Arterial Function Worsens Faster than Renal Function in Autosomal Dominant Polycystic Kidney Disease

Otozomal Dominant Polikistik Böbrek Hastalığında Arteriyel Fonksiyonlar Böbrek Fonksiyonundan Daha Hızlı Kötüleşmektedir

Abdülmecit YILDIZ[1]
Alparslan ERSOY[1]
Saim SAĞ[2]
Ayşegül ORUÇ[1]
Ercan ÇİĞİLLİ[2]
Yavuz AYAR[1]
Sümeyye GÜLLÜLÜ[2]
Cuma Bülent GÜL[3]

1 Uludağ University Faculty of Medicine, Department of Nephrology, Bursa, Turkey
2 Uludağ University Faculty of Medicine, Department of Cardiology, Bursa, Turkey
3 Bursa Yüksek İhtisas Training and Research Hospital, Department of Nephrology, Bursa, Turkey

ABSTRACT

OBJECTIVE: Early arterial stiffness has been shown in autosomal dominant polycystic kidney disease (ADPKD) patients with preserved renal function. However, to our knowledge, no prospective study evaluated changes in arterial functions in patients with ADPKD. The study aimed to monitor the changes in renal and arterial functions in patients with ADPKD with preserved renal functions.

MATERIAL and METHODS: A total of 25 ADPKD patients and 12 controls were included in the study. Data on patient characteristics, biochemical parameters and arterial stiffness were recorded at baseline and at the end of fourth year. Determination of independent correlates of the change in eGFR and arterial functions was performed by linear regression analyses.

RESULTS: There was a similar decline in renal functions over the study period in both groups. However, arterial functions deteriorated more rapidly in the ADPKD group. Having ADPKD was the only independent factor associated with the decline in arterial functions.

CONCLUSION: There were significant decreases in arterial elasticity characteristics in the ADPKD group compared with the control group despite a similar decline in renal functions. Monitoring of arterial stiffness may be as important as monitoring of renal functions in ADPKD patients.

KEY WORDS: Autosomal dominant polycystic kidney disease, Cardiovascular disease, Endothelial dysfunction, Arterial stiffness

ÖZ

AMAÇ: Arteriyel sertlik kötü kardiyovasküler sonuçlar ve mortalitenin artması ile ilişkilidir. Renal fonksiyonları korunmuş otozomal dominant polikistik böbrek hastalığı (ODPBH) hastalarında erken arteriyel sertlik görülmüştür. Bununla birlikte, bildiğimiz kadarıyla, ODPBH'li hastalarda prospektif bir çalışmada arteriyel fonksiyon değişiklikleri değerlendirilmemiştir. Bu çalışma, renal fonksiyonları korunmuş olan ODPBH hastalarında böbrek ve arteriyel fonksiyonlarındaki değişiklikleri izlemeyi amaçlamıştır.

GEREÇ ve YÖNTEMLER: Çalışmaya toplam 25 ODPBH hastası ve 12 kontrol alındı. Hasta özellikleri, biyokimyasal parametreler ve arteriyel sertlik verileri başlangıçta ve dördüncü yılda kaydedildi. eGFR ve arteriyel fonksiyonlarda meydana gelen değişikliğin bağımsız faktörlerinin belirlenmesi doğrusal regresyon analizi ile gerçekleştirildi.

BULGULAR: Her iki grupta da çalışma süresi boyunca böbrek fonksiyonlarında benzer bir düşüş vardı. Bununla birlikte, ODPBH grubunda arteriyel fonksiyonlar daha da kötüleşti. Arteriyel fonksiyonlarda azalma ile ilişkili tek bağımsız faktör, ODPBH olmaktı.

SONUÇ: Bu çalışmada, kontrol grubu ile karşılaştırıldığında, ODPBH grubunda böbrek fonksiyonlarında benzer bir düşüşe rağmen, arteriyel elastisite özelliklerinde anlamlı azalmalar vardı. Noninvaziv olarak kolayca ölçülen arteriyel sertliğin izlenmesi, ODPBH hastalarında böbrek fonksiyonlarının izlenmesi kadar önemli olabilir.

