

Evaluation of post-transplant complications, patient and graft survival in patients with autosomal dominant polycystic kidney disease after renal transplantation; A single center experience

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Abstract

Aim: Autosomal dominant polycystic kidney disease (ADPKD) is systemic, progressive hereditary disease, characterized by cyst formation in multiple organs. Patients with ADPKD mostly develop end stage renal disease (ESRD) and require renal replacement therapy, preferably renal transplantation (RT). In this study, we aimed to compare the post-RT complications, patient and graft survivals in patients with ADPKD and other etiologies of ESRD.

Materials and Methods: We retrospectively evaluated patients' baseline characteristics, post-RT complications, patient and graft survival in patients with ESRD underwent renal transplantation due to ADPKD and other etiologies. We included 28 patients in ADPKD and 28 patients in the control group.

Results: The mean survival time was 224.83 ± 7.53 months in all patients. During follow-up period 1 patient died in both groups and 10 years patients and graft survivals were similar for both groups. The graft survival, acute and chronic rejections and glomerular filtration rate levels were similar in both groups end of the first year of RT but total cholesterol and glucose levels were significantly higher in the ADPKD group. Moreover, developing of ischemic heart disease was significantly higher in ADPKD (32% vs 0%, $p=0.002$), the other complication rates were similar in both.

Conclusion: As a comparison to patients with ESRD underwent RT due to ADPKD and different etiologies, both groups have similar patient and graft survival rates. Patients with ADPKD after transplantation may have a higher incidence of ischemic heart disease.

Keywords: Autosomal dominant polycystic kidney disease; ischemic heart disease; post-transplant complications; renal transplantation; survival

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary disease leading to end stage renal disease (ESRD) in the developed countries with an incidence of 1:400 to 1:1000 (1-5). ADPKD is a systemic disease and may also involve extra-renal organs, including brain, liver, spleen, duodenum, colon, pancreas, lungs, prostate, epididymis and testes (6-9). Renal failure develops slowly and nearly 70% of ADPKD patients will progress to ESRD in their 50s (10). ADPKD is responsible for approximately 7-10% of dialysis patients in United States (4). Renal transplantation (RT), hemodialysis (HD) and peritoneal dialysis (PD) are the primarily preferred

renal replacement therapies (RRTs) in patients with ESRD (6-10). RT is best and desired RRT for patients with ESRD due to ADPKD. A study showed that RT has become a preferred RRT model and numbers of transplantation were increased from 1991 to 2010 in patients with ADPKD (11). RT increases the quality of life, also reduces mortality compared to patients treated with HD and PD. Although, a RT can be a lifesaver treatment model, but it may result in complications that range from minor to catastrophic (12). In the present study, we aimed to compare post-RT complications, patient and graft survivals in the patients with ESRD underwent RT due to ADPKD and other reasons.

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MATERIALS and METHODS

Ethics

This study was approved by the clinical research ethics committee of Istanbul University Istanbul Faculty of Medicine the study (No:212/522-1016).

Setting and Study Population

Patients underwent RT between 2003 and 2012 at the XXX University School of Medicine were screened. Total 1200 patients' files reviewed and patients with lost follow-up data were excluded from the analysis. Patients matched for sex and transplantation time were included study as a control group. A total of 28 patients with ADPKD and 28 patients with other etiologies were caused ESRD and underwent RT included in this retrospective study (Figure 1). Patient baseline characteristics, previous and current smoking status, transplant related outcomes and complications, including new onset Diabetes Mellitus after transplantation (NODAT), hyperlipidemia, post-transplant hypertension (HT) and post-transplant erythrocytosis (PTE) and pos-transplant treatments including immunosuppressive regimens, antihypertensive, antihyperlipidemic and antiaggregants were recorded.

Smoking is a major risk factor developing complications in patients with ESRD before and after RT. However, the subjects smoking history and current status in the records were not reliable due to patients' self reports and and their companies' reports were inconsistent at outpatient visits particularly after RT. We were not able to report patients' smoking status and determine smoking effects on the complications in this study.

