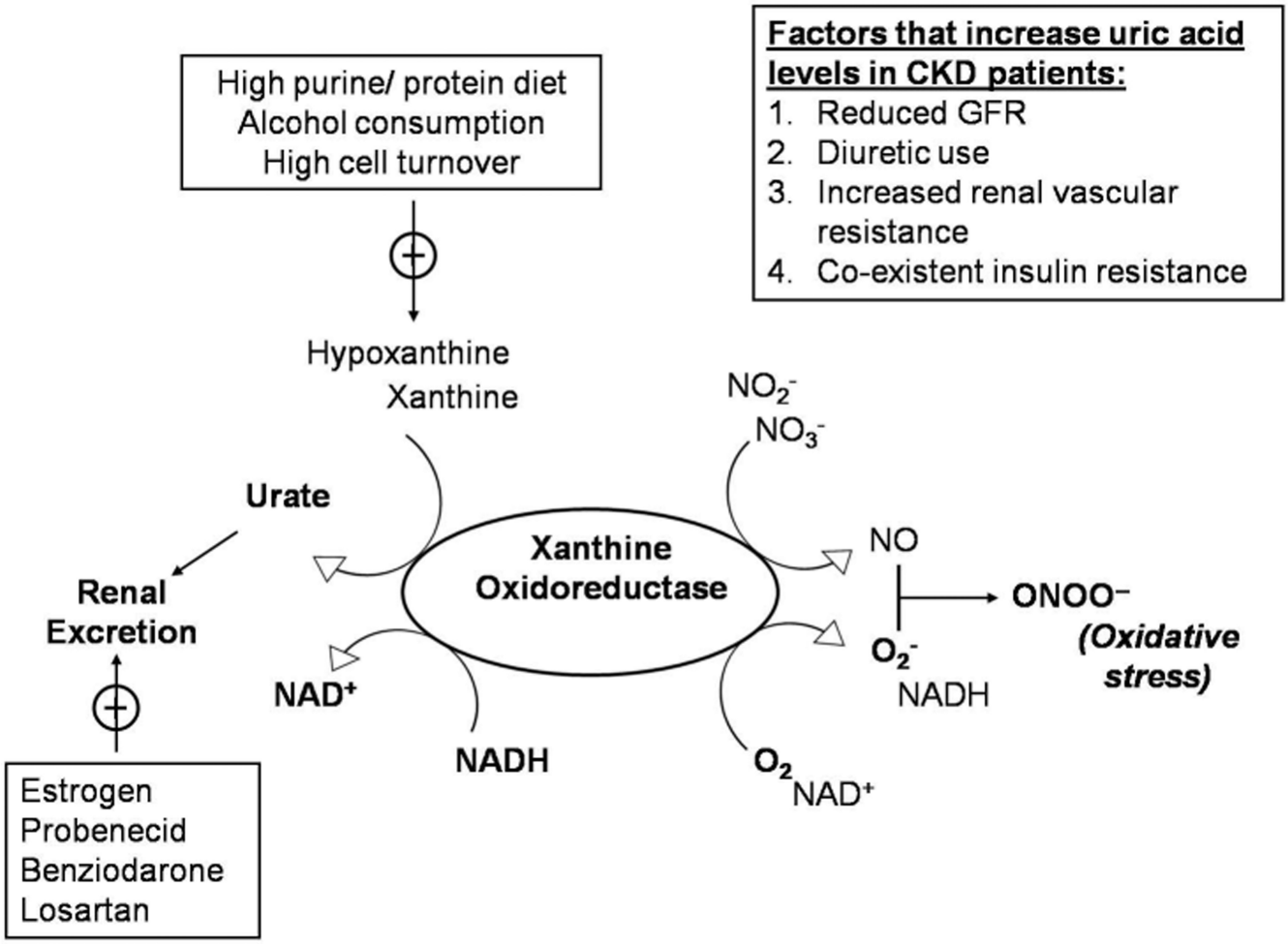

Figure 1.
Schematic representation of uric acid homeostasis.
Abbreviations: CKD, chornic kidney disease; GFR, glomerular filtration rate

