® Postepy Hig Med Dosw (online), 2021; tom 75: 502–510
e-ISSN 1732-2693

www.phmd.pl
Original Article

Received: 28.05.2020
Accepted: 26.02.2021
Published: 01.07.2021

Cardiac involvement in patients with Autosomal Dominant Polycystic Kidney Disease and normal renal function after six years of follow-up

Sześcioletnia prospektywna obserwacja przebudowy mięśnia sercowego u pacjentów z autosomalnie dominującym zwyrodnieniem wielotorbielowatym nerek i prawidłową czynnością nerek

Maria Pietrzak-Nowacka[1,A,B,D,E,F], Krzysztof Safranow[2,C,D,E], Małgorzata Czechowska[3,B,D,E], Grażyna Dutkiewicz[1,E,F], Ewa Gątarska[1,E,F], Kazimierz Ciechanowski[1,A,E,G]

[1]Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland
[2]Department of Biochemistry and Medical Chemistry, Pomeranian Medical University, Szczecin, Poland
[3]Department of Cardiology, Pomeranian Medical University, Szczecin, Poland

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary:

The aim of the follow-up study was to compare the changes of M-mode echocardiographic parameters in autosomal dominant polycystic kidney disease (ADPKD) patients and controls without renal failure during six years of observation and to explore the associations of these parameters with metabolic syndrome components and kidney function. We performed a follow-up examination in 37 ADPKD patients and 40 controls. Anthropometric parameters were measured and fasting venous blood sample from each patient was tested for glucose, insulin, C-peptide, HbA1c, creatinine, and urea concentrations. All subjects underwent standard two-dimensional M-mode echocardiography. Left ventricular hypertrophy (LVH) was diagnosed based on left ventricular mass index (LVMI) adjusted for body surface area (LVMI-S, LVH-S) or for height (LVMI-H, LVH-H). The prevalence of LVH was significantly greater in ADPKD patients than in controls (35% vs. 10%, p=0.012) according to the ESH/ESC criteria from 2013, and (27.0% vs. 7.5%, p=0.032) according to criteria from 2017. In patients with ADPKD, no significant increase of the echocardiographic parameters was observed in the 6 years between the initial examination and the follow-up examination. Cardiac involvement in women with ADPKD occurs at an earlier stage of the disease than in men. In patients with ADPKD treated for hypertension in accordance with the 2013 ESH/ESC Guidelines the progression of LVH was not observed during the 6-year follow-up, despite the deterioration of renal function. Obesity, blood pressure and renal function do not affect LVMI changes.

Keywords: **autosomal-dominant polycystic kidney disease, hypertension, left ventricular hypertrophy, normal renal function**

GICID 01.3001.0015.0108
DOI: 10.5604/01.3001.0015.0108
Word count: 5 448
Tables: 5
Figures: –
References: 30

Adres autorki: Maria Pietrzak-Nowacka, MD, Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Al. Powstańców Wlkp. 72, 70-111 Szczecin, Poland; e-mail: mariola.nowacka@o2.pl

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease with a prevalence of 1:400 to 1:1000 in Caucasians. It is caused by mutations in the PKD1 gene located on chromosome 16p13.3 [27] (in about 85% cases) as well as in the PKD2 gene on chromosome 4q13-23 [14]. These genes encode polycystin-1 (PC1) and polycystin-2 proteins (PC2) [13]. The biological function of polycystins is still under investigation [19].

The presence of kidney cysts is a characteristic feature in the ADPKD patients, necessary to establish the diagnosis [25]. But in the ADPKD patients, cardiovascular abnormalities, high blood pressure (BP), left ventricle hypertrophy (LVH), intracranial and extracranial aneurysms and cardiac valvular defects are significantly more common than in the general population [6].

It has been proven that children with ADPKD and normal BP have significantly higher LVM in comparison to age-matched controls without ADPKD [30]. Some studies in normotensive children and young adults with ADPKD and normal renal function [12, 30] showed increased left ventricle mass index (LVMI), prolonged isovolumetric relaxation time [2], impaired biventricular diastolic function, reduced coronary flow velocity, increased carotid intima-media thickness, and endothelial dysfunction [9].

These findings suggest that cardiovascular involvement starts very early in the course of ADPKD progression and factors other than hemodynamics may be involved in this process.

In adults with ADPKD the prevalence of left ventricle hypertrophy (LVH) varies from 20% to 40% [3]. Some of the differences may relate to the imaging modality, variations in parameters used to define LVH, or demographic differences in the study populations.

Higher blood pressure (BP), male gender, higher body weight, older age [3], microalbuminuria, kidney failure and insulin resistance are the factors that may increase LVM in patients with ADPKD [15, 18]. BP is the most often analyzed factor influencing LVM in patients with ADPKD. It was shown that in normotensive young ADPKD-diagnosed individuals ambulant systolic and diastolic blood pressures (SBP, DBP) were significantly higher than in age- and gender-matched controls [5] and did not decrease at night [29]. Hypertension (HT) occurs in half of the patients with ADPKD and precedes kidney failure. [8]. Martinez-Vea et al. reported a greater prevalence of LVH in hypertensive ADPKD patients than in the general population [20]. In our earlier study, we showed LVH, using echocardiography, in 13% of ADPKD patients with normal renal function and in 19% of their hypertensive subgroup [24].

The aim of the follow-up study was to compare the changes of M-mode echocardiographic parameters in the previously studied groups of ADPKD patients and controls without renal failure after six years of observation and to explore the associations of these parameters with metabolic syndrome (MS) components and kidney function.

