Arterial Dysfunction in Early Autosomal Dominant Polycystic Kidney Disease Independent of Fibroblast Growth Factor 23

Abdulmecit Yildiz,[1] Cuma Bulent Gul,[2] Alparslan Ersoy,[2] Burak Asiltas,[3] Selime Ermurat,[4] Selda Dogan,[5] Kemal Karaağaç,[6] Saim Sag, Aysegul Oruc,[2] Nimet Aktas,[2] Gokhan Ocakoglu,[7] Ibrahim Dogan,[8] Sumeyye Gullulu,[5] Mustafa Gullulu[2]

[1]Department of Nephrology, Cekirge State Hospital, Osmangazi, Bursa, Turkey
[2]Department of Nephrology, Uludag University Medical School, Gorukle, Bursa, Turkey
[3]Department of Biochemistry, Uludag University Medical School, Gorukle, Bursa, Turkey
[4]Department of Internal Medicine, Uludag University Medical School, Gorukle, Bursa, Turkey
[5]Department of Cardiology, Uludag University Medical School, Gorukle, Bursa, Turkey
[6]Department of Cardiology Bursa Ihtisas Training and Research Hospital, Bursa, Turkey
[7]Department of Biostatistics, Uludag University Medical School, Gorukle, Bursa, Turkey
[8]Sevket Yilmaz Research and Training Hospital, Yildirim, Bursa, Turkey

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Introduction. Recent studies report reduced vascular compliance and elevated levels of fibroblast growth factor 23 (FGF23) in patients with autosomal dominant polycystic kidney disease (ADPKD) and preserved kidney function. In the present study, we investigated the relationship between vascular compliance and FGF23 in patients in early phases of ADPKD.

Materials and Methods. We studied 54 ADPKD patients with preserved kidney function and 24 healthy individuals. All participants underwent noninvasive pulse wave analysis in order to determine large arterial elasticity index (LAEI) and small arterial elasticity index (SAEI) using a modified Windkessel model. Levels of FGF23 in addition to several cardiovascular risk factors were evaluated. Linear regression analyses were performed to determine independent correlates of LAEI, SAEI, and FGF23.

Results. In the ADPKD group, 33 patients were hypertensive and the remaining patients were normotensive. Serum FGF23 levels of both ADPKD groups were significantly higher than that in the controls. Both hypertensive and normotensive ADPKD patients had lower LAEI and SAEI levels compared to the controls. There was no significant correlation between vascular compliance parameters and FGF23 levels. Having ADPKD was independently associated with increased FGF23 levels and decreased SAEI.

Conclusions. Fibroblast growth factor 23 was found substantially elevated and arterial compliance was found significantly decreased in early ADPKD patients regardless of hypertension. However, there was no significant correlation between FGF23 levels and arterial function parameters. Additional studies are required to determine possible mechanisms of these disturbances and cardiovascular effects of FGF23 in ADPKD patients.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common life-threatening genetic disease.[1] Cardiovascular disease is a leading cause of morbidity and mortality in patients with ADPKD, with over 80% of deaths attributable to coronary artery disease.[2-4] Systemic vascular dysfunction has been shown in ADPKD patients with preserved kidney function with various methods including applanation tonometry.[5,6]

Fibroblast growth factor 23 (FGF23) is secreted by osteoblasts and osteocytes. Fibroblast growth factor 23 induces phosphaturia by decreasing proximal tubular phosphorus reabsorption, which inhibits renal 1α-hydroxylase and secretion of parathyroid hormone. Fibroblast growth factor 23 increases in response to increase in serum phosphorus levels in patients with chronic kidney disease (CKD). Basically, FGF23 exerts its effects on renal and parathyroid tissue in association with klotho, while its action in cardiomyocytes is independent of klotho.

Increased FGF23 levels have been shown to induce cardiovascular abnormalities like left ventricular hypertrophy and arterial stiffness.[7,8] Markedly elevated circulating FGF23 levels are also found in patients with ADPKD compared with other causes of CKD independent of kidney function and hormones that regulate phosphate metabolism.[9] To our knowledge there is no study investigating the association of increased FGF23 levels with arterial dysfunction in early ADPKD. We aimed to assess arterial function in normotensive and hypertensive ADPKD patients with normal kidney function and seek its association with FGF23 levels.

