Autosomal Dominant Polycystic Kidney Disease Is a Risk Factor for Posttransplantation Diabetes Mellitus: An Updated Systematic Review and Meta-analysis

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Background. Autosomal dominant polycystic kidney disease (ADPKD) is linked with risk for posttransplantation diabetes mellitus (PTDM), but this association has methodologic limitations like diagnostic criteria. The aim of this study was to use contemporary diagnostic criteria for PTDM and explore any risk association for kidney transplant recipients with ADPKD. **Methods.** We undertook a retrospective analysis of 1560 nondiabetic kidney transplant recipients between 2007 and 2018 at a single center, of whom 248 (15.9%) had ADPKD. Local/national data were linked for every patient, with manual data capture of PTDM diagnosis by International Consensus Recommendations. We then pooled our data with eligible studies after an updated systematic review and performed a meta-analysis to estimate the pooled effect. **Results.** Comparing ADPKD versus non-ADPKD kidney transplant recipients, PTDM risk was not significantly different at our center (19.4% versus 14.9%, respectively; $P = 0.085$). ADPKD patients who developed PTDM were older, borderline heavier, and less likely to be recipients of living kidney donor compared with ADPKD patients who remained free of PTDM. Systematic review of the literature identified 14 eligible studies, of which 8 had a PTDM diagnosis consistent with Consensus recommendations. In the meta-analysis, we observed an increased odds ratio (OR) of kidney transplant recipients with ADPKD developing PTDM regardless of all study inclusion (OR, 1.98; 95% confidence interval, 1.43-2.75) or restricted study inclusion based on robust PTDM diagnostic criteria (OR, 1.81; 95% confidence interval, 1.16-2.83). **Conclusions.** ADPKD kidney transplant candidates should be counseled of their increased risk for PTDM, with further work warranted to investigate any underlying metabolic pathophysiology.

(Transplantation Direct 2020;6: e553; doi: 10.1097/TXD.0000000000000989. Published online 27, April, 2020.)

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder[1] and the fourth leading cause of end-stage kidney disease (ESKD) across Europe.[2] As per other individuals living with ESKD, kidney transplantation should be considered the renal replacement therapy of choice. Although ADPKD individuals with ESKD require special consideration as potential kidney transplant candidates, including assessment for native nephrectomy, cystic liver involvement, and/or screening for intracranial aneurysms, long-term patient and graft survival is equivalent for kidney transplant recipients with ADPKD compared with those with other causes of ESKD.[3]

However, metabolic disturbances have been associated with ADPKD[4] and one of the risks identified for ADPKD individuals is an increased susceptibility for developing posttransplantation diabetes mellitus (PTDM). PTDM is a common medical complication after kidney transplantation and associated with increased risk for cardiovascular disease and all-cause mortality.[5] International PTDM Consensus guidelines recommend identifying kidney transplant candidates at increased risk for PTDM and advocate preventative measures to attenuate risk for PTDM.[6] However, published reports are inconsistent with regard to whether ADPKD is a risk factor for PTDM or not.[7–20] In a systematic review and meta-analysis of 12 published cohort studies, the relative risk for development of PTDM was 1.92 (95% confidence interval, 1.36-2.70).[21] However, reported studies that were

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included in this meta-analysis had significant heterogeneity and many used obsolete PTDM diagnostic criteria that are inconsistent with contemporary guidance. Therefore, the question as to whether ADPKD is a risk factor for development of PTDM after kidney transplantation remains unresolved. To investigate this risk further, the aim of this study was 2-fold: (1) to use contemporary diagnostic criteria to determine the incidence of PTDM in a large, single-center retrospective analysis of kidney transplant recipients stratified by ADPKD status and (2) to perform an updated systematic review and meta-analysis of cohort studies reporting PTDM incidence by ADPKD status.

MATERIALS AND METHODS

Study Population

We performed a retrospective cohort study and analyzed all kidney transplant procedures between January 1, 2007, and June 30, 2018, at a single transplant center. We excluded recipients of multiple organ transplants and those with pre-existing diabetes at the time of kidney transplantation.

Data Sources

Local data were electronically extracted by the hospital informatics team for every patient, with manual data linkage to electronic patient records for diagnosis of PTDM. Acute rejection, 1-y creatinine, and patient and graft survival data were acquired and linked from National Health Service Blood and Transplant. Hospitalization data were acquired from Hospital Episode Statistics, an administrative data warehouse containing admissions to all National Health Service hospitals in England. It contains detailed records relating to individual patient treatments; with data extraction facilitated using codes on procedural classifications (Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th Revision) and medical classifications (World Health Organization International Classification of Disease, 10th Revision).

