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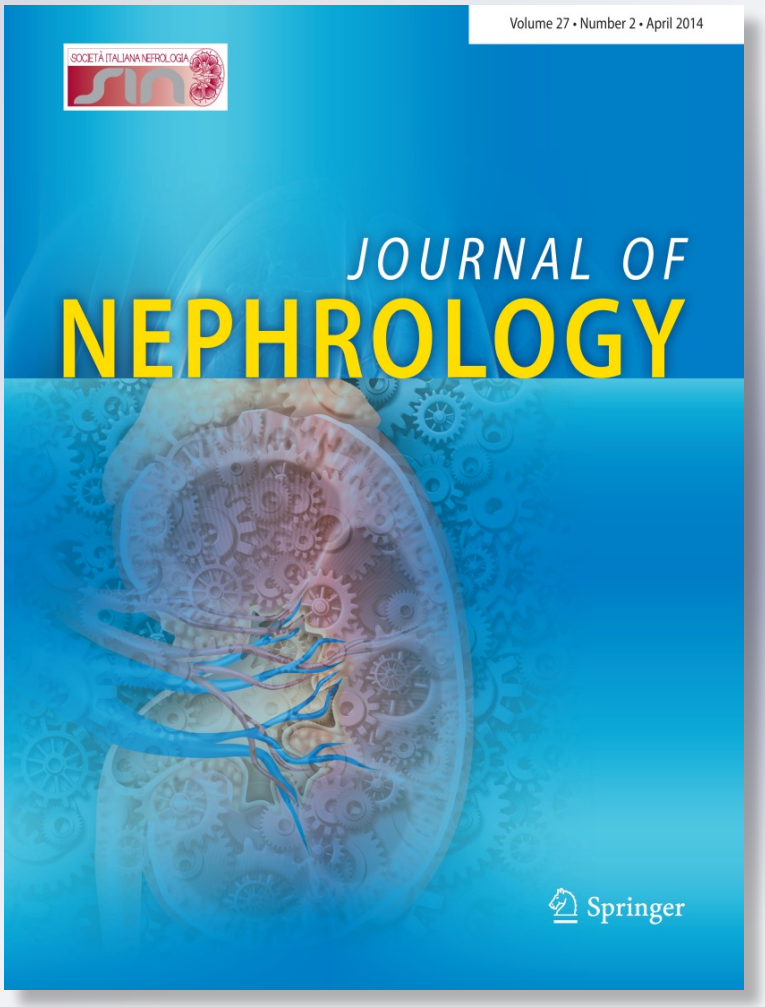

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ORIGINAL ARTICLE

Pentraxin 3 as a novel bio-marker of inflammation and endothelial dysfunction in autosomal dominant polycystic kidney disease

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Abstract
Background/Aims Cardiovascular disease (CVD) is the main cause of mortality in patients with autosomal dominant polycystic kidney disease (ADPKD). Prior to hypertension early vascular changes and inflammation have been reported. We aimed to investigate long pentraxin 3 (PTX-3), which has been recently described as a biomarker of inflammation, and its relation with endothelial dysfunction in early ADPKD patients.
Methods Twenty-five ADPKD patients without hypertension and 25 healthy controls were studied cross-sectionally. Hypertension was diagnosed with ambulatory blood pressure monitoring. Plasma concentrations of PTX-3 and proteinuria levels were obtained from each participant. Endothelial dysfunction was assessed using ischemia-induced forearm flow-mediated vasodilation (FMD).
Results PTX-3 levels were higher in ADPKD patients compared to healthy controls (4.2 [1.2–10.1] vs. 1.4 [0.4–3.1] ng/ml, $p < 0.001$). Additionally, C-reactive protein (CRP) and proteinuria levels were higher in ADPKD patients than in healthy subjects. In the whole cohort, PTX-3 correlated negatively with FMD (r: −0.58, $p < 0.001$) and positively with proteinuria (r: 0.56, $p < 0.001$) and uric acid (r: 0.57, $p < 0.001$). In all subjects, FMD was independently predicted by PTX-3, but not by uric acid, CRP or proteinuria.
Conclusion PTX-3 may be a better biomarker of inflammation than CRP to predict endothelial dysfunction in normotensive ADPKD patients with well-preserved kidney function. Hence, inflammation which is demonstrated by PTX-3 may potentially be used to predict future CVD in this population.