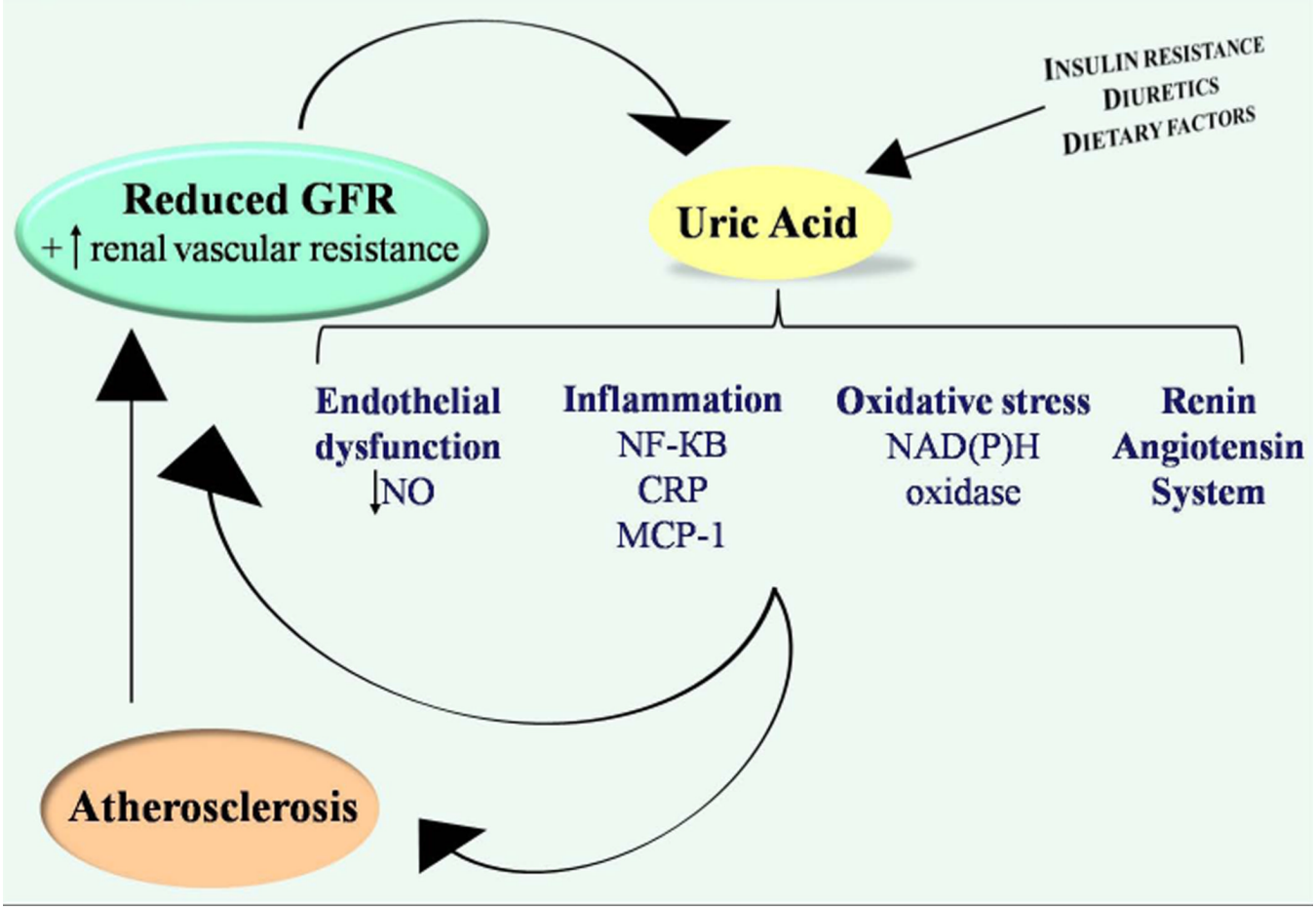

Figure 2.
Putative mechanisms by which elevated serum uric acid level may contribute to CKD development and progression.

TABLE 1

Main prospective studies of the association between elevated serum uric acid level and CKD development or progression.