MATERIALS AND METHODS

The initial study [24] included 47 ADPKD patients (29 females and 18 males) aged 18–61 years, and 49 gender and age- matched healthy controls. The inclusion criteria for the ADPKD group were as follows: presence of cysts in both kidneys, allowing a diagnosis of PKD according to Ravine et al. [25], normal renal function (serum creatinine concentration <1.35 mg/dL). Inclusion criteria for the control group were the following; normal renal function (serum creatinine concentration <1.35 mg/dL), negative family history of ADPKD, absence of cysts in the kidneys (Ravine criteria not fulfilled) and no prior diagnosis of diabetes. After six years of observation we performed a follow-up examination in 39 ADPKD patients: 16 males and 23 females, who gave their consent. Two men from the ADPKD group started dialysis during follow-up period. These two patients were excluded from analysis that finally included 37 patients with ADPKD not requiring renal replacement therapy.

The follow-up examination was performed in 40 subjects from the control group: 17 men and 23 women, who gave their consent. The protocol of the study was approved by the Bioethics Committee of the Pomeranian Medical University (decision BN-001/135/06). Physical examination with anthropometric measurements (body weight, height, waist and hip circumferences) was performed in each subject. The body mass index (BMI) was calculated as weight /height squared (kg/m^2) and WHR as waist/hip ratio. BMI <25 kg/m^2 was classified as normal, 25-30 kg/m^2 as overweight, and ≥30 kg/m^2 as obesity.

BP was measured three times at 2-min intervals in the left arm using a standard mercury sphygmomanometer, in the sitting position, after a 10-min rest with a mean value used in analyses. BP was defined as the use of a hypertensive medication or systolic/diastolic blood pressure ≥ 140/90 mmHg.

The fasting venous blood sample from each patient was tested for glucose, insulin, C-peptide, HbA1C, creatinine, urea, uric acid (UA) concentrations and lipid levels. Glucose concentrations were determined with the enzymatic-amperometric method (Cobas GLUC 800: 04404483190 with a Super GL system, Diagnostic Systems, Germany).

Table 1. Anthropometric, clinical, and biochemical data of the ADPKD and control groups after 6-year follow-up

Parameters	ADPKD group n=37	Control group n=40	p-value * ADPKD vs controls
Age (years)	44.63±10.96	43.97±9.4	0.84
BMI (kg/m^2)	27.12±5.27	25.94±4.42	0.44
WHR	0.89±0.11	0.85±0.090	0.040
BSA (m^2)	1.93±0.22	1.90±0.24	0.57
SBP (mmHg)	130.43±19.62	115.85±14.42	0.006
DBP (mmHg)	89.51±14.28	77.00±10.22	0.001
e-GFR$_{CKD\ EPI}$ [mL/min/1.73 m^2]	80.55±26.4	114.41±26.50	0.038
Hypertension [n, (%)]	30 (81.1%)	7 (17.50%)	<0.001
ACE inhibitors [n, (%)]	26 (70.3%)	5 (12.50%)	<0.001
LVH-S ESH/ESC 2007 (%) **	16.2 (%)	2.5 (%)	0.051
LVH-S ESH/ESC 2013 (%) ***	35.1 (%)	10 (%)	0.012
LVH-H ESH/ESC 2017 (%)****	27.0 (%)	7.5 (%)	0.032

BMI – body mass index; BSA – body surface area; e-GFR – estimated glomerular filtration rate according to CKD-EPI (Chronic Kidney Disease Epidemiological Collaboration) equation; DBP – diastolic blood pressure; LVH – left ventricle hypertrophy; SBP – systolic blood pressure; WHR – waist-to-hip ratio
Data are given as mean±SD
*Mann-Whitney U test was used for quantitative variables and Fisher exact test for qualitative ones.
**LVH-S in accordance with the ESH/ESC Guidelines for the management of arterial hypertension from the year 2007
***LVH-S in accordance with the ESH/ESC Guidelines for management of arterial hypertension from the year 2013
****LVH-H in accordance with the ESH/ESC Guidelines for management of arterial hypertension from the year 2017

Insulin was quantified by a microparticle enzyme immunoassay (MEIA, 2 D01-20, Axsym, Abbott) and C-peptide by electrochemiluminescent method (ECLIA, reagent kit and Cobas 6000 system from Roche). HbA1C was measured in K_3EDTA-sampled blood using the immunoturbidimetric method (Cobas, HbA1c 150: 20753521322). The measurements of serum creatinine, urea, UA and lipid levels were done with the Bio-Autoanalyzer Cobas Integra 800 (Roche).

For insulin resistance, the homeostasis model assessment-% sensitivity (HOMA%S index) [1] was used, while for beta cell function we used the homeostasis model assessment-%beta (HOMA%B index) [17]. Estimated glomerular filtration rate (e-GFR) was calculated based on a single serum creatinine measurement using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [16].

All subjects underwent standard two-dimensional and two-dimensionally guided M-mode echocardiography (General Electric Vivid 9 system, 3.5 MHz transducer) by the same sonographer blinded to the diagnostic category. Two-dimensionally guided M-mode echocardiograms were performed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging Guidelines. The left ventricular end-diastolic diameter (LVEDd), interventricular septal thickness in diastole (IVSd), left ventricular posterior wall thickness in diastole (LVPWd), aortic root diameter (AO), and left atrium diameter (LA) were measured. The left ventricle ejection fraction (LVEF) was estimated by Simpson's method. Two-dimensional studies comprised the parasternal long-axis and short-axis, apical four-chamber, apical long-axis two-chamber, and subcostal views. Estimates of LVM were based on the American Society of Echocardiography convention with the Devereux correction according to the following formula: LVM (g) = 0.8 x 1.04 ([LVEDd+IVSd+LVPWd]^3 – LVEDd^3) + 0.6.

