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Evolution of metabolic syndrome components in patients with autosomal-dominant polycystic kidney disease: a six-year follow-up study

Ewolucja składników zespołu metabolicznego u pacjentów ze zwyrodnieniem wielotorbielowatym nerek – 6-letnia prospektywna obserwacja

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

Summary

Aim: Long-term studies show that some metabolic syndrome (MS) components deteriorate renal function in autosomal dominant polycystic kidney disease (ADPKD) patients. The aim of this 6-year follow-up was to analyze early changes of all MS components and their associations with kidney function in the nondiabetic ADPKD patients with normal renal function, compared to controls.

Material/Methods: The follow-up physical and laboratory examinations were performed for 39 ADPKD patients (age 43.7 ± 11.4 years) and 44 controls (43.5 ± 9.1 years).

Results: We noticed a significant increase in weight, body mass index (BMI), waist, total and LDL cholesterol, C-peptide, uric acid, creatinine and significant decline of HbA_{1c} and e-GFR in the ADPKD group. Increases in waist, uric acid and creatinine concentrations were significantly higher in the ADPKD patients than controls. Both groups showed similar rates of prediabetes, while diabetes developed in 5 controls (with 4 cases of type 2 diabetes and one case of type 1), but not in the ADPKD group (11% vs 0%, $P = 0.06$ for diabetes, 9% vs 0%, $P = 0.12$ for type 2 diabetes). The ADPKD group showed a significantly higher percentage of obesity, waist circumferences, systolic/diastolic blood pressure, concentrations of creatinine, urea and uric acid and lower e-GFR. The MS prevalence was comparable; however, the number of MS components was significantly higher in the ADPKD patients (median 2 vs. 1, $p = 0.001$).

Conclusions: The presence of MS does not influence the rate of renal failure progression in nondiabetic ADPKD patients with normal renal function at a 6-year follow-up.

Keywords: autosomal dominant polycystic kidney disease • kidney function • diabetes • metabolic syndrome

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disease resulting from mutations of *PKD1* (chromosome 16p13.3) [36] and *PKD2* (4q13-23) genes [18], which are responsible for polycystin 1 and 2 proteins synthesis [15].

Its prevalence is 1:400 to 1:1000 in Caucasians, which makes ADPKD the most frequent genetic kidney disease in that group. Biological functions of polycystins and clinical appearance of ADPKD are still being investigated. The most important ADPKD feature is the presence of kidney cysts, required to set the diagnosis [28]. The cysts numbers and sizes increase with age [25], which leads to the enlargement and damage of kidneys and the subsequent loss of their function [3]. Half of 60-year-old ADPKD patients require renal replacement therapy (RRT) [30]. ADPKD patients constitute 4–10% of dialysed patients in the developed countries (9% in Poland in 2010) [33].

The metabolic syndrome (MS) components such as decreased high-density lipoprotein (HDL) cholesterol level or hypertriglyceridemia in patients with chronic kidney disease (CKD) are associated with its progression to the end stage [4, 14, 21]. In ADPKD patients, renal function is affected by both unmodifiable factors such as age, gender and presence of *PKD1* gene, and modifiable factors such as hypertension (HT), hypercholesterolemia, hyperuricemia, and proteinuria, which was shown in long-lasting observational studies [23, 24]. Among ADPKD patients, MS was observed in 15.8% of renal transplant recipients (RTRs) [2].

Our previous study [26] compared the prevalence of the MS components according to the Adult Treatment Panel III (ATP III) and International Diabetes Federation (IDF) guidelines between nondiabetic kidney sufficient ADPKD patients and control groups. We have observed that the presence of ADPKD was associated not only with HT but also with abdominal obesity and higher fasting glycaemia levels.

The aim of this follow-up study was to analyze the evolution of the MS components in the previously studied groups of ADPKD patients and controls after 6 years in order to explore the associations of MS components with kidney function.

