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Serum Uric Acid Levels and Endothelial Dysfunction in Patients with Autosomal Dominant Polycystic Kidney Disease

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Key Words
Uric acid · Endothelial dysfunction · Autosomal dominant polycystic kidney disease

Abstract
Background/Aims: Patients with autosomal dominant polycystic kidney disease (ADPKD) exhibit endothelial dysfunction (ED) despite normal levels of renal function. Hyperuricemia occurs in these patients and has been postulated to affect ED through the generation of oxidative stress. We therefore investigated the prevalence of ED and its association with serum uric acid levels in early-stage ADPKD. ***Methods:*** A cross-sectional design was used for the assessment of prevalent patients with early-stage (normal renal function) ADPKD (n = 91) from two academic medical centers. ED was assessed using ischemia-induced forearm flow-mediated vasodilation (FMD). Serum uric acid levels were evaluated using an Olympus AU2700 autoanalyzer. ***Results:*** ADPKD patients with higher serum uric acid levels had a higher asymmetric dimethylarginine (ADMA) level (1.19 ± 0.2 vs. 1.47 ± 0.3, $p < 0.001$) and lower FMD rates (8.1 ± 1.3 vs. 6.8 ± 0.7, $p < 0.001$). In multiple regression analysis for predictors of cohort FMD, uric acid ($\beta = -0.32$, $p < 0.001$), ADMA ($\beta = -0.36$, $p < 0.001$), high-sensitivity C reactive protein (CRP; $\beta = -0.32$, $p < 0.001$) and estimated glomerular filtration rate (eGFR; $\beta = 0.33$, $p < 0.001$) all predicted FMD. ***Conclusions:*** In early-stage ADPKD patients, uric acid levels, serum ADMA and eGFR all independently predict ED in a similar manner. Future studies are needed to investigate the causes of elevated serum uric acid, ADMA and CRP in these patients.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary systemic disorders associated with renal dysfunction, and is also a cause of cardiovascular, brain and liver abnormalities [1]. Cardiovascular disease is the major cause of mortality in patients with ADPKD [2]. Endothelial dysfunction (ED) is an early indicator of vascular injury and cardiovascular disease [3]. Therefore, it is of interest that patients with ADPKD often exhibit ED, usually attributed to defective endothelial nitric oxide (NO) synthesis [4].

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Recently, elevated serum uric acid levels have been strongly associated with ED [5, 6], putatively through an oxidative-mediated reduction in NO availability that may also contribute to endothelial inflammation [7, 8]. Furthermore, recent studies have demonstrated hyperuricemia to be a risk factor for later cardiovascular events [9, 10]. In ADPKD, hyperuricemia is common and occurs in early stages with normal renal function [11–13]. Although there are substantial data demonstrating increased ED, inflammation and oxidative stress in patients with ADPKD, the association between serum uric acid levels and ED has not been tested in these patients. Therefore, in this study, we aimed to investigate the relationship between serum uric acid levels and ED in normotensive ADPKD patients with preserved renal function.