Statistical Analysis and Ethics

Data analysis was conducted using NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). The parametric variables were presented as mean \pm SD and were analyzed by the student t-test. Statistical analysis was performed using the Mann-Whitney U-test for non-parametric samples. In the comparison of qualitative data Continuity Correction (Yates) Chi-square test and Fisher's exact chi-square test were used. Kaplan-Meier survival analysis and the log rank tests were used in survival analysis. $P < 0.05$ was considered as statistically significant. The sample size was estimated using sample size calculator software with 95% confidence interval and $P < 0.05$.

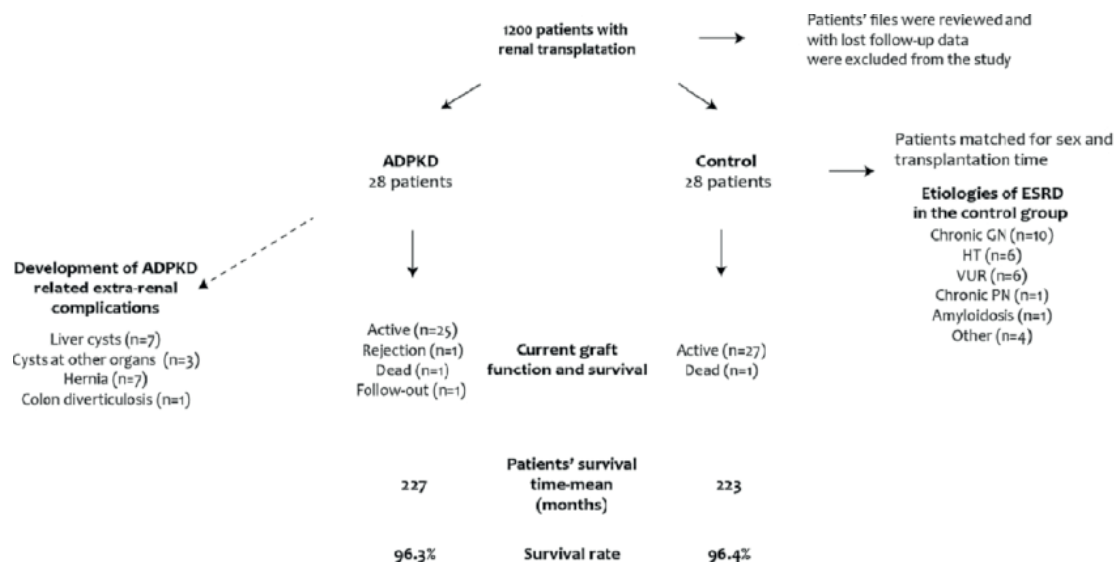


Figure 1. The study design: Total 1200 patients' files reviewed and a total of 28 patients with ADPKD and 28 patients with other etiologies were caused end stage renal disease (ESRD) and underwent renal transplantation included in this retrospective study. ADPKD: Autosomal dominant polycystic kidney disease, GN: Glomerulonephritis, HT: Hypertension, VUR: Vesicoureteral reflux, PN: Pyelonephritis

RESULTS

Baseline Characteristics

There were 28 patients with ADPKD and 28 with other causes of ESRD underwent renal transplantation. Total 55 patients had complete follow-up information, 1 patient lost follow-up on the 18th month after transplantation in ADPKD group. In the control group, the underlying etiologies of ESRD were chronic glomerulonephritis (n=10, 36%), hypertensive nephrosclerosis (n=6, 21%), vesicoureteral reflux (VUR) nephropathy (n=6, 21%), chronic pyelonephritis (n=1, 3.6%), amyloidosis due to Familial

Mediterranean Fever (FMF) (n=1, 3.6%) and other reasons (n=4, 14%) (Figure 1). Mean-follow-up times were similar in both groups, in the ADPKD group 80 ± 58 (median; 70) months, in the control group 84.3 ± 55 (median; 71) months, respectively. Age and body weight of the ADPKD group significantly higher than the control group (Table 1).