MATERIALS AND METHODS

The initial study included 49 ADPKD patients and 50 age- and sex-matched controls without renal disease. Inclusion criteria for the control group were the following: normal renal function (serum creatinine concentration <1.35mg/dl), negative family history of ADPKD, absence of cysts in kidneys (Ravine criteria not fulfilled) or any other kidney disease and no prior diagnosis of diabetes [26]. The 6-year follow-up examination was performed on 39 ADPKD patients (15 males and 24 females), as 3 women refused, 2 women and 3 men did not respond, and 2 patients were excluded because of an initiation of chronic hemodialysis. In the control group 44 subjects remained (19 men and 25 women) as 2 men refused, 3 women and 1 man did not respond.

The study protocol was approved by the Bioethics Committee of the Pomeranian Medical University (decision BN-001/135/06). All participants provided informed written consent.

Physical examination was performed with anthropometric measurements (body weight, height, waist and hip circumferences). The WHR (waist-hip ratio) was calculated as the proportion of waist to hip circumferences and the body mass index (BMI) as the weight/height squared (kg/m^2). BMI <25 kg/m^2 classified patients as normal, 25–30kg/m^2 as overweight, and >= 30 kg/m^2 as obese. The systolic blood pressure (SBP)/diastolic blood pressure (DBP) >= 140/90 mmHg or the use of antihypertensive medications qualified for HT diagnosis. MS was diagnosed according to the ATP III and IDF guidelines [8, 37].

Fasting venous blood samples of each participant were tested for glucose, insulin, C-peptide, hemoglobin A1c (HbA1c), creatinine, urea, uric acid (UA), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triacylglycerides (TG) concentrations. Patients with fasting glucose levels >= 100 mg/dl were subjected to the classical oral glucose tolerance test (OGTT) specified by the WHO

guidelines (75 g glucose) [39]. Glucose levels were assayed with an enzymatic-amperometric method (Cobas GLUC 800: 04,404,483,190 with a Super GL system, Diagnostic Systems, Germany), insulin concentration with a microparticle enzyme immunoassay (AxSym MEIA, Abbott Laboratories, Abbott Park, USA), C-peptide with an electrochemiluminescent method (Cobas 6000 system from Roche, Mannheim, Germany) and 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).

Table 1. Clinical and biochemical characteristics of the ADPKD and the control groups at the 6-year follow-up examination

Parameter	ADPKD group (n = 39)	Control group (n = 44)	P value [a]
Age, years	43.72 ± 11.4	43.49 ± 9.10	0.99
Male gender, n (%)	15 (38.5%)	22 (43.2%)	0.82
Weight, kg	80.35 ± 17.02	75.85 ± 16.32	0.19
BMI, kg/m^2	27.4 ± 5.3	25.7 ± 4.4	0.21
BMI >= 25 kg/m^2, n (%)	23 (58.97%)	25 (56.82%)	1.00
Obesity (BMI >= 30kg/m^2), n(%)	14 (35.9%)	7 (15.9%)	0.045
Waist, cm	92.59 ± 14.91	85.92 ± 12.87	0.03
WHR	0.89 ± 0.86	0.85 ± 0.84	0.06
SBP, mmHg	129.9 ± 19.38	115.34 ± 14.06	0.003
Hypertension, n (%)	32 (79.5%)	8 (18.2%)	<0.001
DBP, mmHg	89.36 ± 13.99	76.57 ± 10.21	<0.001
TC, mg/dl	218.8 ± 36.29	218.4 ± 39.09	0.93
LDL, mg/dl	132.4 ± 27.8	126.6 ± 37.35	0.27
HDL, mg/dl	55.7 ± 11.68	58.02 ± 13.71	0.49
TG, mg/dl	118.7 ± 58.12	119.7 ± 99.18	0.41
Fasting glucose, mg/dl	92.89 ± 14.0	95.0 ± 13.5	0.28
Fasting insulin, µU/ml	10.97 ± 10.31	12.11 ± 14.1	0.61
Fasting C-peptide, µU/ml	2.78 ± 1.43	2.34 ± 1.38	0.07
HbA_{1C}, %	5.22 ± 0.33	5.34 ± 0.56	0.83
Insulin/Glucose ratio	2.01 ± 1.43	2.14 ± 2.14	0.37
HOMA%S	61.23 ± 39.4	69.61 ± 43.58	0.86
HOMA%B	131.03 ± 73.11	133.35 ± 83.26	0.25
IFG, n (%)	7 (17.95%)	7 (15.9%)	1.00
IGT, n (%)	2 (5.13%)	0 (0.00%)	0.22
DM, n (%)	0 (0.0%)	5 (11.4%)	0.06
MS ATP III criteria, n (%)	10 (26.3%)	6 (13.6%)	0.17
MS IDF criteria, n (%)	12 (31.6%)	11 (25.0%)	0.62
Urea, mg/dl	37.49 ± 16.9	28.20 ± 8.61	0.005
Uric acid, mg/dl	6.39 ± 1.95	5.43 ± 1.39	0.03
Creatinine, mg/dl	1.08 ± 0.57	0.82 ± 0.12	<0.001
e-$GFR_{CKD\ EPI}$, ml/min/1.73m^2	81.38 ± 25.94	98.68 ± 11.64	0.001

