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Serum uric acid, kidney volume and progression in autosomal-dominant polycystic kidney disease

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Abstract

Background. Hyperuricemia has been implicated in the development and progression of chronic kidney disease, both in animal experiments and in clinical studies. As a potentially modifiable risk factor, we examined whether serum uric acid levels correlate with early hypertension, kidney volume and progression to end-stage renal disease (ESRD) in autosomal-dominant polycystic kidney disease (ADPKD).

Methods. Retrospective analysis of a prospective observational study of the natural history of ADPKD, conducted at the University of Colorado between 1985 and 2005. Included are 680 ADPKD adults who provided data on blood pressure, renal volume, renal function, uric acid, age at the onset of ESRD or last known age without ESRD. Serum uric acid levels were examined as a continuous variable and as gender-specific quartiles. The main outcome of interest was age at the onset of ESRD; secondary outcomes were hypertension onset before age 30 years and total kidney volume (TKV) at the study visit.

Results. Subjects with early-onset hypertension had higher age-adjusted serum uric acid levels than those with no or late-onset hypertension despite similar creatinine clearance. After adjusting for age, gender and creatinine clearance, there was a 5.8% increase in TKV and 4.1% increase in TKV/body surface area for every 1 mg/dL increase in uric acid ($P = 0.007$). The multivariate-adjusted Cox regression demonstrated a greater hazard ratio for ESRD for subjects in the 4th and 3rd quartiles of uric acid compared with the 1st [4.8 (2.6–8.9; $P < 0.001$) and 2.9 (1.6–5.3; $P < 0.001$)].

Conclusions. Higher serum uric acid levels are associated with earlier onset of hypertension, larger kidney volume and increased hazard for ESRD in ADPKD independent of gender, body mass index and renal function at the study visit. Randomized interventional studies will be necessary to examine whether treating hyperuricemia has a protective role in ADPKD.

Keywords: autosomal-dominant polycystic kidney disease; end-stage renal disease; hypertension; kidney volume; uric acid

Introduction

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common potentially lethal hereditary disease affecting 1:400–1:1000 Americans [1]. It occurs in all races worldwide and leads to end-stage renal disease (ESRD) in ∼50% of affected patients by age 60 and 75% by age 70 years [2]. Most patients, ∼85%, are affected by the more severe form caused by a mutation in the *PKD1* gene located on chromosome 16 as opposed to mutations in the *PKD2* gene located on chromosome 4. However, even for patients with *PKD1* mutations, the pace of progression to ESRD is highly variable between and within families [2]. Apart from the specific gene mutation, one of the strongest and potentially modifiable risk factors for faster progression is an early onset of hypertension. In an earlier study from our center, the onset of hypertension before the age of 35 years was associated with ESRD occurring 14 years earlier than in patients with the onset of hypertension after age 35 years [3]. Other potentially modifiable risk factors for progression are larger kidneys, higher sodium intake and lower HDL-cholesterol levels [4]. Endothelial dysfunction, reduced renal blood flow and left ventricular hypertrophy are other common findings in patients with ADPKD [5–8]. Cardiovascular disease remains the most common cause of death in ADPKD [9, 10].

Although hyperuricemia has long been known to be associated with hypertension and chronic kidney disease, an independent role and potential mechanisms for the development of hypertension, endothelial dysfunction, chronic kidney disease and cardiovascular complications have only recently been demonstrated [11–14]. Several epidemiological studies have shown that hyperuricemia predicts the development of hypertension [11–13] and chronic kidney disease in the general population [15–17]. Higher serum uric acid levels were associated with faster renal function decline in a community-based prospective cohort study [18]. Animal experiments have demonstrated a causal role of increased uric acid levels in the pathogenesis of hypertension and kidney disease. For instance, mild hyperuricemia was induced in rats by the

administration of an uricase inhibitor, and these rats developed hypertension and renal microvascular disease ~3 weeks later, in contrast to their untreated littermates which remained normotensive [19]. Hypertension and renal disease were prevented when allopurinol was also given to these rats. The hyperuricemic animals exhibited a stimulated renin–angiotensin system and inhibited macula densa nitric oxide synthase, both of which can account for hypertension and renal microvascular disease [19]. Stimulation of the renin–angiotensin system is also a feature of ADPKD [20, 21] and may be exaggerated in ADPKD patients with hyperuricemia, thus contributing to early-onset hypertension and faster progression. Interestingly, a recent meta-analysis of 14 genome-wide association studies on serum uric acid concentrations has suggested that the *PKD2* gene may be part of a causal pathway determining uric acid levels in European populations [22].