MATERIALS AND METHODS

Participants

Fifty-four patients with ADPKD (17 men and 37 women) and 26 healthy control subjects (13 men and 13 women) were enrolled. The diagnosis of ADPKD was made by the ultrasonographic criteria described by Pei and Watnick.[10] All of the patients had a family history of ADPKD. Estimated glomerular filtration rate (GFR) was determined using the 4-variable Modification of Diet in Renal Disease equation.[11] Patients with diabetes mellitus, kidney dysfunction (estimated GFR, < 60 mL/min/1.73 m^2), hepatic failure, and major cardiac diseases (heart failure, coronary artery disease, arrhythmia, and cardiac valvular disease) were excluded from the study. The study was approved by hospital's Ethics Committee and patients gave their written informed consent.

During the baseline examination, fasting weight and height were measured by one examiner using the ambulatory standard measurement devices, while the patient was standing. Body mass index (BMI) was calculated using the formula of weight divided by height squared. Clinical blood pressure measurements were performed using a mercury sphygmomanometer following 10 minutes rest in the sitting position. Three consecutive readings were obtained using 2-minute interval settings and the mean of these readings were considered as clinical blood pressure. Participants with systolic blood pressure of 140 mm Hg and higher or diastolic blood pressure of 90 mm Hg and higher or those who were already receiving treatment for hypertension were considered to be hypertensive.

Blood Analyses

Fasting blood glucose, creatinine, total cholesterol, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and triglyceride levels in blood samples were measured by routine techniques. Parathyroid hormone levels were measured by chemiluminescence method on an Immulite 2000 analyzer (Diagnostic Products Corporation, Los Angeles, USA). Serum levels of 25-hydroxyvitamin D levels were measured by high-performance liquid chromatography (Thermo-Finnigan, Waltham, USA) using Vitamin D3 Clin Rep HPLC kits (RECIPE Chemicals + Instruments GmbH, Munich, Germany). Plasma FGF23 concentrations were measured with the human FGF23 (C-Term) enzyme-linked immunosorbent assay kit (Immutopics Inc, San Clemente, CA, USA) according to the manufacturer's instructions.

Measurements of Arterial Stiffness

Arterial stiffness was measured in the morning with the patient in the supine position after 15 minutes of bed rest in a quiet room, following 12-hour abstinence from smoking, alcohol, and coffee consumption. One trained observer performed all the measurements. All subjects underwent pulse wave analysis (HDI/Pulse Wave model CR-2000) to determine large arterial elasticity index (LAEI) and small arterial elasticity index (SAEI). The LAEI and SAEI vessel compliances of the radial artery were determined from an internal algorithm based on diastolic decay features of the calibrated radial pulse contour using a modified Windkessel model.[14]

Statistical Analyses

Statistical analysis was performed using the SPSS

software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). Normal distribution of the data was checked using the Kolmogorov-Smirnov test. Continuous variables are presented as means ± standard deviations and categorical variables are presented as percentages. The differences between the groups for categorical variables were compared by the chi-square test. According to the distribution, the differences between two groups for continuous parameters were compared by the Student *t* test or the Mann-Whitney U test. Normotensive and hypertensive ADPKD patients were compared with each other and also separately with the control group. Comparisons of more than two groups were performed using the 1-way analysis of variance or the Kruskal Wallis test as needed. The correlations among the study variables were examined by the Pearson or the Spearman correlation test according to the distribution of the variable. Independent correlates of arterial function indexes were defined using backward linear regression analysis. The parameters included in this regression analysis were ADPKD, hypertension, sex, age, BMI, family history of coronary artery disease, smoking, glucose, HDLC, LDLC, FGF23, 25-hydroxyvitamin D, and estimated GFR. Independent correlates of FGF23 levels were defined using backward linear regression analysis. The parameters included in this regression analysis were ADPKD, hypertension, sex, age, BMI, family history of coronary artery disease, smoking, glucose, HDLC, LDLC, 25-hydroxyvitamin D, and estimated GFR. The significance level was assumed as a *P* value less than .05.