Patient sex, donor type (live/deceased), and type of RRT before RT were similar in the two groups. However, the ADPKD group live donors were mostly unrelated (n=15, 54%), in contrast the control group donors were mostly relative (n=23, 82%) (Table 1).

Table 1. Demographic and clinical features

	ADPKD (n=28)	Control (n=28)	P
Age	46.3±9.1	37.3±10.6	0.001
Sex (F/M)	5/23	5/23	NS
Weight (kg)	75.6±11.2	65.3±11.3	0.001
Donor type			
Live-Unrelated	15 (%53.6)	1 (%3.6)	0.001
Live-Relative	10 (%35.7)	23 (%82.1)	0.001
Cadaver	3 (%10.7)	4 (%14.3)	NS
RRT before RT			
Preemptive	5 (%17.9)	5 (%17.9)	NS
HD	22 (%78.6)	18 (%64.3)	NS
PD	0	3 (%10.7)	NS
HD+PD	1 (%3.6)	2 (%7.1)	NS
Hypertension before RT	20 (%71.4)	18 (% 64.3)	NS
Native nephrectomy			
Pre-transplant	2 (7.1%)	3 (10.7%)	NS
Simultaneous with RT	5 (17.9%)	2 (7.1)	NS

ADPKD: Autosomal dominant polycystic kidney disease, F: Female, M: Male, RRT: Renal Replacement Therapy, RT: Renal Transplantation, HD: Hemodialysis, PD: Peritoneal dialysis, NS: Not significant

Patient and graft related outcomes and immunosuppressive treatments

The 52 of 55 grafts were active (94.5%) and graft loss occurred in 3 (5%) patients; 1 patient had chronic rejection and 2 patients due to death (Figure 1). The mean graft survival was 220.86 ± 8.37 months. Graft survival rates for 5 years were 96.3% in the ADPKD group and 100% in the control group. Graft survival rates for 10 years were similar for the both groups, this rates was 96.3% in the ADPKD and 96.4% in the control group (Table 2). One death was recorded in the each group, first death recorded at 71th month in the control group and 217th month in the ADPKD group. The causes of death were sepsis due to pneumonia in a patient in the control group and ischemic heart disease in a patient with ADPKD. Patient survival analysis is shown in Table 3.

Table 2. Graft survival analysis

	N	Graft loss	Live	Survival Rate	Cumulative Survival	Mean Survival Time
					Avr.	Std. Error
ADPKD	27	2	25	92.6%	48.1	34.0
Control	28	1	27	96.4%	93.3	6.4

ADPKD: Autosomal dominant polycystic kidney disease

Table 3. Patient Survival Analysis

Group	N	Ex	Live	Survival Rate	Cumulative Survival	Mean Survival Time
					Avr.	Std. Error
ADPKD	27	1	26	96.3%	50.0	35.4
Control	28	1	27	96.4%	93.3	6.4

ADPKD: Autosomal dominant polycystic kidney disease

Patients were treated with six different types of a triple immunosuppressive regimens. Cyclosporin A (CsA) + Mycophenolat Mofetil (MMF) + steroid and Tacrolimus (FK) + MMF + steroid were most common immunosuppressive regimens for both groups (Table 4). Total 22 patients, 7 (25%) in the ADPKD and 15 (54%) in the control group, received CsA + MMF + steroid regimen and 22 patients, 12 (43%) in the ADPKD and 10 (36%) in the control group, received FK + MMF + steroid regimen. However, there were no significant differences between treatment regimen in both groups (Table 4).

Table 4. Immunosuppressive Treatments to Maintain Graft Functions

	ADPKD (n=28) n (%)	Control (n=28) n (%)	P
CsA+MMF+steroid	7 (25%)	15 (53%)	NS
CsA+AZA+ steroid	5 (17.9%)	3 (10.7%)	NS
CsA+Sirolimus+steroid	2 (7.1%)	0	NS
CsA+Everolimus+steroid	1 (3.6%)	0	NS
FK+MMF+ steroid	12 (42.8%)	10 (35%)	NS
Sirolimus+MMF+steroid	1 (3.6%)	0	NS

