Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Outcomes of renal transplantation in patients with autosomal dominant polycystic kidney disease: a nationwide longitudinal study

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Keywords
allograft survival, autosomic dominant polycystic kidney disease, renal transplantation.

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Conflicts of Interest
None.

Received: 22 November 2010
Revision requested: 23 December 2010
Accepted: 1 February 2011
Published online: 26 February 2011

doi:10.1111/j.1432-2277.2011.01237.x

Abstract

Renal transplantation in patients with autosomal dominant polycystic kidney disease (ADPKD) is a medical and surgical challenge. Detailed longitudinal epidemiological studies on large populations are lacking and it is mandatory to care better for these patients. The success of such a project requires the development of a validated epidemiological database. Herein, we present the results of the largest longitudinal study to date on renal transplant in patients with ADPKD. The 15-year outcomes following renal transplantation of 534 ADPKD patients were compared with 4779 non-ADPKD patients. This comprehensive, longitudinal, multicenter French study was performed using the validated database, DIVAT (Données Informatisées et VAlidées en Transplantaion). We demonstrate that renal transplantation in ADPKD is associated with better graft survival, more thromboembolic complications, more metabolic complications, and increased incidence of hypertension, whereas the prevalence of infections is not increased. This study provides important new insights that could lead to a better care for renal transplant patients with ADPKD.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disorder with major renal manifestations and, in some cases, abnormalities in the liver, pancreas, brain, arteries, or a combination thereof. ADPKD leads to kidney failure requiring dialysis in approximately 50% of patients, and typically develops in the fourth to sixth decades of life [1]. ADPKD is the most frequent cause of hereditary kidney disease and represents the cause of 6% of end stage renal disease in the French population [2]. Renal transplantation is usually considered the preferred therapeutic option for these patients, but constitutes a medical and surgical challenge [3–5]. Previous studies suggested that renal transplantation in patients with ADPKD was associated with an increased risk of new onset diabetes after transplantation (NODAT), adverse cardiovascular events, sepsis or various surgical complications [3–12]. However, such studies are often limited by their small size, a center effect or a limited follow-up time or were performed before the advent of modern immunosuppression. Improving graft and patient survival for renal transplant patients with ADPKD requires a better knowledge of long-term outcomes and ways to avoid specific complications. The aim of this study was to compare 534 ADPKD patients,

the largest population of renal transplant patients with ADPKD ever described to date, with 4779 non-ADPKD transplant patients followed up for up to 15 years. This comprehensive, longitudinal, multicenter French study was performed using the computerized and validated database, DIVAT (Données Informatisées et VAlidées en Transplantaion; http://www.divat.fr/).

Patients and methods

DIVAT database

The DIVAT is a renal transplant patient database that collects medical information for kidney transplant patients followed in various French centers including Nantes, Nancy, Montpellier, Toulouse, and Paris (Saint-Louis and Necker Hospitals) [12]. Data collected include donor and recipient baseline characteristics, follow-up of biological and clinical data, immunological and histological parameters, and the causes of graft failure and patient death. Data were prospectively collected and entered into the database by clinical research assistants. The system is validated by an independent annual audit that confirms the accuracy of the data collected. All patients gave written informed consent for their medical information to be collected in DIVAT for clinical research purposes. This consent is given at the time of the transplantation.

Patients

All patients who received a kidney transplant between January 1, 1988 and October 31, 2007, were included in this longitudinal assessment. During this period, 6650 transplants were performed. We excluded patients younger than 18 years of age at the time of transplantation, patients with multi-organ transplants (kidney–pancreas and liver–kidney) as well as patients who had undergone previous renal transplants from the analysis. A total of 5313 transplants were analyzed. The median duration of follow-up was 7 years. Two groups of patients were compared: a group of patients whose initial nephropathy was ADPKD, hereinafter referred to as the ''ADPKD group'' (534 patients, 10.1%) and patients whose renal failure was not related to the ADPKD, termed as the ''control group'' (4779 patients, 89.9%). Demographic data regarding donors and recipients, as well as follow-up medical and biological data, were analyzed. Hyperlipidemia was defined as LDL cholesterol > 2.54 mM and/or triglycerides > 1.7 mM.

Statistical analysis

Qualitative variables were expressed as percentages, and continuous variables were expressed as mean ± standard deviation. Percentage comparisons were performed using the chi-square test. Continuous variables were compared using the Student's *t*-test. Patient and graft survival analyses were performed using the Kaplan–Meier methods and compared with the Log-Rank test. The *P* values <0.05 were considered statistically significant. Statistical analyses were performed using the software R, version 2.11 (http://www.R-project.org).