Keywords Polycystic kidney disease · Pentraxin-3 · Endothelial dysfunction

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystemic and progressive disorder that is characterized by renal and extrarenal manifestations such as cardiovascular, liver and brain abnormalities, and it is also the most common hereditary cause of chronic kidney disease (CKD) [1, 2]. Early occurrence of hypertension prior to loss of kidney function is the prominent feature of ADPKD, unlike other renal diseases, and cardiovascular disease (CVD), which is markedly associated with

hypertension, represents the major cause of death in this population [3, 4]. Endothelial dysfunction (ED) is an early determinant of vascular injury and cardiovascular disease [5] and is present in early ADPKD patients since endothelium-dependent relaxation is impaired and endothelial nitric oxide synthase activity is decreased [6, 7]. Moreover, a link between inflammation and oxidative stress has been observed in APDKD patients with preserved kidney function [8]. More recently, early vascular changes and inflammation have been reported in early ADPKD patients suggesting that atherosclerosis and inflammation start within the early decades and may contribute to increased CVD risk [9, 10].

Long pentraxin 3 (PTX-3) is a recently established multimeric inflammatory mediator that shares a structural homology with hepatic short pentraxins such as C-reactive protein (CRP) and serum amyloid P component, while PTX-3 is derived from several cell types, including vascular endothelial cells and macrophages especially in response to injury and stress [11–13]. PTX-3 is produced at sites of inflammation, is closely linked to ED and is thought to show disease activity better than CRP which is only derived from the liver in contrast to PTX-3 [14]. Indeed, elevated levels of PTX-3 predicted CVD risk in CKD populations independently of traditional risk factors and CRP levels [15]. Moreover, strong relations have been observed between PTX-3 and markers of ED such as soluble vascular adhesion molecule-1, fibrinogen and flow-mediated dilation (FMD) [16, 17].

However, the putative role of inflammation and ED in the development of hypertension and CVD risk has not been well studied in ADPKD patients. Our previous studies have shown that increased CRP levels are associated with ED in normotensive ADPKD patients prior to loss of kidney function [10, 18]. These findings led us to hypothesize that PTX-3 may be linked to ED and, ultimately, cardiovascular outcomes in ADPKD. We tested this hypothesis in a cohort of normotensive ADPKD patients with normal renal function and compared them with healthy subjects in whom measurements of flow-mediated dilation (FMD)—an estimate of endothelium-derived nitric oxide synthesis—as a marker of ED had been performed.

Subjects and methods

Study population

Between February 2011 and June 2013, 90 ADPKD patients with normal renal function who were registered through the Erciyes University School of Medicine in the Turkish Society of Nephrology Polycystic Kidney Disease Working Group Registry were evaluated for the study. The study was approved by the university ethics committee. All of the participants were included after signing written informed consent. 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 were excluded from the study. We also excluded patients with a previous diagnosis of hypertension or newly diagnosed hypertension through ambulatory blood pressure monitoring. Finally, 25 ADPKD patients with normal renal function were enrolled.

The enrolled patients were reevaluated for biochemical and ED parameters as described below. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula: $\text{MDRD} = 186 \times (\text{serum creatinine (mg/dl)}) - 1.154 \times \text{age} - 0.203$. A correction factor of 0.742 was used for women [19].

Biochemical measurements

Blood samples were taken from the vein of the antecubital fossa, with subjects in a seated position and after a 20 min rest following 12 h of fasting. Glucose, creatinine, and lipid profile were determined using standard methods. CRP was measured using a BN2 model nephelometer (Dade-Behring, Marburg, Germany).