ANAHTAR SÖZCÜKLER: Otozomal dominant polikistik böbrek hastalığı, Kardiyovasküler hastalık, Endotel disfonksiyonu, Arteriyel sertlik

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Correspondence Address:
Abdülmecit YILDIZ
Uludağ Üniversitesi Tıp Fakültesi,
Nefroloji Bilim Dalı, Bursa, Turkey
Phone : +90 224 295 24 64
E-mail : mecityildiz@gmail.com

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is among the most common causes of renal dysfunction and end-stage renal disease (ESRD). Vascular endothelial dysfunction (ED) is an early marker of cardiovascular disease (CVD), which leads to mortality and morbidity in patients with ADPKD (1,2). Polycystins-1 and 2 are the products of two mutant genes called PKD1 and PKD2 and are expressed in all cells, especially in endothelial and vascular smooth muscle cells (3). The expression of these genes in nearly all cells explains the extensive involvement of many tissues in the disease. Beside well-known CV abnormalities such as intracerebral and aortic aneurysms and mitral prolapse, vascular abnormalities like ED can be detected at an early stage in ADPKD. Early vascular abnormalities have been shown in ADPKD patients with preserved renal function (4). Identification of vascular dysfunction by readily accessible and noninvasive methods may lead to earlier diagnosis and treatment of vascular abnormalities. Arterial stiffness, measured noninvasively by applanation tonometry, has been shown in the early stages of ADPKD patients (5,6). A commonly used method for evaluation of arterial stiffness is obtained from the diastolic pulse contour analysis of radial artery waveform by applanation tonometry (7). Further information about vascular changes in ADPKD may guide the treatment of this disease. In this study, we aimed to investigate changes in arterial and renal functions over four years in patients with ADPKD who had preserved renal functions.

MATERIALS and METHODS

Study Population

This observational and prospective trial included 25 patients with ADPKD who were older than 18 years. The control group consisted of 20 healthy subjects from the hospital staff. Eight subjects from control group who left the study were not included in the analyses. The exclusion criteria were a history of CV disease, diabetes mellitus, age older than 65 years and a glomerular filtration rate of <60 mL/min. Patients who started antihypertensive medications during the study period were also excluded. The local Ethical Committee in accordance with the Second Declaration of Helsinki approved the study.

Demographic data and smoking and medication history were recorded. The participants' heights, weights, and waist circumferences were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Laboratory Measurements

Venous blood samples were obtained after overnight fasting. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, urea, creatinine, uric acid, and electrolytes were determined with an Autoanalyzer (Abbott-Aeroset kit, Abbott Diagnostics, Chicago, IL, USA). Low-density lipoprotein (LDL) cholesterol concentrations were calculated using the Friedewald formula. We calculated estimated the glomerular filtration rate (eGFR) using the 2009 CKD Epidemiology Collaboration (CKD-EPI) creatinine equation (8,9).

Measurements of Arterial Stiffness

Arterial functions were evaluated at baseline and at the end of the 4th year. All measurements of arterial stiffness were performed on the radial artery. All subjects remained at rest in the supine position for at least 15 min before the measurements. The average of three consecutive measurements at 2-min intervals was taken. Pulse Wave Sensor HDI (Hypertension Diagnostics, Eagan, MN) was used to determine large arterial elasticity index (LAEI) and small arterial elasticity index (SAEI). This technique analyzes the signal-averaged radial artery waveform based on a modified Windkessel model, which analyses the signal-averaged radial artery waveform, and correlates well with other methods that measure hemodynamic parameters in humans.

Statistical Analysis

Categorical data were presented as numbers and percentages, and continuous data with mean ± standard deviations or median (minimum-maximum) where appropriate. The distribution of the data was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared by using Fisher's exact test. Intra- and intergroup comparisons were performed using paired t and unpaired t tests or the Wilcoxon signed-rank test and Mann Whitney test according to the distribution of the data. In groups, percentage changes of numerical variables were also calculated as [(second value – first value)/first value]×100. The correlation analyses were performed by using the Pearson or Spearman tests. The general linear model repeated measures test was used to compare the change in eGFR and percentage changes in LAEI and SAEI. Determination of independent correlates of the change in eGFR, LAEI, and SAEI was calculated by linear regression analyses. A two-sided p value of <0.05 was considered as statistically significant.

RESULTS

The age (39±11 vs. 36±5 years), gender distribution (15 vs. 5 females) and BMI (26±5.1 vs. 27±5.2 kg/m^2) of the ADPKD and control groups were similar, respectively (p>0.05). The ratio of hypertension in the ADPKD group was 56%. All hypertensive patients were under renin-angiotensin-aldosterone system blocker treatment except one. The control group tended to have a higher rate of smoking according to ADPKD group (66% vs. 32%, p=0.051) (Table I). The baseline and four-year follow-up variables of both groups were given in (Table II). In the ADPKD group baseline eGFR values were lower, and baseline creatinine levels were higher. eGFR values of the ADPKD group at the end of the fourth year were lower than that of the control group. The diastolic blood pressures and CRP levels of the ADPKD group at the end of the fourth year were also higher than those of the control group. Serum creatinine levels increased, and eGFR

values decreased in both groups when compared with baseline values. Both LAEI and SAEI values in the ADPKD group were significantly reduced. The only significant decrease in LAEI values was observed in the control group.