ADPKD: Autosomal dominant polycystic kidney disease, AZA: Azathioprine, CSA: cyclosporin A., FK: Tacrilumus, MMF: Mycophenolate Mofetil, NS: Not significant

Chronic allograft nephropathy (CAN) was shown by biopsy in 3 (10.7%) patients in the ADPKD group, while CAN did not detect in the control group (Table 5). However, CAN was not statistically differ in two groups. Post-transplant proteinuria and graft function were similar in the both groups. Post-transplant proteinuria and graft functions at the last outpatient visits are shown in Table 5. Serum creatinine levels and glomerular filtration rates (GFR, MDRD equation) were similar after 1 year follow-up. Fasting glucose, triglyceride and total cholesterol levels were significantly higher in the ADPKD group after 1 year follow-up (Table 6).

Post-transplant Treatments and Complications

There was not significant difference between the two groups regarding the mean number of antihypertensive medications, statin and Acetylsalicylic acid (ASA)

treatments (Table 7). Developing of ischemic heart disease after transplantation period was statistically significantly higher in the ADPKD group compare the control group (Table 8). Total 9 (32%) patients have developed ischemic heart disease in the ADPKD group, 2 patients had signs of previous myocardial infarction (MI) on their ECG and myocardial perfusion scintigraphy, 6 of them had stent placement due to acute MI (AMI) and one patient required coronary artery bypass grafting (CABG) due to three vessel disease detected by coronary catheterization after cardiac arrest. The latter patient died due to another AMI at 217th month after RT. There were no difference between the two groups for other post-transplant complications, including NODAT, hyperlipidemia, post-transplant HT and PTE (Table 8).

Table 5. Graft functions of the patients at last outpatient visits

	ADPKD (n=28)	Control (n=28)	P
CAN (Biopsy-proven)	3 (10.7%)	0	NS
Proteinuria			
No	20 (71.4%)	18 (64.3%)	NS
<1 g/day	6 (21.4%)	8 (28.6%)	NS
1-3 g/day	1 (3.6%)	2 (7.1%)	NS
> 3 g/day	1 (3.6%)	0	NS
Graft Function			
Active	25 (89.3%)	27 (96.4%)	NS
Rejection	1 (3.6%)	0	NS
Mortality	1 (3.6%)	1 (3.6%)	NS
Follow-out	1 (3.6%)	0	NS

ADPKD: Autosomal dominant polycystic kidney disease, CAN: Chronic Allograft Nephropathy, NS: Not significant

Table 6. Average values of biochemical parameters at the first year after transplantation

	ADPKD (n=28) mean±SD (median)	Control (n=28) mean±SD (median)	P
Creatinin	1.63±1.58 (1.35)	1.42±0.39 (1.40)	NS
GFR	70.5±20.7	66.7±21	NS
Uric acid	6.6±1.5	6.10±1.21	NS
Fasting glucose	92±16.8	83.5±12	0.035
Triglyceride	189.6±93.5 (152.5)	144.1±63.9 (128.5)	0.009
Total cholesterol	216.8±51.2	189.3±29.6	0.018
LDL cholesterol	126.4±37	111.5±28.4	NS
HDL cholesterol	49.1±14.3	53.78±13.01	NS
Hemoglobin	13.4±2.0	13.6±1.6	NS
Hematocrit	42.0±7.1	41.6±5.3	NS

ADPKD: Autosomal dominant polycystic kidney disease, GFR: Glomerular Filtration Rate, NS: Not significant. Normal Values: Creatinin: 0.5-1.1mg/dl; GFR: 90-120ml/min/1.73m² (MDRD equation), Uric acid: 2.6-6mg/dL, Glucose: 70-105mg/dL, Triglyceride<150mg/dL, Total cholesterol<200mg/dL, LDL cholesterol: 60-129mg/dL, HDL cholesterol: 0-65mg/dL, Hemoglobin: 12.2-17.2 mg/dl; Hematocrit:36-54%

Table 7. Statistical analysis of current hypertension and hyperlipidemia treatments