Subjects and Methods

Study Population

Between February 2011 and November 2011, 145 ADPKD patients with normal renal function who were registered by the Kayseri Erciyes University School of Medicine and Ankara Gülhane School of Medicine in the Turkish Society of Nephrology Polycystic Kidney Disease Working Group Registry were evaluated for the study. The ethics committees and local hospital institutional review boards of both institutions approved the study. Together, these two academic medical centers serve 5,000,000 residents. All registered ADPKD patients from the two centers were evaluated using registry data, and eligible patients were requested to enroll in the study. All the participants signed written informed consent forms. Patients met the diagnosis for ADPKD according to Ravine et al. [14], so all of the patients' diagnoses were confirmed by a positive family history and the presence of 5 or more renal cysts on renal ultrasound, distributed to both kidneys. Demographic characteristics (e.g. gender, age, education status and smoking history), renal manifestations (e.g. hematuria, urinary system infection, urinary tract stones and renal replacement therapy) and cardiovascular manifestations (e.g. hypertension and mitral valve prolapse) were recorded on Web-based data collection forms. Because of the well-known association between reduced glomerular filtration rate (GFR) and ED, all patients with impaired kidney function as well as those with diagnosed cardiovascular disorders (coronary artery disease, coronary artery disease, peripheral artery disease and stroke) were excluded from the study. We also excluded patients with a previous diagnosis of hypertension, gout, diabetes, current use of oral antidiabetic medication, insulin, thiazides, allopurinol, uricosuric agents, statins or any antihypertensive medication, as well as those with a fasting glucose level ≥126 mg/dl. In addition, subjects with a history of smoking were excluded. All patients were also screened for hypertension using ambulatory blood pressure monitoring, and 8 patients newly diagnosed with possible hypertension on the basis of this screening were also excluded from the study. Finally, 91 ADPKD patients with normal renal function were enrolled (fig. 1).

The enrolled patients were reevaluated for biochemical and ED parameters as described below, and we also clinically examined the occurrences of urinary tract stones and infections. None of the enrolled patients showed any signs of either. The estimated GRF (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula: MDRD = 186 × serum creatinine (mg/dl) – 1.154 × age – 0.203. A correction factor of 0.742 was used for women [15].

Biochemical Measurements

Blood samples were taken from the vein of the antecubital fossa, with subjects in a seated position and following a 20-min rest after 12 h of fasting. Glucose, creatinine and lipid profiles were determined using standard methods. A complete blood count was performed on a Sysmex K-1000 (Block Scientific, USA) autoanalyzer within 30 min of sampling. High-sensitivity C-reactive protein (hs-CRP) was measured using a BN2 model nephelometer (Dade-Behring, Germany). The expected values for hs-CRP in our laboratory ranged from 0 to 3 mg/l.

Uric Acid

Serum uric acid levels were determined in all samples. All assays were performed in the central laboratory of the Gülhane Military Medical Academy Hospital and Erciyes University Gevher Nesibe Hospital with an Olympus AU2700 autoanalyzer using its own kits (Olympus Diagnostics, Hamburg, Germany). Hyperuricemia was defined as uric acid >6.0 mg/dl in women and >7.0 mg/dl in men [16, 17].

Asymmetric Dimethylarginine

Measurement of asymmetric dimethylarginine (ADMA) was accomplished by high-performance liquid chromatography using the method described by Chen et al. [18]. In brief, to 1 ml of serum, 20 mg of 5-sulfosalisilic acid was added and the mixture was left in an ice-bath for 10 min. The precipitated protein was removed by centrifugation at 2,000 *g* for 10 min. Ten microliters of the supernatant, which was filtered through a 0.2-μm filter, was mixed with 100 μl of derivatization reagent [prepared by dissolving 10 mg o-phthaldialdehyde in 0.5 ml of methanol, 2 ml of 0.4 M borate buffer (pH 10.0) and 30 μl of 2-mercaptoethanol] and injected into the chromatographic system. Separation of ADMA was performed on 150 × 4 mm internal diameter Nova-Pak C18 columns with a particle size of 5 μm (Waters, Millipore, Milford, Mass., USA) using 50 mM sodium acetate (pH 6.8), methanol and tetrahydrofuran as the mobile phase (A, 82:17:1; B, 22:77:1), and at a flow rate of 1.0 ml/min. Peak areas as detected by the fluorescent detector (Ex: 338 nm; Em: 425 nm) were used for quantification of the ADMA levels. The variability of the method was less than 7%, and the detection limit of the assay was 0.01 μM.