Results

Patient characteristics

Donor and recipient characteristics are listed in Table 1. Regarding donor characteristics, ADPKD patients were transplanted with significantly older kidneys (44.1 ± 4.4 years vs. 41.1 ± 1.7 years, $P < 0.001$) that were more frequently from a living donor (5% vs. 7%, $P = 0.04$) who more frequently died from complications of cardiovascular disease (43% vs. 37%, $P = 0.005$). Cold ischemia times were also significantly longer in ADPKD patients (24.4 ± 7.4 vs. 23.3 ± 7.1, $P = 0.03$). ADPKD recipients were older and more frequently women than non-ADPKD recipients (52.8 ± 7.7 years vs. 44.3 ± 9.3 years, $P < 0.001$). Dialysis duration before transplantation was 25% shorter in ADPKD patients (3.17 ± 0.7 years vs. 4.14 ± 1.3, years, $P < 0.001$) and they were less sensitized against human leukocyte antigens (HLA) than were non-ADPKD patients (13% vs. 24%, $P < 0.001$). No differences were observed regarding immunosuppressive regimens at the time of the transplantation (Table 1). Before transplantation, 33.1% of the patients underwent a nephrectomy. The most frequent cause of nephrectomy was prophylactic (70.8% of the cases) and the other indications were recurrent infections (15.4%), recurrent hematuria (6.2%), cystic hemorrhages (3%), and cancer (1.5%).

Complications

Complications are listed in Tables 2 and 3. Although the incidence of infection and biopsy-proven acute rejection (BPAR) was similar between groups, the prevalence of metabolic complications was higher in the ADPKD group. ADPKD patients were more frequently hyperlipidemic (49.7% vs. 39.3%, $P < 0.001$) and hypertensive (49.7% vs. 42.3%, $P = 0.001$). We also observed a trend toward an increased prevalence of NODAT (12.4% vs. 9.6%, $P = 0.06$) in the ADPKD group. However, cardiovascular events (4.3% vs. 4.4%, $P = 0.88$) and stroke (1.1% vs. 1.7%, $P = 0.31$) were similar between both groups, even after adjusting for age and gender. Intracranial aneurism rupture has been diagnosed in two ADPKD patients after transplantation. The evolution was favorable with an endovascular procedure in one case, and the other patient deceased soon after the rupture. Heart valve disease was

Table 1. Donors' and recipients' characteristics.

	ADPKD group (n = 534)	Control group (n = 4779)	P-value
Donor characteristics			
Age (years)	44.1 ± 4.4	41.1 ± 1.7	<0.001
Living donors (%)	5	7	0.04
HLA mismatch	2.9 ± 1	2.86 ± 0.9	0.5
Cardiovascular cause of death (%)	43	37	0.005
Cold ischemia time (h)	24.4 ± 7.4	23.3 ± 7.1	0.03
Recipient characteristics			
Age (years)	52.8 ± 7.7	44.3 ± 9.3	<0.001
Gender ratio (male, %)	55	63	<0.001
Dialysis duration (years)	3.17 ± 0.7	4.14 ± 1.3	<0.001
Prior transplantations (%)	6	7	0.76
PRA > 0 (%)	13	24	<0.001
Hyperlipidemia* (%)	15	13	0.2
BMI (kg/cm^2)	23.9	22.8	<0.001
Prior cardiovascular events† (%)	72	68	0.1
Chronic hepatitis C (%)	5	9	0.004
Chronic hepatitis B (%)	0	2	<0.001
Immunosuppressive drugs (%)			
Induction			
None	15.5	14	NS
Anti-thymocyte globulins	73	66	
OKT3	1.5	4	
Anti-CD25	10	16	
Cyclosporine	76	78	0.6
Tacrolimus	22	15.3	0.341
Mycophenolate mofetil	48	37.5	0.21
Azathioprine	50.7	42.3	0.11
Sirolimus	1.1	1.7	0.31

Continuous data are presented as mean ± standard error of the mean (SEM).
ADPKD, autosomal dominant polycystic kidney disease; HLA, human leukocyte antigen; PRA, panel reactive antibody; NS, nonsignificant.
*Hyperlipidemia: defined as LDL cholesterol > 2.54 mM and/or triglycerides > 1.7 mM.
†Prior cardiovascular events: cardiac ischemic event or stroke.

Table 2. Complications.

	ADPKD group (n = 534)	Control group (n = 4779)	P-value
Biopsy-proven acute rejection (%)	24.3	27.4	0.13
NODAT (%)	12.4	9.6	0.06
Hyperlipidemia (%)	49.7	39.3	<0.001
Lipid-lowering therapy use (%)	48	37.5	<0.001
Hypertension (%)	49.7	42.3	0.001
Stroke (%)	1.1	1.7	0.31
Cutaneous cancer (%)	7.9	7.4	0.71
Kidney cancer (%)	0.4	0.6	0.5
Thromboembolic disease (%)	8.6	5.8	0.009

Continuous data are presented as mean ± standard error of the mean (SEM).
ADPKD, autosomal dominant polycystic kidney disease; NODAT, new onset diabetes after transplantation.