	ADPKD (n=28) mean±SD (median) n (%)	Control (n=28) mean±SD (median) n (%)	P
Anti-hypertensive medications	2.25±0.92 (2)	2.03±1.26 (2)	NS
Anti-ihypertensive treatment			
None	0 (0%)	5 (17.9%)	0.048
≤2	16 (57.1%)	12 (42.9%)	NS
>2	12 (42.9%)	11 (39.3%)	NS
0.048	9 (32.1%)	11 (39.3%)	NS
NS	15 (53.6%)	10 (35.7%)	NS
NS	21 (75%)	15 (53.6%)	NS
NS	14 (50%)	7 (25%)	NS

ADPKD: Autosomal dominant polycystic kidney disease, ACE: Angiotensin converting enzyme, ARB: angiotensin II receptor blocker, Statins: HMG-CoA reductase inhibitors, ASA: Acetylsalicylic acid, NS: Not significant

Table 8. Post-surgical and medical complications following transplantation

	ADPKD (n=28)	Control (n=28)	P
Acute rejection attack	0	1 (3.6%)	NS
Postoperative ATN	1 (3.6%)	0	NS
NODAT	7 (25%)	2 (7.1%)	NS
New onset HT after RT	8 (28.6%)	6 (21.4%)	NS
Hyperlipidemia	23 (82.1%)	19 (67.9%)	NS
PTE	7 (25%)	5 (17.9%)	NS
Urinary tract infection	7 (25%)	11 (39.3%)	NS
Lower respiratory tract infection	11 (39.3%)	10 (35.7%)	NS
Zona Zoster	2 (7.1%)	5 (17.9%)	NS
Hyperuricemia	13 (46.4%)	12 (42.9%)	NS
Malignancy after RT	3 (10.7%)	2 (7.1%)	NS
Ischemic heart disease	9 (32.1%)	0	0.002
Osteoporosis	11 (39.3%)	13 (46.4%)	NS
Avascular necrosis	1 (3.6%)	2 (7.1%)	NS
Lymphocele	2 (7.1%)	6 (21.4%)	NS

ADPKD: Autosomal dominant polycystic kidney disease, ATN: Acute Tubular Necrosis, NODAT: New onset Diabetes Mellitus after transplantation, HT: Hypertension, RT Renal Transplantation, PTE: Post-transplant erythrocytosis, NS: Not significant

ADPKD Related Complications

The patients with ADPKD were not routinely screened for developing of related extra-renal complications after RT. However, extra-renal manifestation of ADPKD detected by imaging methods due to the patients' complaints for other reasons at outpatient visit in the post-transplant period. Total 10 (36%) patients had developed new cysts and most of the them were located in the liver (n=7). Moreover, 7 (25%) patients with ADPKD had developed a hernia and 1 (3.6%) had colon diverticulosis (Figure 1).

DISCUSSION

We designed a single center retrospective study to evaluate the post-transplant complications, patient and graft survivals in ADPKD patients treated with RT. Development of ischemic heart disease was the only complication found to be significantly higher in the ADPKD group compared to the non-ADPKD controls after RT. The other complication rates were similar in the both groups in the post-transplantation period. We also found that the patient and graft survival rates were similar in the both groups. Several previous studies showed similar results of patient and graft survival rates after RT in patients with ADPKD as compared with other reasons of ESRD (13-17).

Patient survival rates were 100% for both groups in first and fifth year in our study. Shiroyanagi et al, also showed similar results with our study and they found 5-year patient survival rates of 95% in RT patients with ADPKD (18). Moreover, 10-year patient survival rate was 100% in the ADPKD and 96.4% in the control group in our study. Graft loss has been observed in 2 patients with ADPKD and 1 in the control group. One patient in each group had a graft loss due to death, AMI in the ADPKD group and pneumonia related sepsis in the control group. Furthermore, graft loss caused by chronic rejection in an ADPKD patient at 18th month.