Because hyperuricemia may be a modifiable risk factor for the progression to ESRD in ADPKD, we undertook this retrospective study in a large cohort of ADPKD patients to explore whether hyperuricemia, independent from renal function, is associated with faster progression, as manifest by early-onset hypertension, larger kidney volumes and ESRD at a younger age.

Materials and methods

Study population

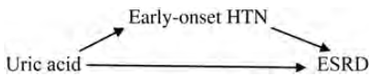
A total of 680 ADPKD adults from the University of Colorado ADPKD registry who were evaluated between January 1985 and October 2005 and had blood pressure (BP), renal function, renal volume and serum uric acid measurements were included. These subjects participated in the NIH-funded Natural History Study of ADPKD and were not on renal replacement therapy at the time of study. The diagnosis of ADPKD was confirmed by ultrasound imaging using Ravine's diagnostic criteria [23]. None had diabetes at their first study visit (although patients with diabetes were not specifically excluded). All patients gave informed consent and were evaluated during a 2-day inpatient visit at the Clinical Research Center at the University of Colorado Hospital. The protocol had been approved by the Colorado Multiple Institutional Review Board and was in accordance with the ethical principles of the Helsinki Declaration. At the study visit, they had a history and physical performed, and had multiple BP measurements under standardized conditions, using a Dinamap BP monitor (Critikon Inc., Tampa, FL). Hypertension was defined as being treated with antihypertensive medication or seated BP $\geq$ 140/90 mm Hg in at least 50% of BP measurements obtained during the study visit. The study did not specify antihypertensive treatments, and all patients were treated by their primary physicians. Antihypertensive medications were not held during the visit but were recorded. Blood was drawn to determine routine serum chemistry values, and two 24-h urine collections were obtained to measure creatinine clearance (CrCl). The mean of the two clearances was used to estimate their renal function and is referred to as their CrCl in this article. Renal volume was defined as the total volume of both kidneys (TKV) and calculated as previously described, based on ultrasound measurements [24]. Serum uric acid was determined by the clinical laboratory using a standard auto analyzer (Hitachi 717 before 1993, Hitachi 747 from 1993 to 1998, Hitachi 917 from 1998 to 2004 and Beckman LXI20 from 2004 to 2007). Only data from the first study visit were complete for each patient and therefore were used for this analysis. Longitudinal follow-up data were obtained through multiple mailings of questionnaires and during recruitment for other studies. Age at ESRD is the age at first dialysis or receipt of a renal transplant. The mean interval between the study visit and ESRD or last age without ESRD was 4.42 ± 4.00 years (0–19 years).

Statistical analysis

Early onset of hypertension was defined as age of hypertension diagnosis ≤30 years of age while those who remained normotensive or developed hypertension after age 30 were considered not to have early-onset hypertension. Independent samples *t*-tests were used to determine the differences in continuous variables between those with early onset of hypertension and those without. The χ^2 test of independence was used to test the difference in distributions among categorical variables. Due to highly skewed distributions, natural log transformations were applied to TKV, TKV/BSA (body surface area), serum creatinine (SCr), CrCl and urinary protein, and analyses were performed on the transformed variables. We examined serum uric acid levels as a continuous variable and as gender-specific quartiles. Quartiles were determined based on the levels observed in the study population. In women, quartiles 1–4 were ≤4.2, 4.3–5.1, 5.2–6.5 and >6.5 mg/dL; in men, quartiles 1–4 were <5.7, 5.71–6.9, 7.0–8.2 and >8.2 mg/dL. Multiple linear regression models were used to determine the independent relationship of serum uric acid with renal volume: Unadjusted model, Model 1: adjusted for age and sex, Model 2: Model 1 + LnCrCl, and Model 3: Model 2 + use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), diuretics or allopurinol. A natural log transformation was used for renal volume; therefore, the exponentiation of the β coefficients (slope) results in the percent increase in renal volume per 1 mg/dL change in uric acid level.

The multivariate Cox regression adjusted for age, CrCl, gender, use of ACEI, ARB, diuretic, allopurinol and early-onset hypertension was performed to examine the relationship of quartiles of serum uric acid to time of the onset of ESRD. Results are reported as hazard ratio (HR) and 95% Wald confidence intervals (CI). Descriptive statistics are presented as mean ± SD, geometric mean and 95% CI or frequency and percent. P-values of <0.05 were considered significant.