Diagnostic Criteria for PTDM

PTDM was diagnosed in accordance with International PTDM Consensus guidelines.[6] In summary, PTDM was officially diagnosed if any of the following were recorded after 6 wk posttransplantation: (1) symptoms of diabetes plus random plasma glucose ≥200 mg/dL (11.1 mmol/L); (2) fasting plasma glucose ≥126 mg/dL (7.0 mmol/L); or (3) glycated hemoglobin (HbA1c) ≥6.5%. Either fasting or random glucose was tested at each clinic visit, with HbA1c performed on a quarterly basis from 3 mo after kidney transplantation. Patients started on antidiabetic therapy before 6 wk posttransplantation who were still on treatment at 6 wk were also classed as PTDM.

Immunosuppression Protocol

All patients received the same immunosuppression over the study period, with minimization of tacrolimus exposure in line with the Efficacy Limiting Toxicity Elimination–Symphony protocol.[22] Induction therapy was with basiliximab (20 mg on days 0 and 4) and methylprednisolone (500 mg on day 0). Maintenance therapy included tacrolimus (target 12-h trough level 5–8 ng/L), mycophenolate mofetil (2 g daily with tapering to 1 g daily after 6 mo), and maintenance corticosteroids (20 mg daily weaned down to 5 mg daily by 3 mo). Biopsies were indication based in the context of transplant dysfunction

(categorized as ≥20% creatinine rise or new-onset proteinuria). Biopsy data were classified in accordance to latest Banff criteria.[23]

Episodes of acute cellular rejection were treated with a bolus of corticosteroids, with T-cell depletion therapy for steroid-resistant rejection. Antibody-mediated rejection was treated with antibody removal by plasmapheresis ± intravenous immunoglobulin. Viral serology (eg, polyomavirus) and/or anti-HLA antibodies were checked by indication basis based on transplant dysfunction.

Definitions of Variables

Baseline and posttransplant data were extracted and classified from our database as follows. HLA mismatch levels were defined and graded in accordance to National Health Service Blood and Transplant classification used during this study period: level 1 (HLA mismatch 0), level 2 (HLA mismatch 0 doctor [DR] and 0/1 B), level 3 (HLA mismatch 0 DR and 2B, or 1 DR and 0/1 B), and level 4 (1 DR and 2B, or 2 DR). Matchability was calculated from a standardized pool of 10 000 recent donors, from which the number of blood group identical donors that recipients are well or favorably HLA-mismatched were counted. This number was converted to a standardized score between 1 and 10, which was used to categorize recipients into 1 of 3 matchability groups: easy (1–3), moderate (4–6), or difficult (7–10) to match. Determination of socioeconomic deprivation was based on the Index of Multiple Deprivation, a model calculated from multiple domains reflective of area socioeconomic deprivation, with 1 the most deprived to 5 the least deprived.

Outcomes

The primary outcome measure was development of PTDM after kidney transplantation. In addition, we looked at various secondary outcome measures including postoperative admission length of stay; rehospitalization episode within 90 d; any admission secondary to a cardiac, stroke, cancer, or infection-related episode; graft function (by estimated glomerular filtration rate in milliliters per minute); and patient or graft survival. Follow-up commenced at the time of transplant, with patients censored at the earliest of their final recorded follow-up or the end of follow-up for the study (October 13, 2018). For analysis of graft survival, patients who died with a working graft were censored at death.

Statistical Analysis

Initially, a range of demographic and transplant characteristics was compared between the follow-up groups. Normality of data was assessed using the Kolmogorov–Smirnov tests. Descriptive statistics were used to estimate the frequencies. Categorical variables are presented as number (%) and continuous variables as mean (± SD) or median (± interquartile range) dependent upon normality of distribution. Difference between groups was assessed with χ^2 or 2-sided Fisher exact test for categorical variables and t test or Mann-Whitney U test to compare continuous variables. A P value of <0.05 and 0.001 in the statistical analysis was considered significant and highly significant, respectively. All analyses were performed using IBM SPSS 25 (IBM Corp., Armonk, NY).