Investigators	Study Population (N)	F/U (y)	Independent Variable	Study Outcome	Adjustments Considered	Findings
Iseki et al. [81]	Okinawa General Health Maintenance Association (6,403)	2	Hyperuricemia (≥8 mg/dl)	Incident CKD (SCr level ≥1.4 [♂] or ≥ 1.2[♀])	Age, sex, BMI, SBP, fasting glucose, sAlb, total cholesterol, proteinuria, hematuria, smoking, alcohol intake, physical activity	Hyperuricemia independently associated with risk of developing higher SCr, aHR: 2.91 (1.8–4.7) in ♂, 10.4 (1.9–56.6) in ♀
Domrongkitchaiporn *et al.*[34]	Employees of the Electric Generation Authority of Thailand (3,499)	12	Hyperuricemia (≥6.3 mg/dl)	Incident CKD (eGFR <60)	BMI, SBP, DBP, DM status, proteinuria, serum cholesterol, smoking history	Hyperuricemia independently associated with increased risk of incident CKD: aOR, 1.82(1.12–2.98)
Weiner *et al.*[35]	ARIC and CHS (13,338)	8.5	Serum uric acid levels (per 1 mg/dL increase)	Incident CKD (eGFR decrease of ≥15 with final eGFR <60, or SCr increase of ≥0.4 with final SCr > 1.4 [♂] or ≥1.2[♀])	Age, sex, race, DM status, SBP, HTN status, CVD, LVH, smoking, alcohol use, education, total cholesterol, HDL-C, sAlb, Hct, baseline kidney function	Serum uric acid independently associated with increased risk for incident CKD: aOR, 1.07(1.01–1.14)
Obermayr *et al.*[36]	The Vienna Health Screening Project (21,475)	7	Hyperuricemia (moderate [7–8.9 mg/dL] and significant [≥9 mg/dL])	Incident CKD (eGFR <60)	Age, sex, waist circumference, HDL-C, blood glucose, triglycerides, eGFR, mean BP, HTN medications	Moderately elevated serum uric acid independently associated with increased risk of incident CKD: aOR, 1.26 (1.02–1.55); for significantly elevated serum uric acid: aOR, 1.63 (1.18–2.27)
Sonoda *et al.*[37]	Health check-up screening of non-DM healthy people (7,078)	4.5	Uric acid levels (per 1 mg/dL increase)	Incident CKD (eGFR <60)	BMI, smoking, SBP, fasting glucose, LDL-C, HDL-C, Hb, eGFR, smoking	Serum uric acid an independent predictor of incident CKD: aOR, 1.09 (1.01–1.18), P=0.03
Wang *et al.*[38]	Retrospective cohort study of Taiwanese adults (94,422)	3.5	Hyperuricemia (≥7.3 mg/dl)	Incident CKD (eGFR <60)	Age, sex, education status, alcohol intake, smoking, HTN, DM status, physical activity, BMI, lipid profile, sAlb, Hb, CRP, GGT, SUN, eGFR, proteinuria, hematuria, medication use[c]	Hyperuricemia independently associated with increased risk of incident CKD: aHR, 1.15(1.01–1.30), P<0.05
Mok *et al.*[39]	The Severance cohort study in Korea (14,939)	10.2	Hyperuricemia (≥6.6 mg/dl [♂] or ≥4.6 mg/dl [♀])	Incident CKD (eGFR <60)	Age, smoking, alcohol consumption, physical activity, BMI, total cholesterol, HTN status, DM	Increased risk of incident CKD with hyperuricemia, aHR: 2.1 (1.6–2.9) in ♂ (P<0.0001), 1.3 (1.0–1.8) in ♀ (P=0.13)
Kuo et al.,[82]	Retrospective study of hospital based cohort (63,785)	3	Hyperuricemia > 7.7 mg/dL [♂] or > 6.6 mg/dL [♀])	Annual eGFR decline of ≥3	Age, sex, baseline eGFR[b], azotemia, hypercholesterolemia, hyperglycemia	Hyperuricaemia associated with accelerated eGFR decline: HR, 1.28 (1.23–1.33), p< 0.001
Hovind *et al.*[40]	T1DM (263)	18.1	Serum uric acid levels (per 1 mg/dL increase)	Incident Micro- or macro-albuminuria	Age, sex, BMI, HbA1c, albuminuria, SCr, total cholesterol, mean BP	Serum uric acid independently associated with subsequent development of persistent