LVH was diagnosed based on the left ventricle mass index (LVMI) adjusted for body surface area (LVMI-S, LVH-S) or for height (LVMI-H, LVH-H). LVH-S was diagnosed when LVMI-S (mass/BSA) was greater than or equal to 125 g/m^2 in males and 110 g/m^2 in accordance with the ESH/ESC Guidelines for the management of arterial hypertension from the year 2007 or when LVMI-S was greater than or equal to 115 g/m^2 in males and 95 g/m^2 in females in accordance with the ESH/ESC Guidelines for the management of arterial hypertension from the year 2013. LVH-H was diagnosed when LVMI-H (mass/height$^{2.7}$) was greater than or equal to 50 g/m$^{2.7}$ in males and 47 g/m$^{2.7}$ in females in accordance with the ESH/ESC Guidelines for the management of arterial hypertension from the year 2017. Delta echocardiographic data were calculated for each subject as differences between the values in the current follow-up examination and the initial examination from our previous study [24].

Table 2. Comparison of the M-mode echocardiographic data of ADPKD patients and control group depending on the gender after six-year follow-upp

Indexes	ADPKD women n=24	Control women n=23	p-value[1]	ADPKD men n=13	Control men n=17	*p*-value[2]
LVEDd (cm)	4.75 (0.40)	4.60 (0.30)	0.20	5.30 (0.4)	5.10 (0.7)	0.98
LVPWd (cm)	1.00 (0.20)	0.90 (0.20)	0.002	1.10 (0.4)	1.00 (0.2)	0.13
IVSd (cm)	1.00 (0.30)	0.80 (0.30)	0.018	1.1 (0.3)	1.00 (0.2)	0.048
AO (cm)	2.85 (0.50)	2.60 (0.40)	0.013	3.20 (0.5)	3.20 (0.2)	0.50
LA (cm)	3.50 (0.60)	3.10 (0.60)	0.015	3.80 (0.7)	3.70 (0.4)	0.98
LVEF (%)	65.0 (5.0)	70.0 (5.0)	0.2	65.0 (5.0)	65.0 (5.0)	0.38
LVM (g)	148.1 (62.2)	122.3 (34.7)	0.0016	226.4 (89.6)	199.3 (63.8)	0.13
LVMI-S g/m^2	83.3 (29.4)	71.4 (17.4)	0.0065	104.6 (35.8)	93.5 (38.2)	0.13
LVMI-H g/m$^{2.7}$	38.3 (12.8)	30.3 (11.4)	0.018	48.0 (28.2)	35.2 (14.9)	0.084

LVEDd, left ventricular end-diastolic diameter; LVPWd, left ventricular posterior wall thickness in diastole;
IVSd, interventricular septal thickness in diastole; AO, aortic root diameter; LA, left atrium diameter;
LVEF left ventricle ejection fraction; LVM left ventricle mass; LVMI-S (mass/BSA), left ventricle mass index adjusted for body surface area; LVMI-H (mass/height) left ventricle mass index adjusted for height
Data are given as median (interquartile range)
p[1] ADPKD women vs control women; p[2] ADPKD men vs control men; Mann-Whitney test

Statistical analysis

Since most of the analyzed quantitative parameters presented distributions significantly different from normal distribution (Shapiro-Wilk test), we used non-parametric tests. Mann-Whitney test was performed to compare values between groups and Wilcoxon signed-rank test was used to check the significance of changes between two time points. Spearman rank correlation coefficients were presented to measure the strength of correlation. The general linear model (GLM) was used for the multivariate analysis of associations between parameters measured at the initial examination (treated as independent variables) and changes of echocardiographic parameters during the follow-up (treated as dependent variable). Standardized beta coefficients (β) were presented to show the direction (β sign) and strength of the associations. Only variables with significant univariate associations, and additionally age, gender and eGFR at the initial examination, were included as independent variables into GLM. Associations with $p<0.05$ were considered statistically significant.

RESULTS

After a 6-year follow-up, the age, BMI and body surface area (BSA) were comparable in the group of ADPKD patients and controls. In patients with ADPKD the WHR, SBP, DBP values and the percentage of patients with BP treated with angiotensin-converting enzyme inhibitors (ACE–I) were significantly higher and the e-GFR value was significantly lower than in the control group. The prevalence of LVH-S in ADPKD patients after six years of observation according to the ESH/ESC criteria from 2007 was higher with the borderline significance in comparison to controls (16% vs. 3%, p=0.051), but a significant difference of LVH-S was observed (35% vs. 10%, p=0.012) according to the ESH/ESC criteria from 2013 and of LVH-H according to the ESH/ESC criteria from 2017 (27.0% vs 7.5%, p=0.032). The prevalence of LVH-S according to the criteria from 2007 in ADPKD patients with HT did not significantly differ from patients without HT (LVH-S: 6/30 vs 0/7, p=0.57), and according to the criteria from 2017 (LVH-H: 10/30 vs 0/7, p=0.16), but a significant difference was observed (13/30 vs 0/7, p=0.038) according to the criteria from 2013 (Table 1).