We undertook a mediation analysis to examine whether early-onset hypertension could be a mediator for the effect of elevated serum uric acid on progression to ESRD. A mediation test for survival analysis was performed using the Sobel test as described by Tein and MacKinnon [25], and a joint significance test of mediation was performed as described by MacKinnon *et al*. [26]. The simple figure is a scheme of mediation analysis:



Results

Serum uric acid, hypertension and kidney volume

A total of 680 adults with ADPKD and data on serum uric acid, hypertension and TKV were included in the analysis. Because an early onset of hypertension is a strong risk factor for ESRD in ADPKD and hyperuricemia has been linked to early hypertension, we determined the characteristics of our study population based on a history of early-onset hypertension, defined as hypertension diagnosis at or before the age of 30 years. The demographic and clinical data are summarized in Table 1. Five hundred and thirty-one subjects had a history of hypertension, while 149 did not. Twenty-three of the 531 hypertensive patients did not have age at hypertension diagnosis available and were excluded from the analysis. Of those with a history of hypertension, 206 had onset of hypertension ≤30 years of age leaving 451 with age of hypertension diagnosis >30 years or no history of hypertension. Those with early onset of hypertension were more often male, had higher serum uric acid levels, higher systolic and diastolic BP, larger kidneys, more proteinuria and most notably, earlier onset of ESRD by over a decade, yet renal function at the clinical visit was similar to those without

Table 1. Characteristics of subjects with early onset of hypertension versus those without hypertension or onset of hypertension >30 year of age

Parameter	No hypertension or hypertension onset >30 years of age	Hypertension onset ≤30 years of age	P-value
Number	451	206	
Age (years)	44.58 ± 12.30	35.65 ± 10.65	<0.001
Male/female	152/299	99/107	<0.001
BMI (kg/m^2)	26.16 ± 5.74	27.21 ± 5.45	0.0287
Hypertension (%)	302 (66.96%)	206 (100%)	<0.001
SBP (mmHg)	128.84 ± 17.55	133.93 ± 17.87	<0.001
DBP (mmHg)	82.78 ± 11.84	85.23 ± 13.52	0.0284
Geometric mean proteinuria (mg/24 h)	144.99 (131.92–159.36)	201.76 (178.14–228.51)	<0.001
Geometric mean CrCl (mL/min/1.73 m^2)	57.52 (54.00–61.27)	57.06 (51.62–63.07)	0.8899
Mean uric acid (mg/dL)[a]	5.77 ± 0.09	6.72 ± 0.13	<0.001
Men[a]	6.85 ± 0.13	7.40 ± 0.19	<0.001
Women[a]	5.22 ± 0.10	6.11 ± 0.16	<0.001
Geometric mean TKV (cm^3)	1162 (1085–1246)	1548 (1412–1697)	<0.001
TKV/BSA (cm^3)	630 (588–674)	800 (731–876)	0.0018
Kidney calculi (%)	67 (14.92%)	32 (15.53%)	0.8324
ARB	9 (2.00%)	10 (4.85%)	0.0425
Diuretic	112 (24.94%)	77 (37.38%)	0.0011
ACEI	133 (29.56%)	121 (59.02%)	<0.001
Allopurinol	30 (6.65%)	7 (3.40%)	0.0933
ESRD	120 (26.73%)	63 (30.58%)	0.3071
Median age of onset of ESRD	64 (61–66) years	51 (48–56) years	<0.001

[a]ANCOVA was used to obtain age-adjusted uric acid ± SE.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CrCl, creatinine clearance; DBP, diastolic blood pressure; ESRD, end-stage renal disease; SBP, systolic blood pressure; TKV, total kidney volume.

hypertension or with hypertension onset after the age of 30 years. Uric acid adjusted for age was significantly higher in both males and females with early-onset hypertension compared with non-hypertensive subjects and those with later onset of hypertension. In a logistic model, uric acid >6.0 mg/dL in females or >7.0 mg/dL in males predicted early onset of hypertension [odds ratio (OR) = 1.14 (1.04–1.24), P = 0.0033]. Only 37 of the 657 patients were taking allopurinol (prescribed by their private physician, indication not recorded), and when they were omitted from the analysis, the results were similar [OR = 1.15 (1.05–1.26), P = 0.0017]. Ultimately, age at the onset of hypertension was highly correlated with that at the onset of ESRD ($Y = 30.15 + 0.601x$, $R^2 = 0.46$, P < 0.001).