Investigators	Study Population (N)		F/U (y)	Independent Variable	Study Outcome	Adjustments Considered	Findings
							macroalbuminuria: aHR, 2.93 (1.25–6.86) per 100 μmol/l increase in uric acid(*P*=0.013)
Jalal *et al.*[41]	Coronary Artery Calcification in T1 DM Study	324	6	Serum uric acid levels (per 1 mg/dL increase)	Composite outcome: incident micro- or macroalbuminuria	Age, sex, duration of DM, BMI, waist circumference, SBP, smoking, HbA1c, albuminuria, SCr, SCysC, HDL-C, triglycerides, use of RAAS blockers	Serum uric acid associated with micro-/macroalbuminuria: aOR, 1.8 (1.2–2.8) per 1-mg/dl increase in uric acid (*P*=0.005)
Ficociello *et al.*[42]	Second Joslin Kidney Study; T1DM	355	6	Serum uric acid categories (<3.0, 3.0–3.9, 4.0–4.9, 5.0–5.9, ≥6 mg/dl)	Early eGFR loss, defined as $eGFR_{cys}$ decline of >3.3%/y	Age, sex, HbA1c, $eGFR_{cys}$, albuminuria	Risk of early eGFR loss increased linearly: 9%, 13%, 20%, 29%, and 36% for uric acid categories in increasing order
Zoppini *et al.*[43]	Verona DM Study; T2DM	1,449	5	Hyperuricemia (>7.0 mg/dl [♂] or >6.5 mg/dl [♀]) or allopurinol use	Incident CKD (eGFR <60 or overt proteinuria)	Age, sex, BMI, smoking status, DM duration, SBP, HTN treatment, insulin therapy, HbA1c, eGFR, albuminuria	Hyperuricemia independently associated with increased risk of incident CKD: aOR, 2.10 (1.16–3.76), *P*<0.01
Altemtam et al.[83]	Retrospective cohort study of elderly patients with T2DM & CKD3–4	270	8	Serum uric acid (per each 1-mg increase)	Progression of CKD (eGFR decline of >2/y)	Age, race, SBP, eGFR, HbA1c, proteinuria, vascular co-morbidities	Serum uric acid independently associated with faster kidney disease progression: aOR, 1.16(1.09–1.39), *P*=0.016
Iseki *et al.*[46]	Okinawa General Health Maintenance Association	48,177	7	Hyperuricemia (≥7 mg/dl [♂] or >6 mg/dl [♀])	ESRD	Age, SBP, DBP, BMI, proteinuria, Hct, total cholesterol, triglycerides, fasting blood glucose, SCr	Hyperuricemia an independent risk factor for ESRD in ♀(aHR, 5.77 ([2.3–14.4], *P*<0.001) but not ♂(aHR, 2.0 [0.90–4.44], *P*=NS)
Yen *et al.*[44]	Community-based cohort of elderly Taiwanese	519	2.7	Serum uric acid levels (per 1 mg/dL increase)	eGFR <60 or kidney disease progression (decrease in eGFR of ≥ 3/y)	Age, sex, BMI, proteinuria, smoking, SCr, Hb, WBC count, HTN and DM status	Serum uric acid independently associated with an increased risk of decline in eGFR (aOR, 1.21 [1.05–1.39]) but not with incident CKD (OR, 0.99 [0.85–1.17])
Sturm *et al.*[50]	The Mild to Moderate Kidney Disease Study	227[a]	7	Serum uric acid levels (per 1 mg/dL) increase	Progression of CKD (doubling of baseline SCr or ESRD)	Age, sex, proteinuria, GFR, allopurinol use	Serum uric acid not associated with increased risk of CKD progression, aHR: 0.95 (0.80–1.13) in all, 1.03 (0.85–1.26) if exclude those taking allopurinol
Chonchol *et al.*[45]	CHS	5,808	5	Quintiles of uric acid	Incident CKD (eGFR<60)or kidney disease progression (decrease in eGFR of ≥ 3/y)	Age, sex, race, SCr, BMI, waist circumference, BP, HTN medications use, diuretics use, allopurinol use, glucose, HDL-C, triglycerides, ankle-arm index, carotid IMT, major ECG abnormalities, Hb, CRP, sAlb	Independent association of serum uric acid with progression of kidney disease (aORs of 1.0, 0.88, 1.23, 1.47, and 1.49 for uric acid quintiles 1 through 5, respectively) but no significant association with incident CKD(aOR, 1.0 [0.89–1.14])
Madero *et al.*[51]	MDRD Study	840	10	Serum uric acid levels (per 1 mg/dL increase)	ESRD and death	Age, sex, history of CVD, DM, BMI, HDL-C, SBP, eGFR, sAlb, diuretic use, proteinuria, allopurinol use	In CKD3–4, hyperuricemia not an independent risk factor for ESRD (HR, 1.02 [0.97–1.07]); serum uric acid significantly associated with all-cause and CV mortality