ADPKD females demonstrated a significantly higher LVPWd, IVSd, AO, LA, LVM, LVMI-S and LVMI-H than control females. IVSd was significantly higher in ADPKD males than in control males (Table 2).

In patients with ADPKD no significant changes of the echocardiographic data was observed during the 6 years between the initial examination and the follow-up examination. A significant increase in AO and LA was observed in the control group (Table 3). The delta of LVEDd value was significantly lower in patients with ADPKD than in the controls, although the change of this parameter was not statistically significant in either group. The delta of AO was significantly lower in patients with ADPKD than in the control group whereas the delta values of LVPVd, IVSd, AO, LA, LVM, LVMI-S and LVMI-H did not significantly differ between the two groups.

Table 4 presents significant correlations of the echocardiographic data from follow-up examination with anthropometric, clinical and biochemical parameters from initial examination in ADPKD patients.

In women with ADPKD there were positive correlations between AO and DBP, between IVSd and SBP or DBP,

Table 3. Changes of the echocardiographic data of ADPKD patients and control group during 6 years between the initial examination and the follow-up examination

Parameter	ADPKD group (n=37)	Control group (n=40)	*p*-value[a]
LVEDd (cm)	-0.08±0.45 0.00 (0.50)	+0.06±0.32 +0.10 (0.40)	0.036
LVPWd (cm)	+0.03±0.18 0.00 (0.20)	-0.01±0.16 0.00 (0.2)	0.49
IVSd (cm)	+0.02±0.20 0.00 (0.20)	+0.02±0.18 0.0 0 (0.2)	0.84
AO (cm)	+0.08±0.33 0.00 (0.40)	+0.28±0.32*** +0.20 (0.5)***	0.0044
LA (cm)	+0.12±0.40 0.00 (0.60)	+0.23±0.38*** +0.20 (0.6)***	0.35
LVEF(%)	+0.42±4.20 0.00 (2.50)	+1.00±4.56 0.0 (5.0)	0.44
LVM (g)	+2.9±34.5 0.0 (32.1)	+4.0±33.2 +7.5 (33.9)	0.26
LVMI-S (g/m^2)	+0.5±18.6 - 2.3 (13.7)	+1.4±17.5 +1.7 (17.3)	0.24
LVMI-H (g/m$^{2.7}$)	+0.7±7.7 0.0 (8.0)	+0.8±8.0 +1.9 (8.3)	0.28

LVEDd-left ventricular end-diastolic diameter; LVPWd-left ventricular posterior wall thickness in diastole; IVSd- interventricular septal thickness in diastole; AO-aortic root diameter; LA-left atrium diameter; LVEF left ventricle ejection fraction; LVM left ventricle mass; LVMI-S (mass/BSA), left ventricle mass index adjusted for body surface area; LVMI-H (mass/height), left ventricular mass index
Data are given as mean ± SD and median (interquartile range)
a ADPKD vs control group, Mann-Whitney test.
***p<0.001 for the significance of difference between the initial examination and the follow-up examination (Wilcoxon signed-rank test)

between LA and fasting insulin, fasting C-peptide, TG and between LVPWd and SBP, DBP and UA. There were a positive correlation between IVSd and SBP, DBP, between LVMI-S and SBP and between LVMI-H and UA, age. In women with ADPKD, a negative correlations was found between LVEDd and HDL, between LA and HOMA%S, HDL, e-GFR and between IVSd, TG and UA.

In men with ADPKD there were positive correlations between LA and BMI, WHR, SBP, DBP, TG, age, fasting C-peptide, between LVPWd and BMI, WHR, between IVSd and SBP, DBP, between LVMI-S and WHR, and between LVMI-H and BMI, WHR, SBP and DBP. In men with ADPKD negative correlations between LA and HOMA%S as well as between LVMI-H and e-GFR was observed.

The analysis of correlations between delta echocardiographic parameters and initial anthropometric, clinical and biochemical parameters from the initial examination revealed a positive correlation between delta LVPWd and SBP, DBP in patients with ADPKD (Table 5). This means that the patients with higher initial SBP and DBP values demonstrated a significantly higher increase in LVPWd during the follow-up. There was a negative correlation between delta IVSd and initial BMI, WHR, HbA1C, TG, which means that higher values of the initial anthropometric and biochemical parameters were associated with a lower increase of IVSd.

Multivariate analysis of associations between delta LVPWd as dependent variable and parameters from the initial examination as independent variables showed that SBP and DBP (analyzed separately due to their strong correlation) remained significantly positive predictors of LVPWd increase during a follow-up in the GLM model adjusted for age and gender (β=+0.40, p=0.025 for SBP, β=+0.37, p=0.031 for DBP), but the significance was lost when e-GFR was added to this model (β=+0.34, p=0.071 for SBP, β=+0.30, p=0.11 for DBP). Similar analysis for delta IVSd as a dependent variable with age, gender, initial WHR, HbA1c and e-GFR as independent variables showed that higher WHR (β=-0.49, p=0.018) and HbA1c (β=-0.47, p=0.006) as well as female gender (β=-0.50, p=0.016) were significantly negative predictors of IVSd increase.