In linear regression, serum uric acid was significantly related to LnTKV ($\beta = 0.16 \pm 0.01$, P < 0.001) and Ln TKV/BSA ($\beta = 0.14 \pm 0.01$, P < 0.001) (Figure 1), which means that there was a 17.6% increase in TKV and a 14.8% increase in TKV/BSA for every 1 mg/dL increase in serum uric acid level. In linear regression adjusted for age and sex, there was an 11.4% increase in TKV

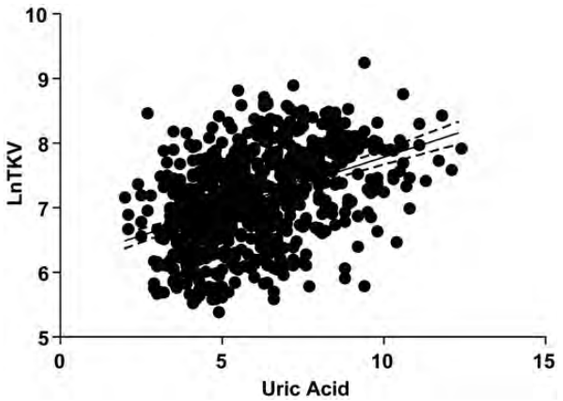


Fig. 1. Relationship between uric acid and LnTKV, $R^2 = 0.1771$, P < 0.001.

(P < 0.001) and 9.9% increase in TKV/BSA for every 1 mg/dL increase in uric acid (P < 0.001). When further adjusted for renal function, there was a 5.8% (P < 0.001) increase in TKV and 4.1% increase in TKV/BSA for every 1 mg/dL increase in uric acid (P = 0.007). Serum uric acid remained related to LnTKV (3.3%, P = 0.0456), but not LnTKV/BSA (1.7%, P = 0.2912) after further adjustment for the use of ACEI, ARB, diuretic and allopurinol. The use of ACEI was associated with an increased LnTKV ($\beta = 0.26 \pm 0.05$, a 30% increase, P < 0.001), likely due to the greater prevalence of hypertension in subjects with larger kidneys, while the use of ARB, diuretics or allopurinol was not. There was no difference in the prevalence of symptomatic renal stones between subjects with early hypertension and those without or late-onset hypertension. There was no significant difference in serum uric acid level in those with kidney stones versus those without kidney stones (6.4 ± 2.0 versus 6.0 ± 1.9 mg/dL, P = 0.0659). Data on the frequency of gout had not been collected.

Uric acid and the progression to ESRD

A total of 645 ADPKD patients had data available on age at ESRD or last known age without ESRD. The Cox regression of ESRD on uric acid as a continuous variable, adjusted for age, creatinine clearance at visit, gender, ACEI, ARB, diuretic, allopurinol use, body mass index (BMI) and early onset of hypertension, demonstrated that a 1 mg/dL increase in serum uric acid resulted in an increased hazard for ESRD [HR = 1.374 (1.240–1.523), P < 0.001] (Table 2). Higher BMI was not correlated with ESRD [HR = 1.008 (0.975–1.041), P = 0.6447] (Table 2). After removing patients taking allopurinol, early onset of hypertension [HR = 1.47 (1.02–2.13), P = 0.0418] and serum uric acid level [HR = 1.39 (1.25–1.55), P < 0.001] remained associated with ESRD in a fully adjusted model. When using sex-specific quartiles of uric acid, the Cox regression adjusted for age, CrCl at visit, gender, ACEI, ARB, diuretic, allopurinol use and early onset of hypertension demonstrated a greater hazard for ESRD in the 4th quartile of uric acid compared with the 1st

Table 2. Adjusted HRs for the prediction of ESRD from the multivariate Cox regression

Parameter	Hazard ratio (95% CI)	P-value
Age	0.725 (0.698–0.754)	<0.001
Sex (male)	0.961 (0.669–1.381)	0.8301
LnCrCl	0.165 (0.130–0.209)	<0.001
ARB	0.448 (0.061–3.292)	0.4303
Diuretic	1.148 (0.820–1.605)	0.4215
ACEI	0.898 (0.635–1.271)	0.5441
Allopurinol	1.800 (1.029–3.148)	0.0392
Early onset of hypertension	1.447 (1.020–2.053)	0.0386
BMI	1.008 (0.975–1.041)	0.6447
Serum uric acid	1.374 (1.240–1.523)	<0.001

Variables are adjusted for all other variables.