The percentage changes of systolic blood pressure, serum glucose, creatinine, eGFR, uric acid, total cholesterol, HDL cholesterol and triglyceride levels at the baseline and fourth years between both groups were comparable (p>0.05). There was a significant difference in the percentage changes of diastolic blood pressure, LDL cholesterol, CRP, LAEI and SAEI between the ADPKD and control groups (Table III). The percentage changes in LAEI and SAEI did not correlate with age, BMI and the changes in other variables (p>0.05).

There was a similar decline in renal functions over the study period in both groups. However, both LAEI and SAEI declined more rapidly in the ADPKD group compared to controls. The multivariate linear regression model to predict the change in GFR consisted of HDL, age, and baseline eGFR. HDL cholesterol tended to predict decline in GFR [unstandardized coefficient (B): 0.264, 95% CI: 0.04-0.6, p=0.086]. The only independent predictors of the percentage changes in LAEI [R^2 of the model: 0.23, the unstandardized coefficient (B): 15.134, 95% CI: 4.95-25, p=0.005] and SAEI [R^2 of the model: 0.24, the unstandardized coefficient (B): 21.6, 95% CI: 3.7-39.5, p=0.02] were having ADPKD.

Table I: Characteristics of both groups.

Variables	Control group (n=12)	ADPKD group (n=25)	p value
Age (years)	36±5	39±11	0.554
Men (males to females)	5/7	10/15	0.482
Body mass index (kg/m^2)	27±5.2	26±5.1	0.911
Hypertension n(%)	0	14(56)	0.001
Use of antihypertensives n(%)	0	13(52)	0.001
Smoking n(%)	4(32)	17(66)	0.077

Table II: Comparison of the baseline and four-year results of both groups.

Variables	Control group (n=12)			ADPKD group (n=25)		
	Baseline	4-year	p value	Baseline	4-year	p value
Systolic BP (mm Hg)	124±10	119±13	0.329	129±18	126±12	0.315
Diastolic BP (mm Hg)	71±7	67±8	0.087	74±11	78±10[a]	0.173
Glucose (mg/dL)	84.6±6.8	85.4±10.1	0.750	87.2±6.3	84.6±11	0.242
Creatinine (mg/dL)	0.7(0.5-0.8)	0.73(0.59-0.88)	**0.033**	0.8(0.6-1.3)[b]	0.86(0.51-1.63)	**0.002**
eGFR (mL/min)	121(110-128)	115(106-119)	**0.002**	109(70-133)[c]	102(42-122)[d]	**0.002**
Uric acid (mg/dl)	3.97±1.54	4.3±1.43	0.246	4.44±1.51	5.07±1.88	0.073
Total cholesterol (mg/dL)	188±21	191±26	0.618	199±26	202±30	0.401
HDL cholesterol (mg/dL)	48±13	47±11	0.788	46 ±9.5	46±8.2	0.475
LDL cholesterol (mg/dL)	112.5(101-137)	119.5(81-163)	0.182	125(82-161)	58.5(28-180)	**0.003**
Triglyceride (mg/dL)	98.5(48-192)	94(50-178)	0.875	115(58-511)	113.5(63-351)	0.819
CRP (mg/dL)	0.33(0.33-0.40)	0.33(0.33-0.34)	**0.043**	0.34(0.32-0.44)	0.35(0.3-1.26)[d]	0.414
LAEI (mL/mmHg×10)	15.1±5.7	13.4±4.9	**0.004**	14.3±4.3	11.0±3.2	**<0.001**
SAEI (mL/mmHg×10)	6.7±2.1	5.6±2.2	0.084	7.0±2.5	4.3±1.7	**<0.001**

[a] p=0.007 vs. fourth year value of control group, [b] p=0.021 vs. baseline value of control group, [c] p<0.001 vs. baseline value of control group, [d] p<0.001 vs. fourth year value of control group

ADPKD: Autosomal dominant polycystic kidney disease, **BP:** Blood pressure, **eGFR:** Estimated glomerular filtration rate, **HDL:** High-density lipoprotein, **LDL:** Low-density lipoprotein, **CRP:** C reactive protein, **LAEI:** Large artery elasticity index, **SAEI:** Small artery elasticity index.