RESULTS

The baseline clinical and laboratory characteristics of the patients and controls are summarized in Table 1. There was no significant difference between the two groups with respect to age, sex, smoking, systolic blood pressure, or BMI. The biochemical characteristics of the patients did not

Table 1. Demographic Data, Laboratory Values, and Cardiovascular Parameters of Patients With Autosomal Dominant Polycystic Kidney disease and Controls*

Parameter	ADPKD (n = 54)	Control (n = 26)	*P*
Age, y	38.1 ± 12.8	35.5 ± 6.4	.22
Sex			
Male	17	13	
Female	37	13	.17
BMI, kg/m^2	25.8 ± 2.5	27.1 ± 3.8	.65
Smoking, n	17 (31.5)	8 (30.7)	.07
Glucose, mg/dL	87.6 ± 8.9	84.3 ± 6.8	.09
Urea, mg/dL	27.5 ± 10.5	24.0 ± 8.2	.09
Creatinine, mg/dL	0.8 ± 0.3	0.7 ± 0.2	.01
Estimated GFR, mL/min	100.7 ± 15.3	116.9 ± 12.8	< .001
Uric acid, mg/dL	4.27 ± 1.37	4.08 ± 1.30	.56
Calcium, mg/dL	9.52 ± 0.45	9.46 ± 0.28	.46
Phosphorus, mg/dL	3.4 (2.9 to 4.3)	3.3 (2.0 to 4.0)	.06
25-hydroxyvitamin D, ng/mL	13.5 (3.2 to 176.6)	14.7(4.7 to 35.9)	.35
Parathyroid hormone, pg/mL	55.3 (17.0 to 148.2)	63.6 (27.9 to 233.0)	.24
Total cholesterol, mg/dL	193 ± 20.1	192.0 ± 23.3	.34
HDLC, mg/dL	45.0 ± 7.3	46.0 ± 7.1	.80
LDLC, mg/dL	114 ± 20.1	120 ± 22.3	.76
Triglycerides, mg/dL	146 ± 29.2	132 ± 35.4	.10
FGF23, RU/mL	340.2 (60.4 to 1770.0)	39.8 (4.0 to 82.6)	< .001
Systolic blood pressure, mm Hg	128 ± 21.1	124.5 ± 22.9	.09
Diastolic blood pressure, mm Hg	72.8 ± 9.2	70.9 ± 8.0	.06
LAEI, mL/mm Hg × 10	12.4 ± 4.2	14.7 ± 5	.03
SAEI, mL/mm Hg × 100	4.9 ± 1.6	6.4 ± 2.8	.01

*ADPKD indicates autosomal dominant polycystic kidney disease; BMI, body mass index; CHD, coronary heart disease; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; FGF23, fibroblast growth factor 23; LAEI, large artery elasticity index; and SAEI, small artery elasticity index. Values are mean ± standard deviation for normally distributed continuous variables, median (10th to 90th percentiles) for non-normally distributed variables, and frequency (percentage) for categorical variables.

differ significantly in serum phosphate, calcium, uric acid, 25-hydroxyvitamin D, parathyroid hormone, and lipid levels except for creatinine and FGF23, which were significantly higher, and GFR which was significantly lower in the ADPKD patients. The LAEI and SAEI were significantly lower in the ADPKD patients compared to the control subjects (Table 1).

Thirty-three of the ADPKD patients were hypertensive and 21 were normotensive. In the control group, 2 participants were found to be hypertensive. In hypertensive ADPKD patients, estimated GFR levels were similar with those of normotensive ADPKD patients ($P = .10$). The normotensive ADPKD patients had slightly but not significantly higher FGF23 levels compared to the hypertensive ADPKD patients. Fibroblast growth factor 23 levels of both ADPKD groups were significantly higher than those of the controls ($P < .001$). The normotensive and hypertensive ADPKD patients had comparable LAEI and SAEI levels. Both hypertensive and normotensive ADPKD patients had lower LAEI and SAEI levels compared to the controls. However, the difference was significant only for SAEI in the normotensive ADPKD group compared to the control group (Table 2).

There was no significant correlation between arterial function parameters and FGF23 levels except for a weakly significant negative correlation between SAEI and FGF23 in all subjects and a moderate borderline negative correlation between SAEI and FGF23 in the normotensive ADPKD group (Table 3). Linear regression analysis revealed independent association of SAEI with ADPKD, estimated GFR, sex, and family history of coronary artery disease; independent association of LAEI with hypertension and HDLC; and independent association of FGF23 with ADPKD, glucose, BMI, and sex (Table 4).

Table 3. Correlation Analysis Between Fibroblast Growth Factor 23 and Arterial Function Parameters*

Group	LAEI and FGF23		SAEI and FGF23	
	r	*P*	r	*P*
All	-0.15	.18	-0.24	.04
ADPKD	-0.07	.62	-0.16	.25
Hypertensive	-0.06	.70	-0.04	.80
Normotensive	-0.09	.70	-0.43	.05
Control	0.23	.25	0.27	.33

*ADPKD indicates autosomal dominant polycystic kidney disease; FGF23, fibroblast growth factor 23; LAEI, large artery elasticity index; and SAEI, small artery elasticity index.