Table 3. Multivariate HRs for the prediction of ESRD from the multivariate Cox regression using sex-specific quartiles of serum uric acid

Parameter	Hazard ratio (95% CI)	P-value
Age	0.724 (0.696–0.753)	<0.001
Sex (male)	1.621 (1.167–2.250)	0.0039
LnCrCl	0.177 (0.140–0.225)	<0.001
ARB	0.389 (0.053–2.875)	0.3547
Diuretic	1.099 (0.783–1.543)	0.5859
ACEI	0.847 (0.597–1.200)	0.3503
Allopurinol	2.021 (1.187–3.442)	0.0096
Early onset of hypertension	1.267 (0.887–1.811)	0.1934
2nd quartile versus 1st quartile	1.054 (0.547–2.029)	0.8756
3rd quartile versus 1st quartile	2.931 (1.616–5.315)	<0.001
4th quartile versus 1st quartile	4.813 (2.613–8.866)	<0.001

Variables are adjusted for all other variables.
ACEI, angiotensin-, angiotensin-receptor blocker; BMI, body mass index; LnCrCl, natural logarithm of creatinine clearance.

[HR = 4.813 (2.613–8.866), P < 0.001] (Table 3). In addition, those in the 3rd quartile of uric acid also showed increased hazard for ESRD when compared with the 1st [HR = 2.93 (1.62–5.32), P < 0.001] (Table 3). Further adjusting for BMI, renal volume, and renal function at the time of the visit still resulted in highly significant associations between the 3rd [HR = 2.20 (1.21–4.02), P = 0.0097] and 4th [HR = 4.0 (2.14–7.36), P < 0.001] quartiles of uric acid with ESRD. In a model testing the interaction between uric acid and gender, the interaction term was not significant (P = 0.6677); therefore, a stratified analysis was not performed.

Evidence for mediation of early onset of hypertension

Mediation analysis was performed by showing the relationship of serum uric acid with early onset of hypertension and ESRD and the association of early onset of hypertension with ESRD independent of uric acid, with the following results: (i) increased serum uric acid level was associated with higher odds of early onset of hypertension [OR = 1.14 (1.04–1.24), P = 0.0033] and (ii) the Cox regression demonstrated that both serum uric acid level [HR = 1.20 (1.11–1.3), P < 0.001] and early onset of hypertension [HR = 3.17 (2.30–4.37), P < 0.001] were predictors of ESRD, which meets the criteria for the joint significance test of mediation. Using the Sobel test, the mediation effect of early onset of hypertension was $Z = 2.7$, P = 0.007, which indicates that early onset of hypertension is a mediator between uric acid level and ESRD.

Discussion

This is the first study in a large group of ADPKD patients to evaluate the relationship between serum uric acid and various renal parameters. As reported previously [3], younger age at diagnosis of hypertension was strongly associated with younger age at ESRD. We also found that female and male subjects with younger age at hypertension diagnosis had significantly higher age-adjusted serum uric acid levels at their study visit, despite similar renal function and similar BMI as subjects without or late-onset hypertension. As suggested by epidemiological studies in the general population, hyperuricemia may be a contributor to the development of early hypertension, by inducing endothelial dysfunction and activating the renin–angiotensin system [14, 19, 27, 28]. Interestingly, in a small clinical trial, newly diagnosed hypertensive adolescents with normal renal function were treated with allopurinol, resulting in a significant reduction in their BP without antihypertensive drugs [29]. Prospective studies are needed in young ADPKD patients to answer the question whether high uric acid levels play any role in the development of early hypertension.

In this study, higher serum uric acid levels were associated with a larger TKV even after adjustment for age, gender, BSA and renal function. Patients with larger kidneys have reduced renal blood flow as shown in the CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) studies where renal blood flow was measured by magnetic resonance imaging [6, 30]. Higher serum uric acid levels could be a marker of decreased renal blood flow. Renal uric acid excretion is dependent on glomerular filtration, tubular reabsorption and secretion. Renal blood flow decreases early in ADPKD patients and prior to a fall in glomerular filtration rate (GFR) [6, 7], an effect which could impair uric acid secretion. Also, a decrease in renal blood flow with preserved GFR results in an increased filtration fraction, which would be expected to increase peritubular oncotic pressure and thereby increase sodium and uric acid reabsorption [31, 32]. Thus, an increase in serum uric acid concentration could be a sensitive and early indicator of reduced renal blood flow in ADPKD patients. Such an early laboratory marker of decreased renal perfusion prior to a fall in GFR could be important for future interventional studies in ADPKD.