ADPKD, autosomal dominant polycystic kidney disease; ATPIII, Adult Treatment Panel III; BMI, body mass index; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration equation; DBP, diastolic blood pressure; DM, diabetes mellitus; e-GFR, estimated glomerular filtration rate; HDL, high density lipoprotein cholesterol; HbA_{1c} hemoglobin A_{1c}; HOMA%B, homeostasis model assessment % beta; HOMA%S, homeostasis model assessment % sensitivity; IDF, International Diabetes Foundation; IFG, impaired fasting glucose; IGT impaired glucose tolerance; LDL, low-density lipoprotein cholesterol; MS; metabolic syndrome, SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHR, waist to hip ratio. Data presented as a mean ± SD or a number (percentage) of patients with a particular feature.

[a] the ADPKD group vs the control group; Fisher exact test for qualitative variables; Mann-Whitney test for quantitative variables

Insulin resistance was expressed as the homeostasis model assessment-% sensitivity (HOMA %S) index and beta cell function as the homeostasis model assessment-% beta (HOMA %B) index [20]. Estimated glomerular filtration rate (e-GFR) was calculated from a single serum creatinine measurement using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [19].

STATISTICAL ANALYSIS

Since most of the analyzed quantitative parameters presented distributions significantly different from the normal distribution (Shapiro-Wilk test), the following non-parametric tests were applied: the Mann-Whitney test was used to compare values between two groups and Wilcoxon signed-rank test was used to assess the significance of changes between the two time points. The correlations were evaluated with Spearman's rank correlation coefficient. Qualitative parameters were compared with the Fisher exact test. Two-tailed *P* value <0.05 was considered as statistically significant. Statistical analysis was performed with Statistica 12 software.

RESULTS

Clinical and biochemical parameters of the ADPKD and control groups at the follow-up examination are presented in Table 1.

Both groups were comparable in age and gender distribution. There were no significant differences between groups in terms of body weight and BMI; however, waist circum-

Table 2. Changes of the clinical and biochemical characteristics of the ADPKD patients and the control group between the initial examination and the follow-up examination after 6 years