Investigators	Study Population (N)		F/U (y)	Independent Variable	Study Outcome	Adjustments Considered	Findings
Ishani et al.[84]	MRFIT	12,866[e]	25	Serum uric acid levels (per 1 mg/dL increase)	Initiation of treatment for ESRD[d]	Age, race, family history of DM, smoking, BMI, SBP, fasting glucose, triglycerides, HDL-C, LDL-C, eGFR, Hct, proteinuria	Serum uric acid independently associated with increased risk of ESRD: aHR, 1.16(1.04–1.29), *P*=0.0006
Hsu *et al.*[47]	A large integrated health care delivery system	177,570	24.5	Uric acid quartiles	ESRD	Age, sex, race, educational level, BMI, HTN status, DM status, history of kidney disease, history of nocturia, LVH, smoking, alcohol intake, occupational exposure to solvents/fumes/ chemicals, SCr, Hb, proteinuria	Higher serum uric acid an independent risk factor for ESRD: HR, 2.14 (1.65–2.77) for highest vs lowest quartile
Bellomo *et al.*[48]	Healthy normotensive adult blood donors	900	5	Serum uric acid levels (per 1 mg/dL increase)	eGFR loss (of >10)	Age, sex, BMI, mean BP, fasting glucose, total cholesterol, triglycerides, UACR, smoking	Serum uric acid an independent risk factor for decreased kidney function: aHR, 1.23(1.09–1.39), *P*=0.001
Ben-Dov *et al.*[49]	The Jerusalem Lipid Research Clinic cohort study	2449	25	Hyperuricemia (upper quintile >6.5 mg/dl [♂] or > 5.3 mg/dl [♀])	ESRD and AKI defined by hospital discharge records	None	Hyperuricemia conferred increased risk of ESRD, aHR: 1.94(1.20–3.14) in ♂, 5.20 (1.90–14.2) in ♀; also significantly associated with increased risk of AKI and all-cause mortality
Syrjanen et al.[85]	IgA nephropathy	223	10	Hyperuricemia (≥7.0 mg/dl [♂] or ≥ 6.5 mg/dl [♀])	Progression of CKD (elevation of SCr above normal and/or SCr ≥20% of baseline)	Age, sex, BMI, proteinuria, HTN status, DM status, dyslipidemia	Hyperuricemia independently associated with CKD progression only among those with initially normal kidney function: aHR, 4.60 (1.1–19.4)
Ohno et al.[86]	IgA nephropathy	56	8	Hyperuricemia (≥7.0 mg/dl)	Progression of CKD (change in CCr)	HTN and kidney pathology	Hyperuricemia associated with increased risk of kidney disease progression (unadjusted change in CCr: −22.3±20.8% vs +2.6±39.4%, *P*=0.0238); Uric acid associated with decline in CCr in adjusted analysis (P=0.046)

Note: eGFR values given in mL/min/1.73 m2; SCr in mg/dL. Values in parentheses for HRs and ORs are 95% confidence intervals

[a] number that completed the study = 177

[b] By MDRD Study equation.