Plasma PTX-3 measurements

Plasma PTX-3 specimens from both patients and healthy controls were stored at −80 °C until the termination of the study. Afterwards, *PTX-3* levels were measured by a commercially available kit based on the quantitative sandwich enzyme immunoassay technique (R&D Systems, Human Pentraxin 3/TSG-14 Immunoassay kit, Catalog Number: DPTX3 Minneapolis, MN, USA).

Endothelial function test

Endothelial dysfunction was assessed according to the method described by Celermajer et al. [20]. Measurements were made by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories Inc., Bothell, WA, 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 end-diastolic brachial artery diameter were made from single 2D frames. All ultrasound images were recorded on a super video home system (S-VHS) videotape for subsequent blinded analysis. 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 Ressurometer Model P6 (Del Mar Reynolds, Irvine, CA, USA) and the results were assessed using the manufacturer's computer software. Ambulatory measurements were conducted once every 15 min from 7 am until 11 pm, and once every 30 min from 11 pm until 7 am. Evaluation was performed taking the mean values of day and night blood pressures into account. Hypertension was considered to be present if the average systolic pressure was $\geq$130 mmHg and/or average diastolic pressure was $\geq$80 mmHg for the whole day, or if the individual took antihypertensive medication.

Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. For continuous variables, results are presented as mean value ± standard deviation (SD) for parametric variables (normal data distribution) or median (minimum, maximum) for non-parametric variables (not a normal data distribution) .The differences between the two groups were evaluated with Student's t-test (normal distribution) or the Mann–Whitney U test (non normal distribution).

Pearson correlation coefficients were calculated to examine the degree of association between variables. A p value <0.05 was considered as significant. Variables for which the unadjusted univariate p value was <0.10 in linear regression analysis were included in the multivariate analysis. We reduced the model by using backward elimination at $p < 0.10$ stringency level in multivariate linear regression analysis. A p value <0.05 was considered as significant, and the confidence interval (CI) was set to 95 %. All statistical analyses were performed using the statistical package SPSS version 15 (SPSS, Inc., Chicago, IL, USA).

Results

The demographic, clinical, and laboratory characteristics of the study population are shown in Table 1. There were no significant differences between the two groups in terms of

Table 1 Clinical and echocardiographic features of ADPKD patients and healthy controls

	APKD patients (n = 25)	Healthy subjects (n = 25)	p
Clinical parameters			
Age, years	35.2 ± 7.3	36.6 ± 8.8	0.75
Gender, F/M	18/11	16/14	0.40
Total cholesterol, mg/dl	182 ± 35	184 ± 33	0.86
Plasma triglycerides, mg/dl	127 ± 64	137 ± 74	0.57
HDL-cholesterol, mg/dl	42 ± 10	46 ± 8	0.10
LDL-cholesterol, mg/dl	114 ± 30	119 ± 36	0.30
CRP, mg/l	3.9 ± 0.9	2.5 ± 0.6	**0.003**
Proteinuria, g/day	0.37 (0.09–1.19)	0.12 (0.07–0.6)	**<0.001**
eGFR, ml/min per 1.73 m^2	101 ± 10	107 ± 9	0.07
FMD, %	6.8 ± 1.0	7.7 ± 1.3	**0.003**
Uric acid, mg/dl	4.7 ± 1.0	4.1 ± 1.1	0.05
PTX3, ng/ml	4.2 (1.2–10.1)	1.4 (0.4–3.1)	**<0.001**
Echocardiographic parameters			
Left ventricular end-systolic diameter, mm	29.1 ± 3.2	30.8 ± 4.3	0.09
Left ventricular end-diastolic diameter, mm	46.4 ± 3.2	46.9 ± 4.7	0.63
Inter ventricular septum diameter, mm	9.2 ± 1.5	9.3 ± 1.0	0.63
Left ventricular posterior wall diameter, mm	8.7 ± 1.2	9.0 ± 1.2	0.30
Left ventricular ejection fraction, %	65.6 ± 5.6	64.1 ± 5.0	0.28
IMT, mm	0.53 (0.45–0.83)	0.49 (0.33–0.64)	0.52