Parameter	ADPKD group (n = 39)	Control group (n = 44)	P value [d]
Weight, kg	+4.65 ± 7.77[a]	+1.93 ± 5.69[c]	0.16
BMI, kg/m^2	+1.91 ± 2.61[a]	+0.94 ± 1.79[a]	0.09
Waist, cm	+7.54 ± 7.10[a]	+4.42 ± 6.32[a]	0.06
SBP, mmHg	-6.38 ± 21.71	-7.93 ± 14.38[b]	0.83
WHR	+0.050 ± 0.037	+0.041 ± 0.039	0.60
DBP, mmHg	-3.92 ± 13.76	-7.02 ± 10.23[a]	0.31
TC, mg/dl	+25.16 ± 24.38[a]	+21.41 ± 37.20[a]	0.57
LDL, mg/dl	+9.08 ± 22.91[c]	+5.18 ± 35.25	0.52
HDL, mg/dl	-1.55 ± 7.90	-4.18 ± 14.67	0.48
TG, mg/dl	+22.24 ± 56.25	+3.68 ± 105.81	0.08
Fasting glucose, mg/dl	+0.39 ± 12.96	+6.59 ± 10.17[a]	0.03
MS components	+0.39 ± 0.92	-0.23 ± 1.19	0.06
Fasting insulin, µU/ml	+1.63 ± 9.08	+3.33 ± 12.8	0.75
Fasting C-peptide, µU/ml	+0.58 ± 1.10[b]	+0.25 ± 1.13	0.07
HbA_{1C}, %	-0.22 ± 0.28[a]	+0.053 ± 0.39	<0.001
INS/GL ratio	+0.21 ± 1.26	+0.38 ± 1.20	0.72
HOMA%S	+2.95 ± 36.15	+2.36 ± 47.56	0.83
HOMA%B	+9.59 ± 76.19	-1.53 ± 128.85	0.18
Urea, mg/dl	+5.35 ± 13.92	+1.96 ± 6.28	0.53
Uric acid, mg/dl	+1.35 ± 1.50[a]	+0.48 ± 0.71[a]	<0.001
Creatinine, mg/dl	+0.24 ± 0.46[a]	+0.027 ± 0.096	<0.001
e-$GFR_{CKD\ EPI}$, ml/min/1.73m^2	-18.75 ± 15.47[a]	-6.70 ± 9.55[a]	<0.001

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration equation; DBP, diastolic blood pressure; DM, diabetes mellitus; e-GFR, estimated glomerular filtration rate; HDL, high density lipoprotein cholesterol; HbA_{1C}, hemoglobin A_{1C}; HOMA%B, homeostasis model assessment % beta; HOMA%S, homeostasis model assessment % sensitivity; IFG, impaired fasting glucose; IGT impaired glucose tolerance; INS/GL, insulin/glucose concentration ratio; LDL, low-density lipoprotein cholesterol; MS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHR, waist to hip ratio.

Data given as a mean ± SD of the differences between the follow-up and the baseline values

[a] $P < 0.001$, [b] $P < 0.01$, [c] $P < 0.05$, used for the significance of the difference between the initial examination and the follow-up examination (Wilcoxon signed-rank test)

[d] ADPKD vs the control group; Mann-Whitney test

ferences and the proportion of obese subjects were significantly higher in the ADPKD group. HT was observed more frequently in ADPKD patients with significantly higher SBP and DBP values. Concentrations of creatinine, urea and UA were significantly higher and e-GFR was lower in the ADPKD group. Fasting C-peptide levels were borderline significantly higher in the ADPKD group, while fasting levels of other metabolic parameters did not differ significantly between groups. Both groups showed similar rates of prediabetes: impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Diabetes was not diagnosed in the ADPKD group, while it developed in 5 patients of the control group (0% vs 11%, $P = 0.06$) as type 2 in 4 cases (0% vs 9%, $P = 0.12$) and type 1 in one case. The prevalence of the MS according to both ATP III and IDF criteria did not differ significantly between groups (Table 1); however, the number of MS components according to the ATP III criteria was significantly higher in the ADPKD patients (median 2 vs. 1, $P = 0.001$).

We have noticed (Table 2) a significant increase of weight, BMI, waist circumference and TC, LDL cholesterol, fasting C-peptide, UA, creatinine levels and a significant decrease of HbA_{1c} concentrations and e-GFR in the ADPKD group. In the control group, we have observed a significant increase in weight, BMI, waist, TC, fasting glucose, UA and a significant decrease in SBP, DBP, and e-GFR. The decline in e-GFR was significantly higher in the ADPKD group. The increases in waist circumference, BMI (border of significance), concentrations of UA and creatinine, C-peptide (border of significance) were significantly higher in the ADPKD patients, while the increase in fasting glucose was higher in the control group. The number of MS components increased only in the ADPKD group with borderline significance ($P = 0.06$), which could be attributed to the increase in waist circumference, as this was the only MS component that increased during the follow-up period.