DISCUSSION

Our previous study concerning M-mode echocardiographic data in patients with ADPKD with normal renal function showed significantly higher LVMI-S in women with ADPKD in comparison to the female control group and a positive correlation of LVMI-S with SBP and DBP. These associations were not observed in men with ADPKD [24]. After a 6-year follow-up, LVMI-S in the female ADPKD subgroup was still significantly higher than in the female control subgroup and there was a positive correlation between LVMI-S and initial SBP and LVMI-H with UA and age. In the male ADPKD patients subgroup, LVMI-S and LVMI-H did not differ significantly in comparison to the male control group. There was a positive correlation between LVMI-S and initial WHR and between LVMI-H and BMI, WHR, SBP and DBP. A negative correlation between LVMI-H at follow-up and initial

Table 4. Significant correlations of the echocardiographic data from follow-up examination with anthropometric, clinical and biochemical parameters from initial examination in ADPKD patients

Parameters at the initial examination	ADPKD patients											
	LVEDd		LA		LVPWd		IVSd		LVMI-S		LVMI-H	
	F	M	F	M	F	M	F	M	F	M	F	M
BMI				+0.8^		+0.62						+0.68
WHR				+0.91^		+0.59				+0.53		+0.66
SBP				+0.67*	+0.58*		+0.44	+0.64	+0.44			+0.59
DBP				+0.67*	+0.50		+0.50	+0.63				+0.57
Fasting glucose												
Fasting insulin			+0.53*									
Fasting C-peptide			+0.67^	+0.56								
HOMA%S			-0.48	-0.56		-0.61						
Cholesterol-HDL	-0.50		-0.46									
TG			+0.42	+0.67*			-0.56*					
UA					+0.42	+0.56	-0.47				+0.41	
e-GFR$_{CKD\ EPI}$			-0.52	-0.77*								-0.65
Age				+0.7							+0.019	

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate according to CKD-EPI (Chronic Kidney Disease Epidemiological Collaboration) equation; F, female; HOMA%S, homeostasis model assessment % sensitivity; M, men; SBP, systolic blood pressure; TG, triacylglicerols; UA, uric acid; WHR – waist-to-hip ratio. Echocardiographic parameters: IVSd – interventricular septal thickness in diastole; LA – left atrium diameter; LVEDd – left ventricular end-diastolic diameter ; LVPWd – left ventricular posterior wall thickness in diastole; LVMI-S (mass/BSA) – left ventricle mass index adjusted for body surface area; LVMI-H (mass/height) left ventricle mass index adjusted for height.
*p<0.01, ^p<0.001

e-GFR in men suggests that even slightly impaired renal function (still in normal range) is a predictor of left ventricular hypertrophy development.

During the follow-up, no significant increase of M-mode echocardiographic data was observed. However, the follow-up showed a deterioration of renal function associated with the disease.

No previous studies concerning M-mode echocardiographic data changes in patients with ADPKD and normal renal function were found in the literature. However, there were a few studies evaluating LVH prevalence during follow-up [28].

Timio et al. analyzed the occurrence of cardiovascular abnormalities in a large group of patients with ADPKD (n=228) and compared them to the control group (n=146) [28]. The M-mode criterion for LVH in adults was LVMI >134 g/m^2 for men and >110 g/m^2 for women. The LVH was present more often in patients with ADPKD than in the control group both at the beginning of the study (24% vs. 6%, p<0.01), after 5 years of follow-up (30% vs. 9%, p<0.05) and after 10 years of follow-up (35% vs. 13% p<0.002). LVMI was significantly higher in patients with ADPKD than in the control group both at the beginning of the study and after 5 and 10 years of follow-up. In our study a higher percentage of LVH according to the ESH/ESC criteria from 2007 was observed in patients with ADPKD than in the control group at the beginning (13% vs. 2%, p=0.050) [24] and with the borderline significance after 6 years of follow-up (16% vs. 3%, p=0.051). The LVH percentage in the cited study was generally higher than in our study, probably because of different population evaluated, e.g. with higher initial serum creatinine (1.79±0.18 mg/dL).

In the general population, LVH occurs more often in men, irrespective of age. Less frequent occurrence of LVH in women, especially in the premenopausal age is associated with the beneficial impact of estrogens and their protective action against LVH [26]. Our study showed that the prevalence of LVH was not significantly different in females and males with ADPKD at the beginning (10 vs 17%, p=0.66) [24] and after 6 years of follow-up, (13 vs. 23%, p=0.64).

Bardaji et al. [2] showed that in young, normotensive patients with ADPKD (n=46) both men and women had higher LVMI-S than controls. We examined the older

Table 5. Correlations of the delta echocardiographic data (the difference between the follow-up and the initial measurements) with anthropometric, clinical and biochemical parameters from the initial examination in the ADPKD patients

Parameters at the initial examination	Delta echocardiographic data in the ADPKD patients	
	LVPWd	IVSd
BMI	+0.03	-0.44^
WHR	+0.10	-0.33+
SBP	+0.44*	-0.06
DBP	+0.36+	+0.08
HbA1c	-0.15	-0.34+
TG	+0.02	-0.43*
e-GFR$_{CKD\ EPI}$	-0.30	+0.14

No significant correlations were found for delta AO, LA, LVMI, LVEDd. +p<0.05, *p<0.01, ^p<0.001

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; DBP, diastolic blood pressure; e-GFR, estimated glomerular filtration rate; SBP, systolic blood pressure; TG, triacylglycerols; WHR – waist-to-hip ratio.
Echocardiographic parameters: AO – aortic root diameter; IVSd – interventricular septal thickness in diastole; LA – left atrium diameter; LVEDd – left ventricular end- diastolic diameter; LVPWd – left ventricular posterior wall thickness in diastole; LVMI – left ventricle mass index.

group of patients with ADPKD, not excluding those with HT. Our study proved that LVMI-S was significantly higher in women with ADPKD both at the beginning of the study and after a 6-year follow-up in comparison to the female control group. At the beginning of the follow-up [24], mean LVMI-S was higher by 10.8 g/m^2 and after 6 years of follow-up by 16.50 g/m^2 in men with ADPKD in comparison to the male control group, but the difference was not significant.