Endothelial Function Test

ED was assessed according to the method described by Celermajer et al. [19]. Measurements were made by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, Wash., USA) with a 12-MHz probe. The subjects remained at rest in the supine position for at least 15 min before the examination started. Each subject's right arm was comfortably immobilized in the extended position to allow consistent recording of the brachial artery 2–4 cm above the antecubital fossa. Three adjacent measurements of the end-diastolic brachial artery diameter were made from single 2D frames. All ultrasound images were recorded on Super Video Home System videotape for subsequent

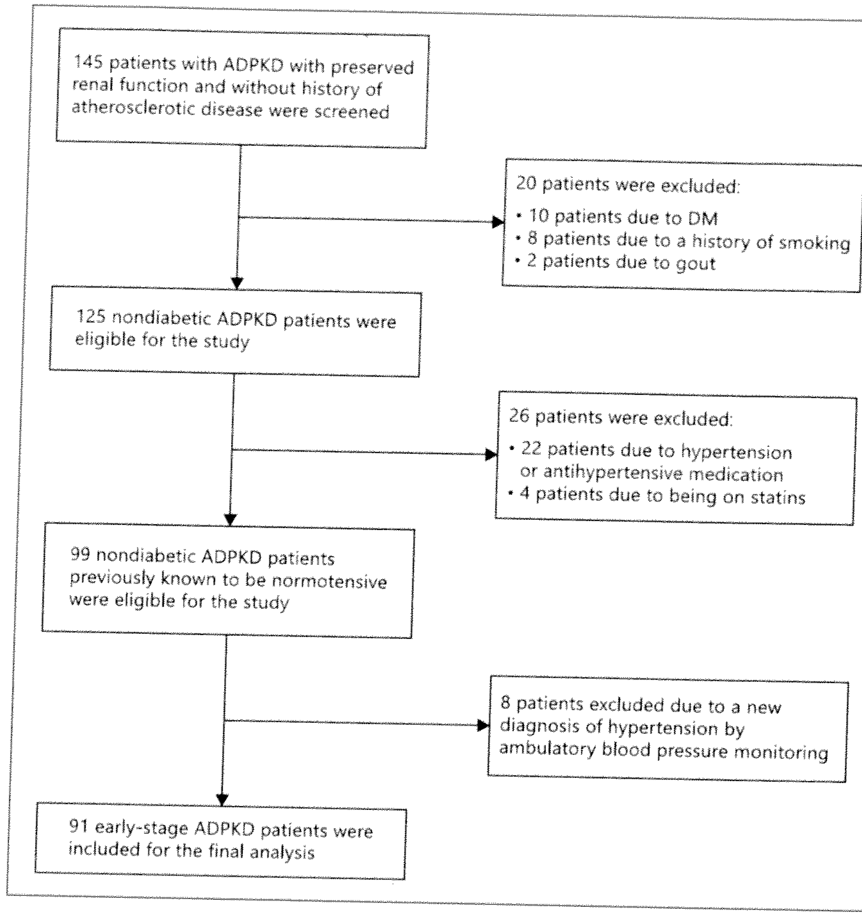

Fig. 1. Patient flow in the study. DM = Diabetes mellitus.

blinded analysis. The maximum flow-mediated vasodilation (FMD) diameters were calculated as the average of the three consecutive maximum diameter measurements after hyperemia and nitroglycerin, respectively. The FMD was then calculated as the percentage change in diameter compared with baseline resting diameters.