DISCUSSION

In this prospective observational study, we have seen significantly more rapid deterioration in arterial functions in patients with ADPKD compared with healthy subjects. Notably, the change in eGFR was similar between the groups. Furthermore, the change in arterial function parameters was independent of the changes in eGFR and other study parameters including hypertension, smoking and cholesterol levels.

It is well known that early functional abnormalities like endothelial dysfunction occur before atherosclerosis leading to vessel occlusion in ADPKD. The assessment of endothelial dysfunction in daily practice is time-consuming and not practical. Arterial stiffness has been shown to be associated with CVD morbidity and mortality in the general population (10.11). Arterial stiffness can be assessed by various methods. Pulse wave velocity (PWV) and augmentation index (AI) are most commonly used methods and highly predictive of future CVD events. Arterial stiffness measurements by pulse contour analysis using a modified Windkessel model, which we used in our study, is a noninvasive and easy to apply method in daily clinical practice. This approach estimates two parameters: the proximal arterial compliance (C1) or large arterial elasticity and the distal arterial compliance (C2) or small arterial elasticity. In two well-designed studies involving 6740 and 870 patients respectively, reduced C2 was found to be related to CV events (11,12). Also, there is a growing body of evidence that C2 may be an early sign of atherosclerosis. Several studies have reported a correlation between C2 and flow-mediated vasodilatation (FMD) Which is the traditional test of ED (13-15). In light of these findings, C2 may be considered to be an available and easily accessible ED marker. The main reason we chose this method was that it has easy applicability and has been validated in various studies (11,12,16). In some studies, early CV abnormalities ranging from oxidative stress to ED have been shown in ADPKD (17-19). These abnormalities are probably due to systemic nature of the disease. Hypertension and ED are early features of ADPKD, and are typically present before renal function starts to decline (4,6). Our study indicates that even in subjects with ADPKD who have preserved renal functions, arterial functions may deteriorate while renal functions seem to be stable over four years.

Limitations of our study include the limited sample size and the observational study design. Availability of the follow-up data in all of the subjects in the ADPKD and control groups and lack of change of antihypertensive medications in the ADPKD group are among the strengths of our study.

To our knowledge, no prospective trials have previously evaluated arterial functions in patients with ADPKD who had preserved renal functions. This is the first preliminary study that monitors arterial functions along with eGFR in patients with ADPKD with preserved renal functions. In our study, we have shown prominent deterioration in arterial functions despite preserved renal functions at baseline and the end of the four-year follow-up period. In patients with ADPKD, arterial functions should be monitored along with kidney functions. There is a need for further large-scale trials to observe the association of these arterial function changes with CVD events.

Table III: Comparison of the percentage changes of parameters in both groups.

Variables (%)	Control group (n=12)	ADPKD group (n=25)	p value
Systolic BP	-0.3(-19.7 to 15.7)	-2.5(-23.7 to 21.2)	0.860
Diastolic BP	-1.9(-16 to 8.5)	1.6(-23 to 50)	0.049
Glucose	1.9(-19.7 to 15.3)	-2.3(27.7 to 28.2)	0.192
Creatinine	8.3(1.4 to 24.2)	4.4(-17 to 64.2)	0.240
eGFR	-4.1(-7.5 to -2.4)	-6.4(-46.5 to 14.8)	0.737
Uric acid	15.1(-35.3 to 41.1)	14.3(-38.2 to 102)	0.958
Total cholesterol	-0.1(-17.4 to 44.4)	1.6(-13.7 to 17.2)	0.856
HDL cholesterol	-3.5(-12 to 35)	-5.2(-16.9 to 90.3)	1.000
LDL cholesterol	3.3(-27 to 49)	-38(-80 to 30)	0.015
Triglyceride	2.7(-46.5 to 105)	-0.2(-12.5 to 250)	0.934
CRP	0(-17 to 3)	2.9(-12 to 250)	0.045
LAEI	-10(-25 to 1)	-22.5(-45 to 2.5)	0.010
SAEI	-9.6(-53 to 37)	-35(-68 to -13)	0.012

ADPKD: Autosomal dominant polycystic kidney disease, **BP:** Blood pressure, **eGFR:** Estimated glomerular filtration rate, **HDL:** High-density lipoprotein, **LDL:** Low-density lipoprotein, **CRP:** C reactive protein, **LAEI:** Large artery elasticity index, **SAEI:** Small artery elasticity index.

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