Our study did not show any significant increase of LVMI during the 6-year follow-up neither in the patients with ADPKD nor in the control group. It should be noted that after the 6-year follow-up no association has been found between delta M-mode echo parameter values and the patient's gender both in patients with ADPKD and in the control group.

The association of hypertension with LVH

In the general population, BP is an important hemodynamic risk factor for LVH [26]. In the ADPKD patients, HT has some specific features which may be responsible for earlier onset of LVH. In normotensive young ADPKD-diagnosed individuals, ambulant SBP and DBP values were significantly higher than those in age- and gender-matched controls [5]. In adults, HT is often diagnosed before any substantial reduction in the e-GFR, and a lower nocturnal dip in BP in comparison to hypertensives in the general population [29].

Perrone et al. in HALT PKD study analyzed the effect of intensive angiotensin blockade on the progression of total kidney volume and LVM in a large group of patients with ADPKD (n=543) [22]. Measurements of LVM were performed using cardiac magnetic resonance (MR). The authors diagnosed LVH in only 3.9% of the patients with ADPKD <50 years old and justified it with a short duration of hypertension and early application of ACE–I or angiotensin receptor blokers treatment. Moreover, they observed significant positive associations of LVMI with SBP, serum creatinine and albuminuria and significant negative associations of LVMI with age and female gender. We also observed that LVMI in ADPKD women positively correlated with SBP values and was significantly lower than in ADPKD men.

Ecder et al. [7] observed a group of middle-aged (about 40-year-old) patients with ADPKD with HT treated with ACE–I (Enalapril). At the beginning of the study LVMI was 146±4 g/m^2 and after 7 years of follow-up it decreased to 98±6 g/m^2. The authors showed that ACE inhibition in hypertensive ADPKD patients provided long-term reversal of LVH in spite of mean 3.6 mL/min/year decline of Ccr. The results of our study seem to correspond with these observations, because after 6 years of follow-up our ADPKD patients (81% with hypertension, 70% treated with ACE–I) showed no significant increase of LVMI-S and even lower delta of LVEDd in comparison to the control group.

Idrizi et al. reported that in patients with ADPKD, LVH occurs more often in the subgroup with HT than in patients with normal BP (40% vs. 16%, p<0.005) [11]. The results of our study after 6 years of follow-up showed that LVH occurred in 20% of patients with ADPKD according to 2007 criteria and in 35% according to criteria from 2013; LVH was diagnosed only among ADPKD patients with HT, and there were no LVH cases among 7 ADPKD patients without HT.

Chen et al. [4] in their recent study estimated the prevalence of LVH using 2D echocardiography in a cohort of ADPKD patients (n=126). Among 126 participants (78% with HT), median age was 46 years, median e-GFR- 63 ml /min/1.73 m^2, and median SBP was 125 [116-133] mmHg. The authors showed that the prevalence of LVH was 21.4% and was not significantly different (p=0.8) between those with and without HT. Our results were partially the same; in ADPKD patients (n=37) with hypertension (81%), median age was 47, median SBP 130 [120-140] mmHg, but with better renal function, median e-GFR$_{CKDEPI}$ - 83.5 ml/min/1.73 m^2 the prevalence of LVH-S according to the criteria from 2007 in ADPKD patients was 16.2% and in patients with HT did not significantly differ from patients without HT (p=0.57). In the ADPKD patients, the prevalence of LVH-H was 27% according to the criteria from 2013 but a significant difference was observed between those with HT and without HT (p=0.038).

The association of other components of the metabolic syndrome with LVH

Lumiaho et al. performed M-mode and color Doppler echocardiography on 176 family members (106 patients and 70 healthy relatives) from 16 families with polycystic kidney disease type 1 (PKD1); they showed that insulin resistance

(HOMA-IR index) was significantly positively associated with LVMI in healthy relatives ($P < 0.01$) and patients with PKD1 ($P < 0.05$) independent of age, weight, SBP, and albuminuria [18].

In our study there was a negative correlation between LA value and HOMA%S (which corresponds to positive correlation with HOMA-IR) both in the male and female subgroup of patients in ADPKD. However, no correlation between LVMI and HOMA%S and delta LVMI value with anthropometric (BMI, WHR), clinical (SBP, DBP) and biochemical parameters ($e\text{-}GFR_{CKD\ EPI}$) was observed.

The associations of echocardiography parameters with HT

In the general population, HT causes not only left ventricle remodeling but also remodeling of the left atrium and ascending aorta [26]. Such a mechanism seems plausible also in relation to our APDKD patients. In the subgroup of the ADPKD women, we showed a positive correlation of the LVPWD and IVSD with SBP and DBP and AO with DBP. In the subgroup of the ADPKD men, we showed positive correlations of the IVSD with SBP and DBP. In the ADPKD men, there was also a positive correlation of LA with SBP, DBP and BMI, WHR while such a correlation did not occur in women. The M-mode echo test in patients with ADPKD showed hypertensive left ventricle, left atrium and ascending aorta remodeling when compared to controls. The remodeling was observed in the female subgroup, but it was not statistically significant in men.