Ambulatory Blood Pressure Measurements

The 24-hour blood pressure monitoring was performed using a Del Mar Medical Pressurometer Model P6 (Del Mar Reynolds, Irvine, Calif., USA) and the results were assessed using the manufacturer's computer software. Ambulatory measurements were conducted once every 15 min from 7 a.m. to 11 p.m., and once every 30 min from 11 p.m. to 7 a.m. Evaluation was performed taking the mean values of day and night blood pressures into account. Hypertension was considered to be present if the systolic pressure was ≥140 mm Hg and/or diastolic pressure was ≥90 mm Hg, or if the individual was taking antihypertensive medication.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as means and SD or medians. We compared continuous variables using Student's t test. Categorical variables were summarized as percentages and compared with the χ^2 test. Pearson correlation coefficients were calculated to examine the degree of association between variables. $p < 0.05$ was considered significant. In multivariate analysis, variables for which the unadjusted univariate p value was <0.10 in linear regression analysis were included. We reduced the model by using backward elimination at a $p < 0.10$ stringency level for multivariate linear regression analysis and compared the remaining risk markers using likelihood ratio tests. Variables were significant at $p < 0.10$ in univariate analysis and included to each multiple model: model A = proteinuria, eGFR, uric acid, hs-CRP and ADMA; model B = ADMA, proteinuria, eGFR, uric acid and hs-CRP, and model C = proteinuria, eGFR, uric acid and hs-CRP. $p < 0.05$ was considered significant, and the confidence interval was set to 95%. All statistical analyses were performed using SPSS version 15 (SPSS Inc., Chicago, Ill., USA).

Results

Characteristics of Patients with High or Low Serum Uric Acid

The demographic, clinical and laboratory characteristics of the study population are shown in table 1. Hyper-

Table 1. Demographics and biochemical data of the patients with ADPKD categorized according to serum uric acid level

Parameters	Uric acid ≤7.0 for males and ≤6.0 for females (n = 22)	Uric acid >7.0 for males and >6.0 for females (n = 69)	p
Age, years	38.8±12.1	35.4±8.2	0.06
BMI, kg/m^2	27.1±3.4	26.7±2.6	0.58
Systolic blood pressure, mm Hg	126.3±8.7	126.8±11.9	0.84
Diastolic blood pressure, mm Hg	78.4±9.6	82.7±6.9	**0.02**
eGFR, ml/min/1.73 m^2	87.3±6.1	85.5±7.4	0.30
Proteinuria, mg/24 h	0.36 (0.06–1.4)	0.44 (0.02–1.53)	0.24
Glucose, mg/dl	86.4±15.3	86.3±13.7	0.98
hs-CRP, mg/dl	7.6±5.1	10.4±5.1	**0.02**
LDL cholesterol, mg/dl	117.8±30.9	119.4±32.6	0.83
FMD, %	8.1±1.3	6.8±0.7	**<0.001**
ADMA, μmol/l	1.19± 0.2	1.47±0.3	**<0.001**

Values are means ± SD or median (minimum–maximum), as appropriate. Bold values indicate significant differences between uric acid groups ($p < 0.05$).

Table 2. Univariate correlates for markers of ED in all 91 study participants

	Age, years		BMI, kg/m^2		LDL, mg/dl		hs-CRP, mg/dl		Proteinuria, mg/24 h		Uric acid, mg/dl		ADMA, μmol/l	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
SBP (mm Hg)	0.15	0.15	0.01	0.92	0.11	0.29	0.17	0.10	0.30	**0.003**	0.05	0.60	**0.19**	**0.006**
DBP (mm Hg)	−0.02	0.81	−0.02	0.82	0.01	0.90	**0.44**	**<0.001**	**0.29**	**0.006**	0.19	0.07	**0.30**	**0.003**
MAP (mm Hg)	0.07	0.49	0.03	0.74	0.11	0.30	**0.42**	**<0.001**	**0.34**	**0.001**	0.17	0.10	**0.32**	**0.002**
FMD (%-point)	−0.05	0.59	0.01	0.87	0.16	0.12	**−0.40**	**<0.001**	−0.14	0.18	**−0.50**	**<0.001**	**−0.63**	**<0.001**
ADMA (μmol/l)	−0.02	0.79	−0.06	0.57	0.001	0.98	**0.51**	**<0.001**	**0.33**	**0.001**	**0.42**	**<0.001**	–	–
Uric acid (mg/dl)	−0.18	0.07	0.05	0.62	−0.15	0.14	0.17	0.09	−0.001	0.85	–	–	**0.42**	**<0.001**

Bold values indicate significant value ($p < 0.05$). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

uricemia was defined as uric acid >6.0 mg/dl in women and >7.0 mg/dl in men. Compared with patients in the normouricemic group, subjects with hyperuricemia had higher diastolic blood pressure ($p = 0.02$), hs-CRP ($p = 0.02$) and serum ADMA levels ($p = 0.018$), but lower FMD ($p < 0.001$).The other parameters were similar between the groups.