Data are mean ± SD for parametric data, median for non parametric data (minimum, maximum), or frequency counts, as appropriate

ADPKD autosomal-dominant polycystic kidney disease, *eGFR* estimated glomerular filtration rate, *F/M* female/male, *FMD* flow mediated dilatation, *HDL* high-density lipoprotein, *CRP* high-sensitivity C-reactive protein, *IMT* intima media thickness, *LDL* low-density lipoprotein, *PTX3* pentraxin 3

Bold values indicate the significant values ($p < 0.05$)

Table 2 Data from ambulatory blood pressure measurements of the study subjects

Parameters	APKD patients (n = 25)	Healthy subjects (n = 25)	p
Average 24-h systolic BP, mmHg	114 ± 9	111 ± 6	0.26
Average daytime systolic BP, mmHg	120 ± 11	118 ± 7	0.51
Average nighttime systolic BP, mmHg	108 ± 9	104 ± 6	0.14
Average 24-h diastolic BP, mmHg	74 ± 5	71 ± 4	0.07
Average daytime diastolic BP, mmHg	79 ± 6	76 ± 5	0.10
Average nighttime diastolic BP, mmHg	69 ± 4	66 ± 4	0.07
Average 24-h mean BP, mmHg	87 ± 6	85 ± 4	0.10
Average daytime mean BP, mmHg	93 ± 6	90 ± 5	0.17
Average nighttime mean BP, mmHg	81 ± 5	79 ± 4	0.07

Data are expressed as mean ± SD

ADPKD autosomal-dominant polycystic kidney disease, *BP* blood pressure

baseline and echocardiographic parameters. However, PTX-3 levels were higher in ADPKD patients than healthy controls (4.2 ng/ml [1.2–10.1] vs. 1.4 ng/ml [0.4–3.1], $p < 0.001$). In addition, CRP and proteinuria levels were higher in ADPKD patients than in healthy subjects (3.9 ± 0.9 vs. 2.5 ± 0.6 mg/l, $p = 0.003$) and (0.37 g/day [0.09–1.19] vs. 0.12 g/day [0.07–0.6], $p < 0.001$), respectively. Additionally 24-h ambulatory blood pressure monitoring confirmed the status of all study participants (Table 2).

The univariate correlations of selected markers in all 50 study participants are listed in Fig. 1. In the whole cohort, PTX-3 correlated with FMD (r: −0.58, $p < 0.001$), proteinuria (r: 0.56, $p < 0.001$) and uric acid (r: 0.57, $p < 0.001$) (Fig. 1).

The independence of multiple correlations was analyzed with multivariate linear regression analyses. The original model included eGFR, proteinuria, uric acid, PTX3 and high-sensitivity (hs)-CRP. In all subjects, FMD was independently predicted by PTX-3 (β −0.32, $p = 0.01$), but not by uric acid, CRP or proteinuria (Table 3).

Discussion

The present study proposes two major findings in normotensive ADPKD patients with preserved kidney function. First, both PTX-3 and FMD levels are significantly increased in ADPKD patients compared with matched healthy subjects. Secondly, only PTX-3 levels independently correlated with ED as shown by ultrasonographically measured FMD in ADPKD patients. Whereas CRP is known to be a major inflammatory marker, our study suggests a link between inflammation, which is drastically demonstrated by PTX-3 but not by CRP, and ED in normotensive ADPKD patients without renal dysfunction.