Left ventricular systolic function assessed by evaluating the LVEF was normal both at the beginning and after 6 years of follow-up. The studies on associations between M-mode echo parameters and the parameters listed above were not found in the available literature.

Multivariate analysis showed that SBP and DBP remained significant positive predictors of LVPWd increase during the follow-up after adjustment for age and gender, but the significance was lost when e-GFR was added to this model. It is thought that an interaction between elevated BP and impaired renal function amplifies their influence on incrising LVPWd. Similar analysis for delta IVSd as the dependent variable with age, gender, initial WHR, HbA1c and e-GFR as independent variables showed that higher WHR and HbA1c as well as female gender were significant negative predictors of IVSd increase. This is contrary to what could be expected. The anthropometric factors (higher WHR) and biochemical parameters (higher HbA1c) associated with the metabolic syndrome do not contribute to hypertrophy of interventricular septum (IVSd increase).

Our results suggest that in ADPKD patients there are other factors involved in the process of hypertrophy of the posterior wall of left ventricle (low WHR and HbA1c) and intraventricular septum (high BP). Heart remodeling is a complex process with a different LVH risk factor profile than in the general population. This hypothesis must be confirmed by further prospective studies in a larger groups of patients.

According to the data from the literature, LVH in patients with ADPKD starts at an early stage of the disease [6, 30]. Our study showed that cardiac involvement in Caucasian adults with ADPKD with normal renal function depends on gender and occurs earlier in women than in men [24].

The natural course of the disease has been assumed to be a consequence of renal hypertension and activation of renin/angiotensin/aldosterone (RAAS) pathway. However, the expression of PC1 and PC2 in cardiac tissue suggests additional direct effects of these proteins on cardiac function [13]. Polycystin-2 (PC2) is a nonselective cation channel with Ca^{2+} permeability expressed in renal epithelial cells and in cardiomyocytes, and is thus hypothesized to modulate intracellular calcium signaling and affect cardiac function [10].

In our previous study [23], we found that ADPKD patients with normal renal function had higher Ca2+ concentrations in serum and erythrocytes and higher serum PTH levels (borderline significance) compared to non-ADPKD controls. It is thought that renal epithelial cell hyperplasia in patients with ADPKD is a consequence of dysfunctional calcium metabolism following mutations of polycystin proteins. A defect in Ca2+ binding mediated by mutations in polycystin proteins is a hypothetical factor contributing to LVM increase. Experimental evidence suggests the important role of polycystins in cardiac development and myocardial function [21].

CONCLUSIONS

We have observed that during the 6 years of follow-up in patients with ADPKD and normal renal function who received treatment consistent with hypertension treatment guidelines, the adverse changes in echocardiographic data can be avoided in spite of the deterioration of the renal function. Gender, age, BMI, WHR, SBP, DBP and e-GFR do not seem to have impact on LVH in such patients but to confirm these results further studies, on larger groups of patients, are required.

REFERENCES

[1] Abbasi F., Reaven G.M.: Evaluation of the quantitative insulin sensitivity check index as an estimate of insulin sensitivity in humans. Metabolism, 2002; 51: 235–237

[2] Bardají A., Vea A.M., Gutierrez C., Ridao C., Richart C., Oliver J.A.: Left ventricular mass and diastolic function in normotensive young adults with autosomal dominant polycystic kidney disease. Am. J. Kidney Dis., 1998; 32: 970–975

[3] Chapman A.B., Johnson A.M., Rainguet S., Hossack K., Gabow P., Schrier R.W.: Left ventricular hypertrophy in autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol., 1997; 8: 1292–1297

[4] Chen H., Watnick T., Hong S.N., Daly B., Li Y., Seliger S.L.: Left ventricular hypertrophy in a contemporary cohort of autosomal dominant polycystic kidney disease patients. BMC Nephrol., 2019; 20: 386

[5] de Almeida E.A., de Oliveira E.I., Lopes J.A., Almeida A.G., Lopes M.G., Prata M.M.: Ambulatory blood pressure measurement in young normotensive patients with autosomal dominant polycystic kidney disease. Rev. Port. Cardiol., 2007; 26: 235–243

[6] Ecder T.: Cardiovascular complications in autosomal dominant polycystic kidney disease. Curr. Hypertens. Rev., 2013; 9: 2–11

[7] Ecder T., Edelstein C.L., Chapman A.B., Johnson A.M., Tison L., Gill E.A., Brosnahan G.M., Schrier R.W.: Reversal of left ventricular hypertrophy with angiotensin converting enzyme inhibition in hypertensive patients with autosomal dominant polycystic kidney disease. Nephrol. Dial. Transplant., 1999; 14: 1113–1116

[8] Ecder T., Schrier R.W.: Hypertension in autosomal-dominant polycystic kidney disease: Early occurrence and unique aspects. J. Am. Soc. Nephrol., 2001; 12: 194–200

[9] Ecder T., Schrier R.W.: Cardiovascular abnormalities in autosomal-dominant polycystic kidney disease. Nat. Rev. Nephrol., 2009; 5: 221–228

[10] Hanaoka K., Qian F., Boletta A., Bhunia A.K., Piontek K., Tsiokas L., Sukhatme V.P., Guggino W.B., Germino G.G.: Co-assembly of polycystin-1 and -2 produces unique cation-permeable currents. Nature, 2000; 408: 990–994