Table 2. Demographic Data, Laboratory Values, and Hemodynamic Parameters of Patients With Autosomal Dominant Polycystic Kidney disease With and Without Hypertension and Controls*

Parameter	ADPKD		Controls	*P*			
	Normotensive	Hypertensive		Overall	Normotensive Versus Control	Hypertensive Versus Control	Hypertensive Versus Normotensive
Age, y	27.0 (20.0 to 47.8)	44.0 (27.4 to 60.8)	35.0 (24.0 to 53.0)	…	.008	.004	< .001
Sex							
Male	6	11	13				
Female	15	22	13	.26	…	…	…
BMI, kg/m^2	22.2 (18.2 to 29.3)	27.8 (22.1 to 35.7)	27.1 (19.1 to 40.2)	…	.003	.15	< .001
Estimated GFR, mL/min	105.8 ± 16.4	97.5 ± 14.0	116.9 ± 12.8	…	.03	<.001	.10
Calcium, mg/dL	9.7 (9.0 to 10.2)	9.5 (9.1 to 10.1)	9.4 (8.9 to 10.0)	.60	…	…	…
Phosphorus, mg/dL	3.6 (2.9 to 4.3)	3.4 (2.9 to 4.0)	3.3 (2.0 to 4.0)	.15	…	…	…
25-hydroxyvitamin D, ng/mL	13.5 (3.7 to 28.9)	13.8 (5.6 to 25.8)	14.8 (4.7 to 36.0)	.60	…	…	…
Parathyroid hormone, pg/mL	50.0 (28.1 to 140.0)	58.9 (37.0 to 114.0)	63.6 (27.9 to 233.0)	.20	…	…	…
FGF23, RU/mL	407 (71 to 1422)	338 (73 to 891)	40 (4 to 83)	…	< .001	< .001	.7
Systolic blood pressure, mm Hg	119.6 ± 8.4	136.3 ± 16.9	123.4 ± 11.5	…	.60	.001	< .001
Diastolic blood pressure, mm Hg	69.0 (57.4 to 80.0)	81.0 (62.4 to 95.2)	70.5 (51.0 to 84.0)	…	.43	.003	.001
LAEI, mL/mm Hg × 10	12.2 ± 4.2	12.9 ± 4.3	14.8 ± 5.0	.09	…	…	…
SAEI, mL/mm Hg × 100	5.0 (3.0 to 7.6)	4.9 (2.2 to 10.2)	6.5 (2.8 to 15.7)	…	.007	.08	.80

*ADPKD indicates autosomal dominant polycystic kidney disease; BMI, body mass index; GFR, glomerular filtration rate; FGF23, fibroblast growth factor 23; LAEI, large artery elasticity index; and SAEI, small artery elasticity index. Values are mean ± standard deviation for normally distributed continuous variables and median (10th to 90th percentiles) for non-normally distributed variables.

Table 4. Multivariable Regression Analysis of Correlates of Fibroblast Growth Factor 23 and Arterial Function Parameters

Independent Variable	Beta	*P*	Model R2
LAEI			
HDLC	-0.13	.003	
Hypertension	-2.68	.02	0.14
SAEI			
ADPKD	-2.3	.003	
Estimated GFR	-0.06	.006	
Male sex	1.17	.09	
Family history of CAD	-1.14	.10	0.21
FGF23			
ADPKD	444.90	< .001	
Blood glucose	-15.40	.001	
BMI	21.40	.007	
Male sex	-143.50	.07	0.39

*LAEI indicates large artery elasticity index; HDLC, high-density lipoprotein cholesterol; SAEI, small artery elasticity index; ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; CAD, coronary artery disease; FGF23, fibroblast growth factor 23; and BMI, body mass index.

DISCUSSION

In this study, we found worse arterial function indexes in ADPKD patients with preserved kidney function compared to the controls. We also found significantly higher levels of FGF23 both in normotensive and hypertensive ADPKD patients compared to the controls. However, there was no significant correlation between arterial function indexes and FGF23 levels. Having ADPKD was independently associated with worse LAEI and higher FGF23 levels.