PTX-3 was recently described as an early marker of innate immunity and inflammatory responses which is structurally linked to short pentraxins including CRP [11, 13] and is highly expressed in atherosclerotic lesions and in patients with chronic kidney disease [14, 16]. While CRP is derived only from hepatocytes, PTX-3 seems to be synthesized by several tissues and cells, including fat tissue, vascular endothelial cells and macrophages [12, 15–17]. While CRP has been shown to be a well-established risk factor for CVD [21] in epidemiologic studies of both the general population and CKD patients [22], it does not seem to be causally linked to vascular damage [23]. Therefore, it is thought that PTX-3 reflects changes in local vascular health better than CRP does. Indeed, increased PTX-3 levels have been shown in a variety of atherosclerotic diseases and independently associated with morbidity and mortality in patients with CKD, heart failure, and stroke [24–27]. More recently it has been shown that ED, a predictor of cardiovascular mortality, was correlated with PTX-3 in patients with CKD [17, 24]. Although it has been recently reported that ED is common in ADPKD [7, 9, 10, 18], the putative role of PTX-3 has not been tested yet in this population.

We therefore aimed to investigate PTX-3 and ED in a cohort of early ADPKD patients and compare them with healthy controls. Thus we excluded other conditions that potentially affect PTX-3 levels and ED such as infection, hypertension and chronic kidney failure. Our study demonstrated that both CRP and PTX-3 levels increase in ADPKD; however in our stepwise multiple regression models, only PTX-3 was associated with FMD.

Cardiovascular events are the main cause of mortality in patients with ADPKD [1, 2]. However, hypertension is more common and also associated with CVD in ADPKD. Early vascular changes have been recently reported in ADPKD patients prior to hypertension and loss of kidney function, meaning that other pathophysiological pathways may also be involved [3, 4, 9]. Wang et al. [6] demonstrated that endothelium-dependent relaxation is impaired and endothelial nitric oxide synthase activity is diminished in normotensive ADPKD patients before the deterioration of renal function. In keeping with this study, endothelial dysfunction due to impaired release of nitric oxide has been shown in these patients [7]. On the other hand, Menon et al. [8] showed a link between inflammation and oxidative stress in both normotensive and hypertensive ADPKD patients. Also, ED precedes future cardiovascular events