Univariate Correlations with Endothelial Function Markers

Univariate correlations of measured markers of ED are shown in table 2. In the whole cohort, systolic blood pressure correlated with proteinuria and ADMA, but not with age, BMI, hs-CRP, LDL cholesterol or uric acid. Meanwhile, diastolic blood pressure correlated with hs-CRP and ADMA, but not with age, BMI, LDL cholesterol or uric acid. Mean arterial pressure (MAP) correlated with hs-CRP and ADMA, but not with age, BMI, LDL cholesterol or uric acid. FMD inversely correlated with hs-CRP ($r = -0.40$, $p < 0.001$), uric acid ($r = -0.50$, $p < 0.001$; fig. 2) and ADMA ($r = -0.63$, $p < 0.001$), but not with age, BMI or LDL cholesterol. ADMA correlated with hs-CRP, proteinuria and uric acid, but not with age, BMI or LDL cholesterol (fig. 3).

Multivariate Regression Analysis

As shown in table 3, we constructed several multivariate regression analysis models to assess the relative independence of observed correlations. Models were adjusted for uric acid, MAP, hs-CRP, ADMA and FMD. We used multivariate linear regression analysis with backward elimination and compared retained predictors using like-

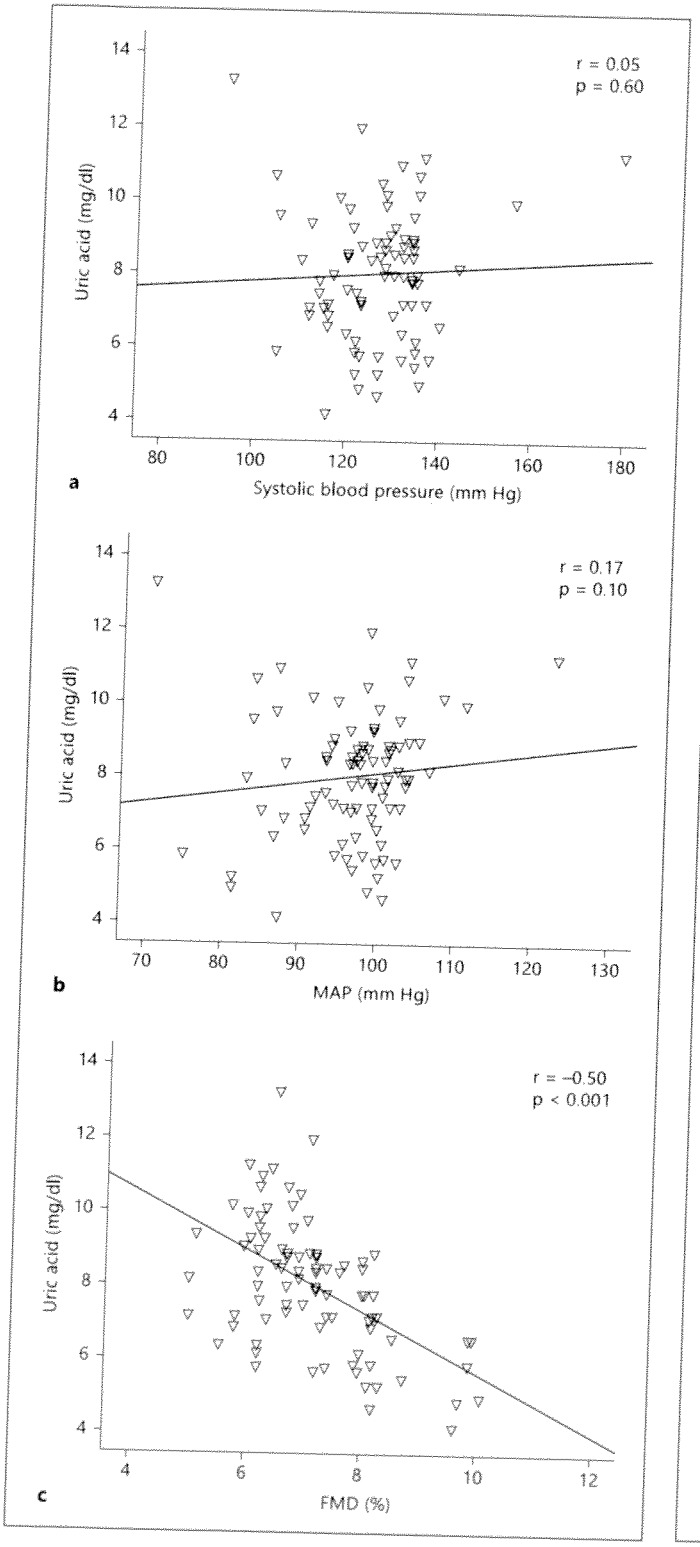

Fig. 2. Correlation between uric acid and systolic blood pressure (**a**), MAP (**b**) and FMD (**c**) in 91 patients with normotensive ADPKD and normal GFR.