Systematic Review and Meta-analysis

Two investigators (A.C., A.S.) independently searched published studies indexed in MEDLINE, EMBASE, and the

Cochrane database from inception through September 2019 using a similar search strategy as utilized by Cheungpasitporn et al[21] (described in **Supplemental Appendix 1,** http://links.lww.com/TXD/A249). In addition, a manual search was performed for additional relevant studies using references from all retrieved articles. The primary data extracted from each study included all PTDM event rates and total numbers for each patient cohort stratified by available ADPKD status. The inclusion criteria for studies were as follows: (1) randomized clinical trials or observational studies (case-control, cross-sectional, or cohort studies) published as original studies that evaluated the risk for PTDM in kidney transplant recipients with ADPKD; (2) studies that included extractable data for PTDM event rates and total at-risk numbers; and (3) a reference group composed of kidney transplant recipients who did not have ADPKD. No restrictions were applied for language. This study is reported in accordance with the Meta-Analyses and Systematic Reviews of Observational Studies checklist for reporting meta-analyses of observational studies (**Supplemental Appendix 2,** http://links.lww.com/TXD/A249).[24]

Study eligibility was independently determined by the 2 investigators noted above, with any discrepancy resolved by mutual consensus. Review Manager 5.3 software (Cochrane Collaboration, London, United Kingdom) was used for data analysis. We first conducted a meta-analysis using all eligible studies identified in our systematic review. We subsequently performed an additional meta-analysis after limiting studies to those where diagnosis of PTDM was consistent with contemporary diagnostic classification.[6] Given the high likelihood of interstudy variances, we used a random-effect model rather than a fixed-effect model to determine effect size by odds ratio (OR). Statistical heterogeneity was assessed using the Cochran Q test. This statistic was complemented by the I^2 statistic, which quantifies the proportion of the total variation across studies due to heterogeneity rather than chance. A value of I^2 of 0%–25% represents insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity, and >75% high heterogeneity.

Approvals

This study received institutional review board approval and was registered as an audit (audit identifier: CARMS-12578). The corresponding author had full access to all data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Study Cohort

In the study time period, a total of 1770 kidney transplant procedures were performed, of which 210 occurred in recipients with a known diagnosis of diabetes at the time of transplant surgery (including only 13 ADPKD patients) and were excluded from any further analysis. This left a final study cohort of 1560 nondiabetic kidney transplant recipients. From this cohort, 248 (15.9%) kidney transplant recipients had a diagnosis of ADPKD versus 1312 non-ADPKD recipients. Median follow-up for the study cohort was 4.7 y (interquartile range, 2.3–7.5 y). Table 1 outlines baseline characteristics comparing ADPKD versus non-ADPKD kidney transplant recipients.

TABLE 1.

Baseline demographics of kidney transplant recipients stratified by ADPKD status

Variable	ADPKD	No ADPKD	P
No.	248	1312	—
Recipient age, mean (SD)	49.5 (12.7)	45.2 (14.0)	<0.001
Male gender, n (%)	136 (54.8)	770 (58.7)	0.262
Recipient BMI, mean (SD)	26.7 (4.3)	27.0 (5.0)	0.366
D waiting on list, mean (SD)	1251 (966)	1079 (938)	0.023
Ethnicity, n (%)			
White	189 (76.2)	856 (65.2)	0.009
Black	8 (3.2)	80 (6.1)	
South Asian	38 (15.3)	243 (18.5)	
Mixed	10 (4.0)	95 (7.2)	
Other	3 (1.2)	38 (2.9)	
Socioeconomic deprivation, n (%)			
1 (most deprived)	68 (28.0)	476 (37.0)	0.044
2	46 (18.9)	254 (19.8)	
3	55 (22.6)	245 (19.1)	
4	40 (16.5)	155 (12.1)	
5 (least deprived)	34 (14.0)	155 (12.1)	
HLA level, n (%)			
1 (best match)	38 (15.5)	136 (10.4)	0.171
2	59 (23.8)	361 (27.5)	
3	115 (46.4)	652 (49.7)	
4 (worst match)	36 (14.4)	161 (12.3)	
Matchability, n (%)			
Low	93 (37.7)	506 (38.6)	0.721
Moderate	117 (47.2)	580 (44.2)	
Hard	38 (15.1)	226 (17.2)	
Recipient CMV serostatus+, n (%)			
Negative	127 (59.3)	571 (53.0)	0.065
Positive	48 (22.4)	327 (30.4)	
Unknown	39 (18.2)	179 (16.6)	
Recipient hepatitis C+, n (%)	1 (0.4)	5 (0.4)	1.000
ABO incompatible, n (%)	18 (7.3)	59 (4.5)	0.077
Type of donor, n (%)			
DBD	112 (48.1)	578 (45.5)	0.745
DCD	30 (12.9)	179 (14.1)	
Living	91 (39.1)	514 (40.4)	
Cold ischemic time (min), mean (SD)	721 (487)	678 (477)	0.264
Repeat kidney transplant, n (%)	31 (12.8)	143 (11.3)	0.512
Previous MI, n (%)	5 (2.0)	28 (2.1)	1.000
Previous CVA, n (%)	5 (2.0)	19 (1.4)	0.570
Previous PVD, n (%)	1 (0.4)	12 (0.9)	0.705
Charlson comorbidity index, mean (SD)	3.3 (5.3)	3.1 (4.9)	0.676
Donor age, mean (SD)	48.6 (13.0)	47.3 (14.2)	0.168
Donor BMI, mean (SD)	26.7 (5.5)	26.3 (4.8)	0.380
Donor male gender, n (%)	109 (50.9)	532 (49.4)	0.940
Donor CMV serostatus+, n (%)			
Negative	101 (47.2)	502 (46.6)	0.045
Positive	108 (50.5)	503 (46.7)	
Unknown	5 (2.3)	72 (6.7)	