We did not find any correlations between delta e-GFR and any baseline anthropometric or biochemical parameters in the ADPKD group while in the control group they positively correlated with fasting C-peptide (Rs = 0.31, $P = 0.04$) and the TG level (Rs = 0.34, $P = 0.02$) (Table 3). We also did not observe significant correlations between the delta e-GFR and deltas of other anthropometric and biochemical parameters in any of studied group (data not shown).

The comparison of delta e-GFR between different subgroups of ADPKD patients and controls stratified by gender and the presence of particular MS components in the initial examination (Table 4) showed only a significant difference between gender subgroups in ADPKD patients: e-GFR decreased significantly more in ADPKD women than men.

DISCUSSION

Our study of ADPKD patients with normal renal function and no diabetes is to our knowledge the first prospective study that evaluates the relationships of MS components with renal function.

We have shown that MS does not affect the rate of renal failure progression during the 6-year follow-up in ADPKD patients with initially normal renal function. According to long-lasting observational studies [23, 24], factors such as HT, hypercholesterolemia, hyperuricemia can deteriorate kidney function in ADPKD patients. Also, a decreased HDL cholesterol level or hypertriglyceridemia can affect kidney function in patients with CKD of etiology different than ADPKD [4, 14, 21]. We have not observed such relationships in our study, likely because the observation period was short and patients in the study group initially had normal kidney function.

We have observed MS (ATP III criteria) in 14% of ADPKD patients at the initial examination and in 26% at the follow-up examination, which was similar to the controls. The number of MS components increased only in the ADPKD group, which could be attributed to an increase in the waist circumference, since there was no other MS component that increased during the follow-up period.

There is no data on the prevalence of the MS syndrome in the ADPKD patients with normal renal function; however, MS was diagnosed in 16% of renal transplant ADPKD recipients [2].

After the 6-year period, we have observed a significant increase of waist circumferences in both groups, which was significantly higher in ADPKD patients and made the difference between groups significant, while it was not significant at the initial examination [26]. One of the reasons for waist increase could be the expansion of cystic kidneys. Chapman et al. in the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP study) [3] showed that the number of new cysts and cyst volumes in ADPKD patients increase gradually with age, leading to an increase of the total kidney volume (TKV). Another possible reason could be hepatomegaly due to cysts present also in the liver, which was observed at the initial examination significantly more often in our ADPKD group than in the controls [27]. A cross-sectional analysis of liver volumes measured with MRI showed that both cysts and parenchyma contribute to hepatomegaly in early ADPKD [12].

It is worth noting that the weight and BMI did not differ between groups at both examinations points. The weight gain was similar for both groups, while the increase in BMI was higher at borderline significance in the ADPKD patients. In this group the weight and BMI increases could also partially result from the enlarging cystic kidneys. The mean weight of a removed cystic kidney of ADPKD patients of a mean age of 52.2 years was 1515 g [1].

At the follow-up we have noticed a significant decrease in SBP and DBP only in the control group, so the ADPKD patients still showed higher values of SBP, DBP, and significantly higher percentage of HT (79.5% vs. 18.2%). Our results are consistent with the research of Kelleher et al. [17], who observed that the prevalence of HT in

Table 3. Correlations between delta e-GFR (the difference between the follow-up and the initial measurements of e-GFR) and the initial anthropometric and biochemical parameters in the ADPKD patients and the control groups. The Spearman's rank correlation coefficients (Rs) and the corresponding *P* values are presented