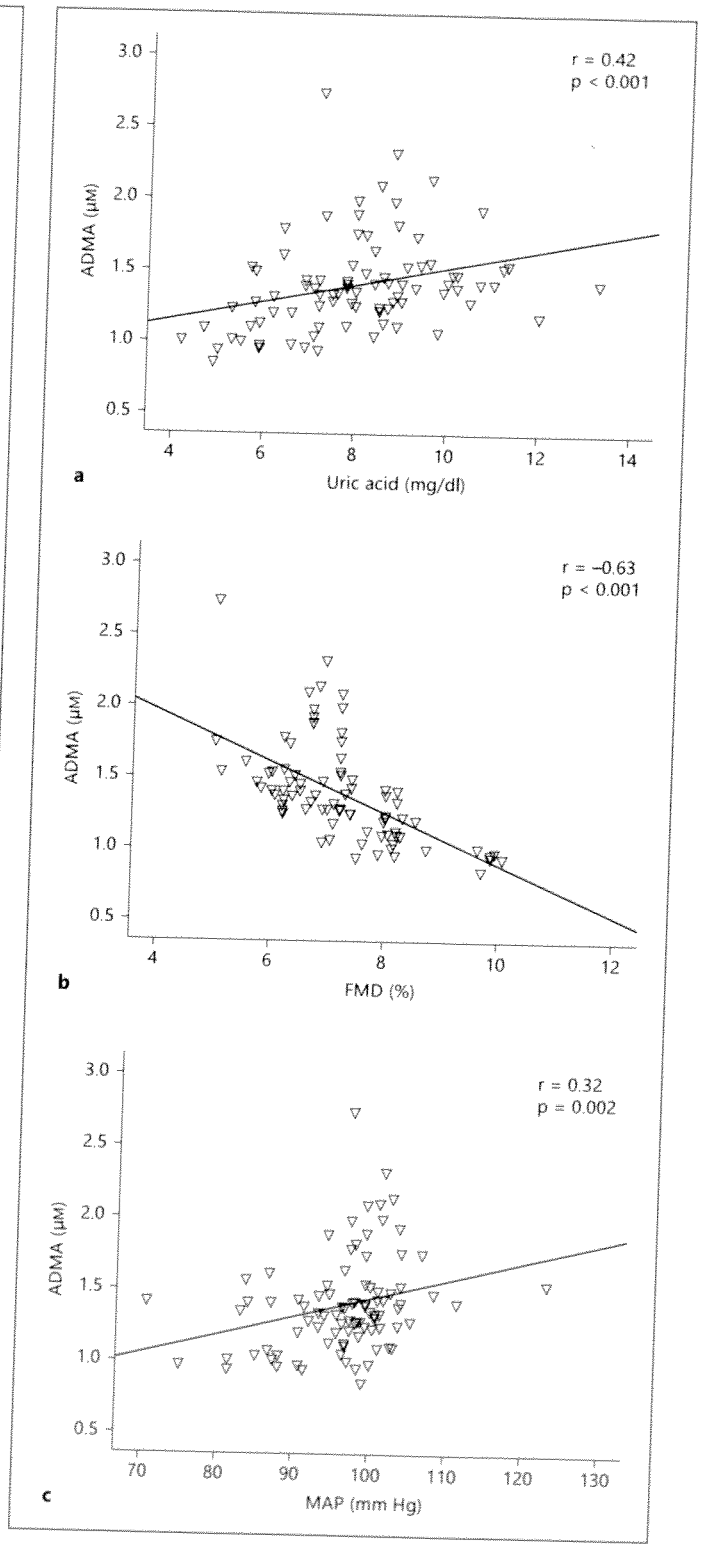

Fig. 3. Correlation between ADMA and uric acid (**a**), FMD (**b**) and MAP (**c**) in 91 patients with normotensive ADPKD and normal GFR.

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Table 3. Three multiple regression models using factors associated with the dependent variable in univariate analysis to predict MAP, FMD and ADMA in all study subjects (n = 91)

Variables	β	p
MAP (mm Hg; model adj. $r^2 = 0.19$)		
Intercept	87	0.001
Proteinuria	0.37	0.037
FMD (%; model adj. $r^2 = 0.59$)		
Intercept	6.2	<0.001
ADMA	−0.36	<0.001
Uric acid	−0.32	<0.001
eGFR	0.33	<0.001
hs-CRP	−0.32	<0.001
ADMA (μmol/l; model adj. $r^2 = 0.35$)		
Intercept	0.9	0.052
hs-CRP	0.30	0.004
Proteinuria	0.27	0.007
Uric acid	0.28	0.004

lihood ratio tests. MAP was only predicted by proteinuria. Meanwhile, FMD was predicted by uric acid ($\beta = -0.32$, $p < 0.001$), ADMA ($\beta = -0.36$, $p < 0.001$), hs-CRP ($\beta = -0.32$, $p < 0.001$) and eGFR ($\beta = 0.33$, $p < 0.001$). Finally, ADMA was predicted by hs-CRP ($\beta = -0.30$, $p = 0.004$), proteinuria ($\beta = 0.27$, $p = 0.007$) and uric acid ($\beta = 0.28$, $p = 0.004$).

Discussion

In a study of predictors of ED, a clinically important predictor of outcome measured by FMD, we report novel and independent associations with both serum uric acid and ADMA levels in normotensive ADPKD patients with preserved renal function. Indeed, we found that low FMD and increased serum ADMA levels could be detected already in early-stage ADPKD. Our study thus demonstrates that ED is linked to serum uric acid level in these patients, and hypothesizes that the uric acid level may be a clinically useful marker of future cardiovascular outcome.

In this study, we for the first time investigated the predictive value of serum uric acid levels, a potential marker of inflammation and ED in patients with early-stage ADPKD. In multivariate analysis, we found that both CRP, an indicator of inflammation, and serum uric acid levels were independent predictors of FMD. FMD was utilized as a marker of endothelial function, as it had been validated and used in multiple studies of CKD vasculature [20, 21]. Thus, numerous studies have demonstrated an inverse relationship between uric acid and ED [5, 6, 12, 22]. However, our study adds to these results by demonstrating that increased uric acid levels correlate closely with a reduction in FMD and an increase in ADMA levels in patients with early-stage ADPKD.