Apart from serving as a marker, hyperuricemia may also directly contribute to decreased renal blood flow by inducing endothelial dysfunction. In the rat model, hyperuricemia was shown to inhibit vascular endothelial nitric oxide production under basal and stimulated conditions [14]. In cell cultures, uric acid stimulates vascular smooth muscle proliferation [27]. In humans, elevated uric acid levels correlate with endothelial dysfunction and increased

plasma renin activity [13]. Treatment with allopurinol improved endothelial dysfunction in patients with chronic heart failure [33], diabetes [34], chronic kidney disease [35] and in asymptomatic hyperuricemic subjects with normal renal function [36]. Endothelial dysfunction and activation of the renin–angiotensin–aldosterone system are prominent features in early stages of ADPKD [20, 21]. Multiple studies of young ADPKD patients have demonstrated significant endothelial dysfunction even in normotensive subjects and more pronounced in hypertensive patients [5, 37, 38]. Clinically, endothelial dysfunction is reflected in the reduced coronary flow velocity reserve in normotensive ADPKD patients with normal renal function compared with healthy controls [39]. Improving endothelial dysfunction should be a therapeutic target in ADPKD, not only to postpone ESRD but also to improve cardiovascular function.

The most important finding of our study is the fact that higher serum uric acid levels were associated with an increased hazard of ESRD on follow-up even after adjustment for renal function at the study visit, adjustment for age, gender, BMI, early onset of hypertension and use of ACEI, ARB, diuretics and allopurinol. This was true in analyses of uric acid as a continuous variable and when using sex-specific quartiles of uric acid. Subjects in the 3rd and 4th quartile had significantly higher hazard of ESRD compared with those in the first quartile, after adjustment for renal function, age, early onset of hypertension and medication use. This finding suggests an independent effect of hyperuricemia on the progression of ADPKD and is consistent with studies in the general population that have indicated a role for uric acid in the development and progression of chronic kidney disease [15–18]. Experimentally, in the remnant kidney rat model, mild hyperuricemia accelerated preexisting renal disease, by promoting glomerulosclerosis, interstitial fibrosis and arteriolosclerosis [40], which are also prominent histological findings in advanced ADPKD [41]. Allopurinol prevented severe histological changes in this model [40].

Although the effect of elevated serum uric acid levels may in part be mediated by early onset of hypertension, as suggested by our mediation analysis, other potential mechanisms are the induction of endothelial dysfunction, inflammation and oxidative stress [14, 27, 28, 42]. These effects occur, at least in part, because uric acid stimulates the renin–angiotensin system and inhibits vascular nitric oxide synthesis [14, 19, 27, 28]. Oxidative stress leads to cell injury, up-regulation of proinflammatory cytokines, renal interstitial inflammation and fibrosis, which are all hallmarks of progressive parenchymal damage in ADPKD [41, 43]. Experimentally, in the rat model of unilateral ureteral obstruction, reducing serum uric acid levels by the administration of a xanthine oxidase inhibitor resulted in decreased oxidative stress, reduced interstitial macrophage infiltration, diminished transforming growth factor-β expression and improved renal histology [44]. Clinically, two randomized trials in patients with chronic kidney disease have shown that allopurinol use for 1–2 years slowed progression compared with the control group [45, 46].

Therapeutic measures in ADPKD are currently limited to controlling BP and treating complications including ESRD. However, many lines of investigation are targeting the growth of the cysts using antiproliferative agents [47–49], which have the potential for considerable long-term adverse side effects, as seen in the clinical trials with everolimus and sirolimus [50, 51]. Because treatment in ADPKD needs to start early, long before a fall in GFR is apparent [43], and needs to continue for a long time, medications with a low side effect profile are absolutely necessary. Allopurinol was well tolerated in the two randomized trials of patients with chronic kidney disease [45, 46]. Our study reported here suggests that hyperuricemia may play a role in the progression of ADPKD, and that it could be a therapeutic target with not only renal but also cardiovascular benefits.

In summary, in this observational study, we show that elevated uric acid levels are associated with an early onset of hypertension in men and women with ADPKD and with younger age at the onset of ESRD, independent from age and renal function at study visit, and independent from BMI and use of medications such as ACEI, ARB, diuretics and allopurinol. Part of the association with earlier onset of ESRD is mediated by early onset of hypertension. Elevated uric acid levels may be a marker of decreased renal blood flow in ADPKD, but may also directly contribute to progression by inducing endothelial dysfunction and oxidative stress. An interventional trial with a xanthine oxidase inhibitor is needed to determine whether treatment of hyperuricemia confers clinical benefits in ADPKD.

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Conflict of interest statement. None declared.

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