Parameters at the initial examination	ADPKD group (n = 39)		Control group (n = 44)	
	Delta e-GFR		Delta e-GFR	
	Rs	P value	Rs	P value
Age	0.15	0.37	0.12	0.46
Weight, kg	0.24	0.15	0.1	0.52
BMI, kg/m^2	0.14	0.39	0.23	0.13
Waist, cm	0.19	0.23	0.20	0.19
WHR	0.28	0.08	0.22	0.15
SBP, mmHg	-0.13	0.44	-0.01	0.97
DBP, mmHg	-0.16	0.32	0.16	0.30
Total body fat, %	-0.05	0.78	-0.08	0.61
Body fat, kg	0.08	0.64	-0.03	0.87
Total body water, %	0.09	0.58	0.08	0.60
Fasting glucose, mg/dl	0.1	0.55	-0.08	0.59
2h-OGTT glucose, mg/dl	-0.25	0.12	0.13	0.41
Fasting insulin, µU/ml	0.13	0.45	0.14	0.37
2h-OGTT insulin, µU/ml	-0.01	0.95	0.13	0.41
Fasting C-peptide, µU/ml	0.08	0.64	0.31	0.04
2h-OGTT C-peptide, µU/ml	-0.13	0.42	0.26	0.09
TC, mg/dl	0.02	0.93	0.19	0.22
LDL, mg/dl	-0.03	0.87	0.05	0.76
HDL, mg/dl	-0.03	0.84	0.06	0.71
TG, mg/dl	0.13	0.43	0.34	0.02
Uric acid, mg/dl	0.059	0.72	0.15	0.33
The number of MS components	-0.12	0.47	0.12	0.43

BMI, body mass index; DBP; diastolic blood pressure, e-GFR; estimated glomerular filtration rate, HDL; high density lipoprotein, LDL; low density lipoprotein, MS; metabolic syndrome, OGTT; oral glucose tolerance test, SBP; systolic blood pressure, TC; total cholesterol, TG; triglycerides, WHR; waist to hip ratio

ADPKD patients was much higher than in the general population and it had been increasing with age. HT is a common feature of ADPKD patients that appears even before a renal failure onset [7] and is associated with an increase of the total kidney volume, the renin-angiotensin-aldosterone system activation, and a progression of kidney dysfunction [34].

Panizo et al. [24] studied a group of ADPKD patients followed over a median period of 69 months to determine the time to reach the primary end-point of either a 50% e-GFR decrease since the first-time visit or an initiation of RRT. Patients that achieved the primary end point had higher SBP, DBP, serum LDL-cholesterol, creatinine, UA and proteinuria levels. A higher SBP and a younger age at the first visit were independent variables associated with a poorer renal outcome. The lack of similar correlations between e-GFR changes and SBP/DBP in our study group can be explained by its smaller group size, a better control of HT as well as the exclusion of ADPKD patients with diabetes. A larger proportion of our ADPKD patients were treated with angiotensin-converting enzyme (ACE) inhibitors (69% vs 41%), calcium antagonists (18% vs 10%) and some patients additionally received diuretics (21%) and beta-blockers (18%).

Table 4. The delta e-GFR (the difference between the follow-up and the initial measurements of eGFR) in the subgroups of ADPKD patients and controls stratified by gender and the presence of particular MS components in the initial examination

Subgroups at the initial examination	Delta e-GFR$_{CKD-EPI}$, ml/min/1.73 m^2					
	ADPKD patients (n = 39)			Control group (n = 44)		
	mean± SD	n	P value[a]	mean ± SD	n	P value[a]
Women vs Men	-22.09 ± 12.70	24	0.009	-6.61 ± 9.70	25	0.51
	-13.40 ± 18.29	15		-6.82 ± 9.61	19	
BMI <25 kg/m^2 vs BMI >= 25 kg/m^2	-18.67 ± 13.70	19	0.84	-9.19 ± 10.04	25	0.06
	-18.82 ± 17.35	20		-3.43 ± 7.97	19	
BMI <30 kg/m^2 vs BMI >= 30 kg/m^2	-20.03 ± 14.85	31	0.16	-6.34 ± 9.97	39	0.29
	-13.77 ± 17.86	8		-9.15 ± 5.00	5	
No HT vs HT	-20.73 ± 15.73	17	0.53	-6.21 ± 9.69	40	0.19
	-17.20 ± 15.46	22		-11.59 ± 7.22	4	
No IFG or IGT vs IFG or IGT	-20.39 ± 16.70	28	0.23	-7.20 ± 9.74	38	0.28
	-14.56 ± 11.54	11		-3.52 ± 8.28	6	
No MS vs MS (ATP III criteria)	-18.29 ± 16.30	32	0.53	-7.16 ± 10.10	37	0.45
	-20.86 ± 11.30	7		-4.27 ± 5.75	7	
No MS vs MS (IDF criteria)	-18.11 ± 14.10	28	0.90	-7.3 ± 10.07	34	0.54
	-20.38 ± 19.20	11		-4.68 ± 7.60	10	