In the general population, serum uric acid is an important risk marker of cardiovascular disease [23]. Recent studies suggest that high levels of serum uric acid are a clinically useful marker of ED in subjects with normal renal function [24]. Meanwhile, ED is an established early manifestation of vascular damage in CKD, and predates hypertension and cardiovascular disease [25, 26]. Recent clinical studies have thus focused on the underlying mechanism for the association between uric acid and ED. Indeed, Khosla et al. [5] demonstrated that uric acid itself impairs NO synthesis in cultured endothelial cells, suggesting that serum uric acid levels could directly reflect xanthine oxidase generation of oxidant species, putatively an important cause of ED [27]. On the other hand, uric acid is also known to be a scavenger of oxidative radicals, but multiple studies suggest that it gains pro-oxidative properties when entering cells and thus directly contributes to ED [5, 28–32].

Clinically, asymptomatic hyperuricemia is commonly encountered and treatment is not usually recommended [33]. However, Kanbay et al. [34] have demonstrated that treatment of subjects with asymptomatic hyperuricemia can improve ED. Additionally, several studies and meta-analyses have demonstrated that increased uric acid levels are associated with a wide variety of vascular diseases, including hypertension, stroke, diabetes and heart failure [35–37]. These findings may be important as hyperuricemia is common in the high-risk ADPKD population [11, 12]. In the present study, we demonstrate for the first time that serum uric acid levels relate to ED even in the absence of renal dysfunction. Our data also reinforces our earlier observation that ADMA, a potent NO synthase inhibitor, is a useful marker of ED, reflecting decreased NO activity [38]. Indeed, ADMA is now widely accepted as an independent predictor of ED as well as FMD [39].

The main causes of mortality and morbidity in patients with ADPKD is due to cardiovascular problems [2, 40]. Early vascular changes have been reported in patients with ADPKD with normal blood pressure [40]. Wang et al. [4, 41] demonstrated that endothelium-dependent relaxation is impaired and endothelial NO synthase activity is diminished in patients with early-stage ADPKD. In keeping with these studies, ED due to impaired release of NO appears to be highly prevalent in these patients [42].

Several studies have reported that ED is one of the major determinants of cardiovascular events in ADPKD [43, 44]. Moreover, Zoccali et al. [45] reported that ADMA is a strong, independent predictor of cardiovascular outcomes and overall mortality in dialysis patients. More recently, it has been suggested that oxidative stress contributes to cardiovascular disease in early-stage ADPKD and that the levels of pro-oxidants is correlated to circulating levels of ADMA [46]. Kocaman et al. [47] demonstrated ED in normotensive ADPKD patients with well-preserved renal function and suggested that atherosclerosis starts in the early stages of the disease. Nevertheless, our study is the first to examine the relationship between uric acid and ED in early-stage ADPKD patients, and we demonstrated that hyperuricemia is associated with ED in patients with early-stage ADPKD.

The possible limitations of our study are (1) including only patients with ADPKD without any form of other kidney diseases, (2) the small number of patients and (3) the limited availability of markers of oxidative stress. However, our population contained homogenous early-stage ADPKD patients whose renal function was preserved and who did not have hypertension, thus mirroring the clinical reality. Additionally, the oxidant-antioxidant balance was likely reliably reflected by ADMA. Because it has been reported that prediction formulas unreliably estimate actual GFR values and fail to detect their changes over time in ADPKD, another possible limitation of this study is the method that used eGFR instead of direct kidney measurements [48].

In conclusion, ours is the first study to evaluate the relationship between uric acid and ED in patients with early-stage ADPKD. We demonstrated that increased uric acid levels in early-stage ADPKD patients is a risk factor for ED, possibly leading to cardiovascular diseases, a major killer of CKD patients, thus suggesting that early treatment or preventive measures for hyperuricemia may be considered.

Acknowledgements

This study is registered under the name 'The Relation between Uric Acid Level and Endothelial Dysfunction in Patients with Polycystic Kidney Disease' on ClinicalTrials.gov, with identifier No. NCT01589705.

Disclosure Statement

The authors declare no conflict of interest. No funding has been received for this study.

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