[11] Idrizi A., Barbullushi M., Strakosha A., Kodra S., Thereska N., Zaimi E., Gjyzari A., Petrela E.: The relation of hypertension, renal function and cardiovascular events in autosomal dominant polycystic kidney disease. G. Ital. Nefrol., 2007; 24: 595–599

[12] Ivy D.D., Shaffer E.M., Johnson A.M., Kimberling W.J., Dobin A., Gabow P.A.: Cardiovascular abnormalities in children with autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol., 1995; 5: 2032–2036

[13] Joly D., Hummel A., Ruello A., Knebelmann B.: Ciliary function of polycystins: A new model for cystogenesis. Nephrol. Dial. Transplant., 2003; 18: 1689–1692

[14] Kimberling W.J., Kumar S, Gabow P.A., Kenyon J.B., Connolly C.J., Somlo S.: Autosomal dominant polycystic kidney disease: Localization of the second gene to chromosome 4q13-q23. Genomics, 1993; 18: 467–472

[15] Lai S., Mastroluca D., Matino S., Panebianco V., Vitarelli A., Capotosto L., Turinese I., Marinelli P., Rossetti M., Galani A., Baiocchi P., D'Angelo A.R., Palange P.: Early markers of cardiovascular risk in autosomal dominant polycystic kidney disease. Kidney Blood Press. Res., 2017; 42: 1290–1302

[16] Levey A.S., Stevens L.A., Schmid C.H., Zhang Y.L., Castro A.F. 3rd, Feldman H.I., Kusek J.W., Eggers P., Van Lente F., Greene T., Coresh J., CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. Ann. Intern. Med., 2009; 150: 604–612

[17] Levy J.C., Matthews D.R., Hermans M.P.: Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care, 1998; 21: 2191–2192

[18] Lumiaho A., Pihlajamäki J., Hartikainen J., Ikäheimo R., Miettinen R., Niemitukia L., Lampainen E., Laakso M.: Insulin resistance is related to left ventricular hypertrophy in patients with polycystic kidney disease type 1. Am. J. Kidney Dis., 2003; 41: 1219–1224

[19] Mao Z., Xie G., Ong A.C.: Metabolic abnormalities in autosomal dominant polycystic kidney disease. Nephrol. Dial. Transplant., 2015; 30: 197–203

[20] Martinez-Vea A., Valero F.A., Bardaji A., Gutierrez C., Broch M., Garcia C., Richart C., Oliver J.A.: Left ventricular hypertrophy in hypertensive patients with autosomal dominant polycystic kidney disease: Influence of blood pressure and humoral and neurohormonal factors. Am. J. Nephrol., 2000; 20: 193–200

[21] Paavola J., Schliffke S., Rossetti S., Kuo I.Y., Yuan S., Sun Z., Harris P.C., Torres V.E., Ehrlich B.E.: Polycystin-2 mutations lead to impaired calcium cycling in the heart and predispose to dilated cardiomyopathy. J. Mol. Cell. Cardiol., 2013; 58: 199–208

[22] Perrone R.D., Abebe K.Z., Schrier R.W., Chapman A.B., Torres V.E., Bost J., Kaya D., Miskulin D.C., Steinman T.I., Braun W., Winklhofer F.T., Hogan M.C., Rahbari-Oskoui F., Kelleher C., Masoumi A., et al.: Cardiac magnetic resonance assessment of left ventricular mass in autosomal dominant polycystic kidney disease. Clin. J. Am. Soc. Nephrol., 2011; 6: 2508–2515

[23] Pietrzak-Nowacka M., Safranow K., Bober J., Olszewska M., Birkenfeld B., Nowosiad M., Ciechanowski K.: Calcium-phosphate metabolism parameters and erythrocyte Ca2+ concentration in autosomal dominant polycystic kidney disease patients with normal renal function. Arch. Med. Sci., 2013; 9: 837–842

[24] Pietrzak-Nowacka M., Safranow K., Czechowska M., Dutkiewicz G., Kornacewicz-Jach Z., Ciechanowski K.: Autosomal dominant polycystic kidney disease and hypertension are associated with left ventricular mass in a gender-dependent manner. Kidney Blood Press. Res., 2012; 36: 301–309

[25] Ravine D., Gibson R.N., Walker R.G., Sheffield L.J., Kincaid–Smith P., Danks D.M.: Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. Lancet, 1994; 343: 824–827

[26] Rostoff P., Gackowski A., Nessler J., Piwowarska W.: Left ventricular hypertrophy – current views on the pathophysiology, association with cardiovascular risk, and therapeutic options. Kardiol. Pol., 2010; 68: 815–823

[27] The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. The European Polycystic Kidney Disease Consortium. Cell, 1994; 77: 881–894

[28] Timio M., Monarca C., Pede S., Gentili S., Verdura C., Lolli S.: The spectrum of cardiovascular abnormalities in autosomal dominant polycystic kidney disease: A 10-year follow-up in a five-generation kindred. Clin. Nephrol., 1992; 37: 245–251

[29] Valero F.A., Martinez-Vea A., Bardají A., Gutierrez C., Garcia C., Richart C., Oliver J.A.: Ambulatory blood pressure and left ventricular mass in normotensive patients with autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol., 1999; 10: 1020–1026

[30] Zeier M., Geberth S., Schmidt K.G., Mandelbaum A., Ritz E.: Elevated blood pressure profile and left ventricular mass in children and young adults with autosomal dominant polycystic kidney disease. J. Am. Soc. Nephrol., 1993; 3: 1451–1457

The authors have no potential conflicts of interest to declare.