A variety of subclinical organ damage markers such as left ventricular hypertrophy, increased carotid intima-media thickness, endothelial dysfunction, microalbuminuria, decreased coronary flow velocity reserve, and low-grade systemic inflammation and chronic oxidative stress have been reported in several studies of patients with ADPKD with well-preserved kidney function.[12-15] Endothelial vasodilatation and constitutive nitric oxide synthase activity are reduced in subcutaneous resistance vessels from patients with ADPKD with normal GFR. Flow-induced vasodilatation of the brachial artery has been found to be inconsistently impaired,[16] in support of this finding amplification of pulse wave reflection suggesting a predominant involvement of small resistance vessels.[6]

Klotho receptor downregulation in the vascular bed is associated with endothelial dysfunction and ageing.[17,18] Fibroblast growth factor 23, which is associated with klotho, may be responsible for vascular abnormalities; thus, endothelial dysfunction has been shown to correlate with increased FGF 23 in the general population.[8] Recent prospective studies showed a powerful dose-dependent association between increasing FGF23 levels and greater risk of mortality among patients with CKD.[19-21] The action of FGF23 in the kidney and the parathyroid gland is different from that in the heart. In renal and parathyroid tissue, FGF23 acts via the classical pathway, by stimulating FGF receptor and klotho, the obligatory coreceptor, to inhibit both renal phosphorous reabsorption and 1,25-hydroxyvitamin D synthesis through ras/mitogen-activated protein kinase pathway. In contrast, at the level of cardiomyocytes, FGF23 acts through the phospholipase C gamma/calcineurin pathway, independent of klotho.[19,22] A recent trial in ADPKD patients at different stages of CKD showed markedly elevated levels of FGF23 compared with other CKD etiologies.[9] The same researchers have found decreased levels of klotho independent of FGF23 levels in ADPKD patients compared to X-linked hypophosphatemia, which is characterized by severe hypophosphatemia, inappropriately low 1,25-hydroxyvitamin D, and high FGF23 levels. Loss of klotho might be a consequence of cyst growth and thus prevents the phosphaturic effect of FGF23 in subjects with ADPKD.[23] These findings may explain preserved calcium and phosphate metabolism despite very high levels of FGF23 in ADPKD patients. Likewise, ADPKD subjects had higher levels of FGF23 but normal calcium and phosphate levels when compared to the controls in our study. Because of the absence of klotho in cardiomyocytes, increased FGF23 levels maybe an important factor underlying increased rates of left ventricular hypertrophy in normotensive ADPKD patients with normal kidney function.

There is limited data about the association of FGF23 with arterial function. Mirza and colleagues found some association between FGF23 levels and arterial function in a community-based cohort study.[8] However, Manghat and colleagues did not find any association between FGF23 and arterial functions in patients with CKD stage 1 to 4.[24] Likewise, Ford and coworkers found a significant association between FGF23 and myocardial damage but not arterial function in patients with CKD stage 3 to 4.[25] Taken together, these findings indicate that FGF23 may have a more significant effect on

the heart than on the arteries. Although several studies indicate influenced arterial functions in early ADPKD,[6,26] to our knowledge, there is no study exploring the association between FGF23 levels and arterial function in ADPKD patients with preserved kidney function. Our study indicates that in ADPKD, some factors other than FGF23 influence arterial function before the onset of kidney dysfunction and hypertension. The study of Donate-Correa and associates indicate that Klotho but not FGF23 is expressed in vascular tissue.[22] Thus, we speculate that significantly increased FGF23 levels in early stages of ADPKD may influence the heart.

The limitations of our study are the absence of a hypertensive control group and the small sample size. We cannot make conclusions about the association of increased FGF23 levels and development of kidney dysfunction because of the cross-sectional nature of our study. However, there are 2 main results of our study that deserve consideration. First, we found markedly elevated FGF23 levels in both hypertensive and normotensive ADPKD patients with preserved kidney function. Secondly, vascular dysfunction as shown by decreased LAEI and SAEI was present in both hypertensive and normotensive ADPKD patients. Of note, normotensive ADPKD patients had significantly worse arterial function indexes than control subjects who were older and had more cardiovascular risk factors such as obesity.

CONCLUSIONS

Factors underlying impaired arterial function and effects of significantly increased FGF23 levels, especially on the heart in ADPKD patients with preserved kidney function, deserve further investigations. These investigations may lead to effective treatments to decrease coronary artery disease and cardiovascular mortality in these patients.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Abdulmecit YILDIZ, MD
Cekirge State Hospital
16052 Osmangazi, Bursa, Turkey
Tel: +90 224 295 14 40
Fax: +90 224 295 00 19
E-mail: mecityildiz@gmail.com

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