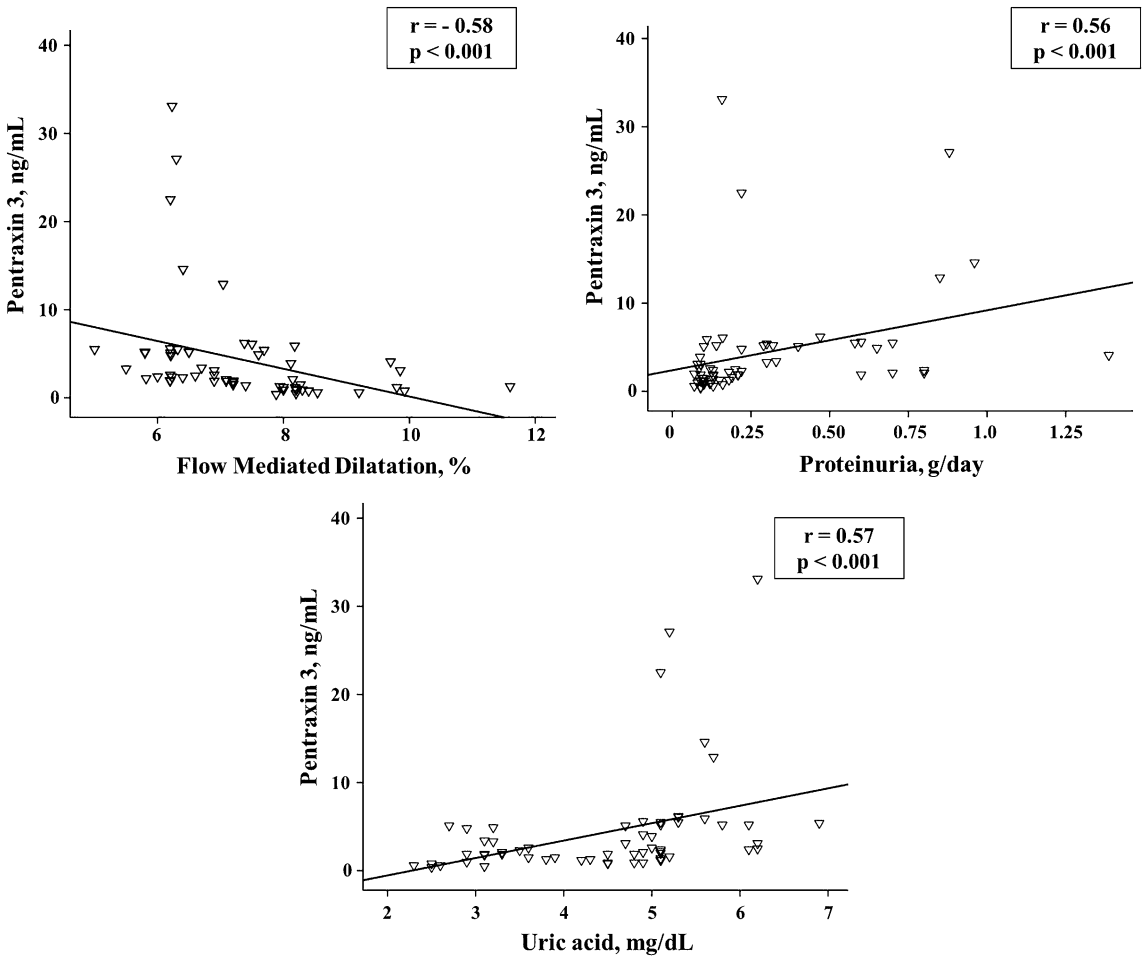

Fig. 1 Univariate correlations of FMD with uric acid, proteinuria and PTX-3

Table 3 Multivariate linear regression analysis for FMD in all study subjects

Parameters	FMD, %	
	Beta	p
Intercept	7.62	**<0.001**
CRP	−0.24	0.09
PTX3	**−0.32**	**0.01**
Proteinuria	−0.05	0.67
Uric acid	−0.04	0.73

The original model included eGFR, UPro/UCre, uric acid, PTX3 and CRP

Bold values indicate the significant values ($p < 0.05$)

FMD flow mediated dilatation, *CRP* high-sensitivity C-reactive protein, *PTX3* pentraxin, *UPro/UCre* urinary protein:creatinine ratio

Adjusted $r^2 = 0.19$

and ultrasonographically measured FMD is a widely accepted method for screening ED [5, 28]. In this regard, we recently demonstrated the relationship between inflammation and ED in normotensive ADPKD patients with preserved renal function and suggested that a common pathophysiological mechanism might be present likewise in atherosclerotic diseases [10, 18]. While previous studies in ADPKD have used CRP or interleukin (IL)-6, we tested the role of PTX-3 as a potentially better marker of inflammation in our early ADPKD patients to predict FMD. Our observational study demonstrates for the first time that increased levels of PTX-3 are associated with ED in a normotensive ADPKD population, even when GFR seems to be normal.

Possible limitations of this study warrant consideration when evaluating the relevance of our findings. First, we should mention the small sample size, design and the cross-sectional nature of this analysis. However, our population contained homogenous ADPKD patients whose renal function was preserved and who did not have hypertension, therefore mirroring the real world scenario. Second, we could not measure PTX-3 levels in the urine. Indeed, to the best of our knowledge, there is no current information about renal PTX-3 elimination in both ADPKD patients and healthy controls. Also renal function was similar in the two groups and this may minimize this limitation.

In conclusion, our study suggests that PTX-3 could be a better potential biomarker of inflammation than CRP to predict ED in normotensive ADPKD patients with well-preserved kidney function. Therefore, inflammation which is demonstrated by PTX-3 may possibly predict future CVD in this population. Further prospective studies are needed to clarify the role of PTX-3 as an alternative to CRP in future atherosclerotic complications in ADPKD.

Conflict of interest The authors declare that they have no conflicts of interest.

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