ATP III, Adult Treatment Panel III; BMI, body mass index; CKD-EPI formula, chronic kidney disease epidemiology collaboration; HT, hypertension; IDF, International Diabetes Foundation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; e-GFR, estimated glomerular filtration rate; MS, metabolic syndrome.
Data presented as a mean ± SD.
[a] *P* value used for the comparison between the indicated subgroups; Mann-Whitney test

Ozkok et al. [23] showed that older age, HT and proteinuria were risk factors of CKD progression and that baseline proteinuria positively correlated with annual delta % e-GFR decrease. In our study proteinuria was observed in only 3 ADPKD patients, which was not enough to achieve sufficient statistical power in the analysis of its relationship with delta e-GFR. We have observed a significant HbA1C and an insignificant glucose concentration decrease in the ADPKD group, while in the control group glucose concentration significantly increased. Our results seem to confirm observations made by Rowe et al. [32], who noticed that glucose metabolism of ADPKD patients is altered. Cells isolated from cysts show intensive glycolysis, upregulation of genes encoding glycolytic enzymes and downregulation of most of those involved in gluconeogenesis [35]. Rowe et al. suggested that higher glucose consumption and enhanced glycolysis may be the feature of ADPKD kidneys which potentially protect against the development of diabetes. In our study pre-diabetes (IFG or IGT) occurred equally frequently in both groups at each examination. Diabetes was an exclusion criterion in the initial examination [26] and no ADPKD patient developed diabetes during the 6 years of the follow-up, despite a significantly higher percentage of obesity, which is a risk factor for diabetes. In contrast, four controls developed type 2 and one type 1 diabetes. The last patient in 2013 showed a concentration of C peptide as 0.58 ng/ml and of anti-GAD antibodies as 885.38 U/ml and in April 2014 the concentration of C peptide was already 1.9 ng/ml. Based on the C-peptide concentration course, the diagnosis should be explained as a "slow progressive" type 1 diabetes (formerly LADA), which had been at least temporarily improving. That patient, showing the BMI on the border of overweight, the waist circumference qualifying for abdominal obesity (according to the IDF criteria) and normal current C-peptide concentration, without the anti-GAD antibodies determination would likely be diagnosed with type 2 diabetes.

Reed et al. [29] found only 22 patients with diabetes among 1340 ADPKD patients and they were of the age of 47.8 ± 10.8 years and BMI 33.6 ± 7.9 kg/m^2. Our ADPKD patients were 4 years younger, had slightly higher BMI and were Caucasian, while in the study of Reed et al. some patients were probably African Americans, who are more genetically predisposed to diabetes [13]. It is likely that ADPKD patients with severe obesity are at a higher risk of diabetes, while overweight ADPKD patients are sufficiently protected by the suggested hypothetical mechanisms associated with glucose metabolism modification. Mao et al. [22] considered that polycystin proteins, being expressed in pancreatic beta cells, could regulate insulin secretion, which can explain the lack of higher insulin concentrations in the ADPKD group despite a significantly higher percentage of obesity.