Table 3. Infectious complications.

	ADPKD group (n = 534)	Control group (n = 4779)	P-value
All types (%)	67.7	70.4	<0.18
Lower urinary tract infections (%)	48.4	44.9	0.12
Pyelonephritis (%)	6.2	7.6	0.22
Abdominal (%)	6.5	5.6	0.4
Pulmonary (%)	15.9	18	0.25
Bacteriemia (%)	7.5	5.6	0.07
Others (%)	15.5	18.3	0.3

ADPKD, autosomal dominant polycystic kidney disease.

diagnosed in 19 ADPKD patients (3.5%), usually in the form of mitral or aortic insufficiency, and cardiac failure occurred in two (10%) of these patients during the

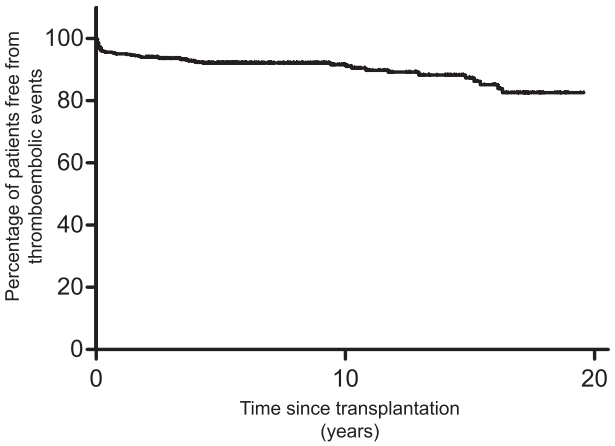

Figure 1 Incidence of thromboembolic events in autosomal dominant polycystic kidney disease (ADPKD) patients. The incidence of thromboembolic events over the follow-up period in ADPKD patients was established with the Kaplan–Meier method.

follow-up. The prevalence of cutaneous malignancies (7.9% vs. 7.4%, $P = 0.71$) and kidney cancers (0.4% vs. 0.6%, $P = 0.50$) was similar between groups.

Importantly, thromboembolic complications (venous thrombosis and/or pulmonary embolisms) were more frequent in the ADPKD group (8.6% vs. 5.8%, $P = 0.009$). Thromboembolic events in the ADPKD group occurred 28.4 ± 47 months after transplantation and their incidence was stable over the follow-up period (Fig. 1). Interestingly, the mean ± SE body mass index in ADPKD patients was significantly higher than that found in ADPKD patients without thromboembolic complications: 25.1 ± 5.2 vs. 23.0 ± 4.6, respectively, $P = 0.02$. Post-transplantation erythrocytosis occurred in 17 ADPKD patients (3.1%) and was not associated with the occurrence of thromboembolic complications or patients and grafts survivals.

Hepatic cysts were reported in 80.7% of the ADPKD group. Complications related to these cysts occurred in 4.3% of the patients (infection: two patients, pain: two patients, hepatomegaly with ascites: one patient). Two patients underwent surgery related to cysts complications. Liver polycystic disease was not associated with thromboembolic events.

Patients and grafts survivals

Patient survival was similar between groups [ADPKD vs. non-ADPKD: 93.4% vs. 93.4% at 5 years, 87.4% vs. 87.2% at 10 years and 78.7% vs. 82.4% at 15 years ($P = 0.464$)] (Fig. 2). Graft survival, measured after censoring death, was higher in the ADPKD group [90.4% vs. 86.9% at 5 years, 81.1% vs. 75.4% at 10 years and 76% vs. 66% at 15 years ($P = 0.0187$)] (Fig. 3). Of note, recurrence of nephropathy was diagnosed in 6.7% of non-ADPKD patients. Nephrectomy status did not influence graft and patients' survival.

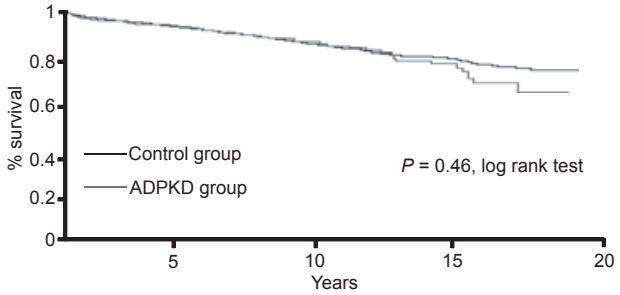

Figure 2 Patients survival. Patient survival curves were established with the Kaplan–Meier method and were compared using the Log-Rank test. *P* values <0.05 were considered statistically significant.