[c] allopurinol, lipid-lowering drug, Chinese herbal medicine

[d] ascertained with USRDS registry data

[e] all men

Abbreviations: aHR, adjusted hazard ratio; AKI, acute kidney injury; aOR, adjusted odds ratio; ARIC, Atherosclerosis Risks in Communities; BMI: body mass index; BP, blood pressure; CCr, creatinine clearance; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; CRP: C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG,

electrocardiogram; eGFR, estimated glomerular filtration rate; eGFRcys, estimated glomerular filtration rate based on serum cystatin C level; ESRD, end-stage renal disease; F/U, follow-up; GFR, glomerular filtration rate; GGT: gamma-glutamyl-transpeptidase; Hb, hemoglobin; HbA1c, hemoglobin A1c; Hct, hematocrit; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; HTN, hypertension; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MDRD, Modification of Diet in Renal Disease; MRFIT, Multiple Risk Factor Intervention Trial; NS, nonsignificant; OR, odds ratio; RAAS: renin angiotensin aldosterone system; sAlb, serum albumin; SBP: systolic blood pressure; SCr, serum creatinine; SCysC, serum cystatin C; SUN, serum urea nitrogen; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UACR, urine albumin-creatinine ratio; USRDS, United States Renal Data System; WBC, white blood cell

TABLE 2

Main interventional studies to lower serum uric acid levels in CKD

Investigators	Study Design and Population	Treatment	Study Endpoints	Main findings
Siu et al. [63]	RCT of 54 hyperuricemic patients with mild to moderate CKD	12 mo of either allopurinol 100–300 mg/d or no treatment	Decreased kidney function with SCr level ≥40% of baseline, or initiation of dialysis, or death	Nonsignificant trend toward a lower SCr level in the treatment group (P=0.08); overall, 16% (4/25) of allopurinol group reached the combined end-points, vs 46.1% (12/ 26) in control group (P=0.015)
Goicoechea et al. [64]	RCT of 113 hyperuricemic patients with mild to moderate CKD	24 mo of either allopurinol 100 mg/d or no treatment	Progression of CKD (defined as eGFR decrease > 0.2/mo), or CV events, or hospitalizations of any cause, or death	ΔeGFRs of −3.3 ±1.2 (control) and +1.3 ±1.3 (allopurinol group), P =0.018; compared with controls, allopurinol treatment slowed CKD progression in a Cox regression model (adjusted for age, sex, diabetes, uric acid), and reduced risk of CV events and number of hospitalizations (aHR, 0.29; 95%CI, 0.09–0.86; P=0.026)
Kanbay et al.[87]	Case-control study of 59 hyperuricemic patients with eGFR >60 and 21 normouricemic controls; only hyperuricemic patients received allopurinol[a]	3 mo of allopurinol 300 mg/d	eGFR <60	eGFR significantly increased (from 79.2±32 to 92.9±37; P=0.008) and BP and plasma CRP decreased in the allopurinol group; no significant change in the control group
Talaat et al.[33]	Intervention trial of allopurinol withdrawal in 50 hyperuricemic patients with CKD3–4 treated with allopurinol	12 mo after allopurinol withdrawal	Changes in eGFR and urinary TGF- β1	Significant acceleration of the rate of eGFR loss and significant increases in BP values and urinary TGF- β1 only among those who were not receiving ACEi
Miao et al[67]	Placebo-conrolled RCT of patients treated with losartan in a post-hoc analysis of the RENAAL Trial, N=1,342 patients with type 2 diabetes and nephropathy	Post-hoc analysis of the first 6 mo of treatment	Progression of CKD defined as doubling of SCr or ESRD	Losartan lowered serum uric acid by 0.16 (95% CI, 0.30–0.01) mg/dL (P=0.031) vs placebo; risk of renal events was decreased by 6% (95% CI, 10%–3%) per 0.5-mg/dL decrement in serum uric acid during the first 6 mo of treatment after adjustment for age, sex, treatment assignment (losartan or placebo), eGFR, SBP, albuminuria, serum albumin, ACEi or ARB use at baseline, changes in albuminuria and eGFR

Note: eGFR values given in mL/min/1.73 m2;

[a] Ie, not a placebo-controlled RCT

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; OR, odds ratio; HR, hazard ratio, CI, confidence interval, SBP: systolic blood pressure; SCr, serum creatinine; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; aHR, adjusted hazard ratio; TGF, transforming growth factor; BP,

blood pressure, ACEi, angiotensin-converting enzyme inhibitor; ARB, antiotensin receptor blocker; RCT, randomized clinical trial; CV, cardiovascular; CRP, C-reactive protein

TABLE 3

Observational studies evaluating uric acid as a predictor of graft dysfunction in patients with a kidney transplant