The C-peptide concentration was borderline significantly higher in the ADPKD group at both examinations and it increased in both groups significantly, borderline significantly more in the ADPKD group. C-peptide is metabolized primarily by the kidneys [16], so its higher concentration could hypothetically result from metabolic function deterioration of the polycystic kidney. Insulin is metabolized mainly in the liver, which explains the lack of differences in its concentrations between groups at both examinations.

The concentration of UA, which is one of the additional MS components, did not differ significantly between groups in the initial study [26]. At the follow-up, the concentration of UA increased in both groups, significantly more in the ADPKD patients, which made the difference between groups statistically significant. The UA concentration increase in ADPKD can be partly attributed to the e-GFR decrease. We did not show a correlation between the initial UA concentration and the e-GFR value. Similarly in the CRISP study, serum UA was not associated with the e-GFR decline [38]. Also, the study of Han et al. of 365 ADPKD patients with e-GFR >= 15 ml/min/1.73m^2 showed that, even though hyperuricemia was associated with reduced e-GFR, it was not an independent factor of renal insufficiency progression during a 6-year follow-up [9]. However, other studies reported that in ADPKD patients serum UA may be considered as an independent factor for renal insufficiency progression and is associated with earlier kidney enlargement, HT, and increased hazard for the end stage renal disease (ESRD) [10]. The retrospective analysis of 680 ADPKD patients made by Riviera et al., which revealed that higher UA levels were associated with an increased risk of ESRD independently of gender, BMI, and renal function, also confirm this relationship [31].

The value of e-GFR, which did not differ between groups in the initial study [26], decreased significantly at the follow-up in both groups. The e-GFR decrease was twice as much in the ADPKD group than in the controls and became significantly lower (by 17 ml/min/1.73m^2) with the annual decline rate of -3 ml/min/1.73m^2 per year. Two patients that developed ESRD and had been initiated on hemodialysis were excluded from our study to prevent non-ADPKD influence of ESRD and RRT on analyzed metabolic parameters and to make the study group more homogenous.

In the study by Higashihara et al. [11], the annual e-GFR decline rate in ADPKD patients in stage 2 of CKD (n = 60) and age of 42.4 ± 10.2 years was -3.5 ± 4.1 ml/min/1.73m^2. The authors showed that e-GFR decline rate after adolescence was relatively constant and was not correlated to age or baseline e-GFR values. Panizo et al. [24] observed the mean annual GFR decrease of -3.52 ± 7.3 ml/min/1.73 m^2 in 101 ADPKD patients aged 43± 17.3 years. In our ADPKD patients of similar age, the delta e-GFR was comparable and also did not correlate with age.

The e-GFR decrease was significantly greater in ADPKD women subgroup compared to men (Table 4). Our results differ from the retrospective study of Ozkok et al., who observed 323 ADPKD patients aged 53 ± 15 years for 100 ± 38 months and showed that delta e-GFR did not significantly differ between males and females

(2.04% vs 2.22% per year, $P = 0.08$) [23]. The difference might have resulted from patients in that group being approximately 10 years older than in our study.

We have also observed a significant decrease in e-GFR at a rate of slightly more than1 ml/min/1.73m^2/year in the control group. Structural and functional changes in healthy kidney associated with age are proven in literature [6]. It is also known that the presence of accompanying diseases: HT, diabetes, or IGT can lead to a decrease in e-GFR. The annual decline of e-GFR in population of healthy individuals between 41–50 years was observed at a rate of -1.07 ± 0.08 ml/min/1.73 m^2 [5], which is similar to our control group. In our study 18.2% of the controls were diagnosed with HT, 16% had IFG, and several developed diabetes; however, these conditions were unrelated to e-GFR changes.

In the short observation period (6 years) we have not observed any significant correlations between e-GFR and MS components (including UA as additional component) or anthropometric data in our ADPKD group. We can conclude that ADPKD was the only significant factor responsible for renal function deterioration and the accompanying MS components showed no significant impact.

CONCLUSIONS

The presence of MS components in ADPKD patients with normal renal function and no diabetes does not affect the progression of renal failure in a 6-year follow-up period.

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