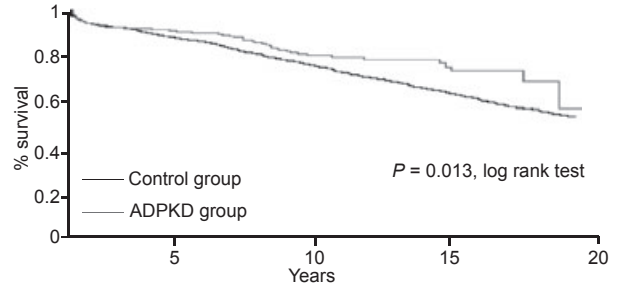

Figure 3 Allografts survival. Allograft survival curves censored for patient death were established with the Kaplan–Meier method and were compared using the Log-Rank test. *P* values <0.05 were considered statistically significant.

Discussion

Detailed longitudinal epidemiological studies on large populations are needed to obtain a comprehensive view of a specific medical situation. The success of such studies requires the establishment and management of validated epidemiological databases [13–15]. Herein, we present the largest multicenter, nationwide, and longitudinal study focusing on the outcomes of renal transplantation in patients with ADPKD. This detailed analysis of a population of 5314 renal transplant recipients, including 534 ADPKD patients, demonstrates that (i) graft survival is better in ADPKD than in control patients, (ii) thromboembolism is an important complication of renal transplantation in ADPKD patients, (iii) metabolic complications and hypertension are more prevalent in ADPKD patients after transplantation than in non-ADPKD patients, and (iv) infections rates are similar between groups.

Graft survival was significantly higher in ADPKD patients than in non-ADPKD patients. This result is unexpected because ADPKD were at higher risk for graft failure because they were transplanted with older kidneys with a more significant proportion of donors who died due to a cardiovascular cause, a smaller proportion of living donors and more prolongated cold ischemia times [16]. Such a difference is explained, at least in part, by the absence of initial nephropathy recurrence; it has been shown recently that the recurrence of initial nephropathy is one the most important causes of graft loss [17]. However, no comprehensive histological study exists to explain the causes of graft loss in our population. Another explanation could be that ADPKD patients are the less immunized against HLA antigens than non-ADPKD patients. Although the prevalence of BPAR was similar between the two groups, it is possible that this could impact the development of chronic rejection. Once again, detailed histological data are lacking to characterize the role of chronic rejection in graft loss.

For unclear reasons, thromboembolic complications are significantly more frequent in ADPKD patients; this finding has not been previously reported. ADPKD is not an established risk factor for venous thromboembolism before transplantation. One can speculate that multiple factors are involved in the elevated frequency of thromboembolic complications after transplantation, including vessel compression by the hypertrophied liver and kidneys, surgical stress, prolonged bed rest, and shortening of partial thromboplastin time [18]. However, precise data, including coagulation studies, are lacking to better characterize this complication and further studies are required to understand the association between ADPKD and thromboembolic events. Although the risk of development of venous thromboembolism did not impact survival, our data emphasize that transplanted ADPKD patients would benefit from venous thromboembolism prevention.

Metabolic complications are a major concern in the setting on chronic renal failure. ADPKD is associated with NODAT in various studies [6,8,19]. Although not statistically significant, our results suggest that NODAT and ADPKD may be linked. Although the precise mechanisms are not known, pancreatic and hepatic factors related to insulin resistance genes co-transmitted with PKD1 and PKD2 mutations could interfere with insulin secretion and gluconeogenesis. Hypertension is extremely frequent among ADPKD patients before transplantation [20]. Thus, the increased frequency of hypertension among ADPKD patients after transplantation is not surprising as the mechanisms for generating hypertension before transplantation could be responsible for hypertension after transplantation. Of note, our data as well as prior studies suggest that cardiovascular complications are not higher among ADPKD patients than those among non-ADPKD patients; such a high cardiovascular risk does not translate into increased cardiovascular events [5,21,22].

The influence of ADPKD on bacterial infections after transplantation is a matter of debate. One study highlighted a higher frequency of urinary tract infection in the ADPKD group [5], a finding not confirmed by other studies [21]. An increased rate of death from infectious complications has been described in ADPKD patients [11]. Together, our results suggest that bacterial infections are not increased in ADPKD patients post-transplantation.

In conclusion, we present the results of the largest longitudinal descriptive study to date on the outcomes of renal transplant patients with ADPKD. We demonstrate that renal transplantation in patients with ADPKD is associated with better graft survival, more thromboembolic complications, more metabolic complications, and increased rates of hypertension, whereas the prevalence of bacterial infections is not increased. This comprehensive study provides important new insights that could lead to improved care for renal transplant patients with ADPKD.

Authorship

AJ: performed the study. MK, MH, VG, LR, and HK: managed the DIVAT database. MFM and CL: supervised the study. AJ and NP: wrote the paper.

Funding

None.

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