Investigators	N	F/U (y)	Independent Variable	Study Outcome	Adjustments Considered	Findings
Armstrong et al.[76]	90	7	Hyperuricemia (> 7 mg/dl for men, and > 6 mg/dL for women) at least 6 mo posttransplantation	eGFR, and change eGFR[a]	Age, sex, race, weight, BMI, time since transplantation, history of CVD, dyslipidemia, DM, smoking status, baseline eGFR and proteinuria, calcium, phosphate, albumin, Hb, homocysteine, CRP, medications	Hyperuricemia independently predictive of eGFR (β estimate, −22.2; 95% CI, −41 to −3.2; P = 0.02); hyperuricemia not associated with change in eGFR
Akalin et al. [75]	307	4.3	Hyperuricemia 6 mo posttransplantation (≥ 7 mg/dl for men, and ≥ 6.5 mg/dL for women)	Composite of death, graft loss, new CV event, or biopsy proven CAN	Age, race, sex, eGFR < 50, cyclosporine use, cadaveric kidney	Hyperuricemia associated with more events (P <0.001 for K-M curve); among group with eGFR < 50, hyperuricemia associated with 45% event rate vs 21% in normouricemia (p=0.038)
Meier-Kriesche et al. [74]	852	3	Serum uric acid levels 1 month posttransplantation (per 1 mg/dL) and uric acid tertiles	eGFR[b]	Donor type, immunosuppressive treatment arm, ethnicity, baseline eGFR	Uric acid and eGFR were collinear; Uric acid associated with reduced eGFR at 3 y (p=0.005), but this became not significant after adjusting for baseline eGFR
Akgul et al. [77]	133	3	Hyperuricemia 1 month posttransplantation (> 7 mg/dl for men, and > 6 mg/dL for women)	CAN (biopsy proven)	Age, donor source, no. of HLA mismatches, duration of dialysis, HTN, acute rejection, and serum cholesterol	Uric acid not associated with CAN (p> 0.05)
Haririan et al. [78]	212	6	Serum uric acid level within the first 6 mo posttransplantation (per 1 mg/dL) and hyperuricemia (> 7 mg/dl for men, and > 6.5 mg/dL for women)	Graft and patient survival, graft function	Age, sex, race, re-transplantation, BMI, HLA mismatch, early graft function, SCr, DM, induction agent, acute rejection	Uric acid associated with graft loss (HR, 1.26 [95% CI 1.03–1.53] per1 mg/dL increase, p=0.026) and hyperuricemia independently predicted graft loss (HR, 1.92 [95% CI 1.1–3.4], p=0.029)
Kim et al.[80]	556	4	hyperuricemia (> 7 mg/dl for men, and > 6 mg/dL for women)	Graft dysfunction with >50% loss of kidney function (eGFR[a])	Age, sex, weight, donor type, time since transplantation, HTN, DM, immunosuppressive regimen, serum calcium, serum phosphorus	Hyperuricemia associated with graft dysfunction: unadjusted HR = 1.31 (p<0.001), aHR=1.45 (p<0.001)

Investigators	N	F/U (y)	Independent Variable	Study Outcome	Adjustments Considered	Findings
Kim et al. [71]	356	5	Mean uric acid levels obtained every 3 mo (starting 6 mo posttransplantation) modeled as a continuous variable (per 1 mg/dL) and categorical hyperuricemia (> 7 mg/dL for men and >6 mg/dL for women)	eGFR[a]	Age, sex, weight, donor type, time since transplantation, HTN, DM, immunosuppressive regimen, serum calcium, serum phosphorus	Uric acid did not predict eGFR
Boratynska et al.[79]	98	2.5	Hyperuricemia (> 7 mg/dL for men and >6 mg/dL for women)	eGFR	NA	eGFR significantly higher in normo- vs hyperuricemic patients at baseline, but SCr and eGFR were similar in both groups at study end

Note: **eGFR values given in mL/min/1.73 m2;**

[a] eGFR calculated using the MDRD Study equation.

[b] eGFR calculated using creatinine clearance

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; BMI, body mass index; CVD, cardiovascular disease; HR, hazard ratio, CI, confidence interval; CAN, Chronic allograft nephropathy; NA, not applicable; K-M, Kaplan- Meier; DM, diabetes mellitus; CRP, C-reactive protein; HTN, hypertension; CV, cardiovascular; SCr, serum creatinine