Cardiovascular diseases and complications including, ischemic heart disease, HT, cardiac valvulopathy and pericardial effusion are the most common known cause of death in the post-transplant period and lead to approximately 30% death of patients with functional grafts (6-10,19). Wang et al.(20), found that patients with ADPKD are thought to be at increased risk for cardiovascular complications due to endothelial dysfunction and accelerated atherosclerosis. In contrast, Kanaan et al. (21) found that patients with ADPKD are not associated with increased cardiac morbidity and mortality in the post-transplant period.

In our study, we found that developing of ischemic heart disease was remarkably higher in patients with ADPKD after RT (Table 8). We have analyzed risk factors for developing ischemic heart disease including HT (22), NODAT (23), hyperlipidemia and treatments of these risk factors in the both groups. The rate of HT before and after RT were similar in both groups, but these rates tend to be higher in the ADPKD compare to the control group (Table 1 and 8). However, the mean number of antihypertensive drugs was similar in both groups (Table 7). Providing effective blood pressure control with ACE inhibitors and ARBs is extremely important for improvement of patient survival and graft function and reducing cardiovascular risk in patients with ADPKD (24). NODAT is another risk factor for developing ischemic heart disease. Fasting glucose levels were significantly higher in the ADPKD group and rate of NODAT tend to be higher in the ADPKD group, but there was not any difference in both groups. Several studies have shown that patients with ADPKD

have increased risk for developing NODAT compared with other kidney transplant patients (25-27). However, some studies suggested that there was no association between ADPKD and increased incidence of NODAT (23,27-28). Our result on NODAT may not be conclusive due to a limited number of the subjects. Thus, further studies are needed to show association between ADPKD and NODAT. In our study, the average age, body weight, glucose and total cholesterol levels, but not LDL, were significantly higher in the ADPKD group than the control group. These factors may contribute to the development of ischemic heart disease more in ADPKD group (29-31). Smoking is another major risk factor for developing ischemic heart disease; unfortunately, we were not able to have reliable data to show in this study (in the method section). Thus, we are not able to determine the effects of smoking in our study.

Salehipour et al. (33), showed that patients with ADPKD had higher incidence of urinary tract infection than patients who underwent RT due to other etiologies of ESRD. Native kidneys could be a target for infection in the patients with ADPKD (32). However, the incidence of urinary tract infection tends to be higher, but not significant in the control group compared to the ADPKD group (Table 8). This result may be explained by two factors in our study; first reason is that 7 (25%) patients in ADPKD group had native nephrectomy either in pre-RT period or simultaneously with RT (Table 1). The second reason is that the control group has a quite considerable proportion of patients with VUR (n=6, 21%) (Figure 1). A study supporting our findings showed that native nephrectomy prior to RT is important to reduce the risk of urinary tract infections that may arise in the post-RT period in ADPKD patients (32).

PTE is developed in 10-20% in patients after RT and most of these patients had a history of polycystic kidney disease (33). We did not find any difference in the development of PTE in both groups (Table 7). PTE didn't emerge in patients having a bilateral nephrectomy before RT are suggesting that native nephrectomy may reduce the development of PTE. In a retrospective analysis of 500 recipients, 20% of patients developed PTE after RT and none of the patients had native nephrectomy prior to transplantation (35). Furthermore, native bilateral nephrectomy reduced high hematocrit and erythropoietin levels in a patient with PTE (36).

CONCLUSION

In a conclusion, we found that the incidence of ischemic heart disease is higher in patients with ADPKD. However, this is a single-center, retrospective and registry-based study, therefore reason and effect relationship cannot be established. In addition, we were not able to determine smoking effects on complications in our study. Our results need to confirm within prospective and large cohort studies. However, in conjunction with previous studies, cardiovascular diseases are one of the most important causes of patient and graft loss in post-RT period in patients with ADPKD. In order to reduce post-

RT cardiovascular complications in ADPKD, management of patients are considered that effective blood pressure and hyperlipidemia control, the prevention of obesity and diabetes, initiation of antiaggregant therapy in appropriate cases and cessation of smoking.

Competing Interests: The authors declare that they have no competing interest.

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Ethical Approval: This study was approved by the clinical research ethics committee of Istanbul University Istanbul Faculty of Medicine the study (No:212/522-1016).

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