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CMV, cytomegalovirus; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; MI, myocardial infarct; PVD, peripheral vascular disease.

Risk for PTDM and Other Posttransplant Outcomes

Comparing ADPKD versus non-ADPKD kidney transplant recipients, the risk for PTDM was not found to be significantly different (19.4% versus 14.9%, respectively; P = 0.085). We did not identify any significant difference in any

other clinical outcome after kidney transplantation when comparing ADPKD versus non-ADPKD kidney transplant recipients (Table 2).

Subgroup Analysis of ADPKD Patients Developing PTDM

Comparing ADPKD patients who developed PTDM versus ADPKD patients who did not, we identified the former at baseline to be older (53.9 versus 48.4 y, respectively; $P = 0.003$), borderline heavier body mass index (27.7 versus 26.5, respectively; $P = 0.088$), and less likely to be recipients of a living donor kidney (22.2% versus 43.1%, respectively; $P = 0.011$). There was no difference in other baseline variables.

We did observe a trend toward more rejection episodes within the first year after kidney transplantation in ADPKD patients who subsequently developed PTDM compared with those without any rejection (14.6% versus 5.2%, respectively; $P = 0.081$). There was no difference in weight gain over the first 6 or 12 mo for ADPKD patients who did or did not develop PTDM.

Systematic Review and Meta-analysis of Published Studies

Figure 1 highlights our Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlining the systematic review and selection of studies for meta-analysis. Table 3 summarizes the main features of the 14 studies selected for meta-analysis after the systematic review. Only 2 new studies were available because the previous meta-analysis of 12 studies,[21] which undertook quality assessment using the Newcastle-Ottawa scale, and therefore repeat quality assessment was not undertaken. Extracting the primary data for all PTDM event rates and total cohort numbers for patients stratified by ADPKD status, we synthesized the data from these studies with our data. We observed an increased OR of kidney transplant recipients with ADPKD developing PTDM (OR, 1.98; 95% confidence interval, 1.43-2.75) (see Forest plot in Figure 2) when all 14 studies were combined with our data. We then repeated the meta-analysis after restricting selected studies to those that diagnosed PTDM in accordance with contemporary diagnostic criteria aligned with international

recommendations.[6] After pooling our data to these selected 8 studies, we still observed an increased OR of kidney transplant recipients with ADPKD developing PTDM (OR, 1.81; 95% confidence interval, 1.16-2.83) (see Forest plot in Figure 3). Significant heterogeneity was observed in both Forest plots.

DISCUSSION

Previous work has reported heterogenous findings with regard to whether ADPKD is a risk factor for the development of PTDM. Although a positive association was identified after previous meta-analysis of published studies,[21] the combined empirical data were methodologically flawed as the diagnosis of PTDM in many studies was not compatible with International Consensus Recommendations. Our retrospective analysis of single-center data, using recommended PTDM diagnostic criteria, did not identify a statistically significant difference in the incidence of PTDM comparing kidney transplant recipients with versus without ADPKD. No difference was observed in any other clinical outcomes between ADPKD and non-ADPKD kidney transplant recipients in agreement with previous studies. However, after pooling our results with existing empirical data extracted from published cohort studies, our meta-analysis did identify increased odds for kidney transplant recipients with ADPKD developing PTDM. This remained consistent regardless of whether the diagnosis of PTDM was heterogenous or robustly defined according to recommended classification.

It has been suggested that individuals with ADPKD have significant underlying insulin resistance[25] or impaired insulin secretion,[26,27] both of which are considered key pathophysiologic defects in the development of PTDM.[5] Although multiple genes are indicated in the pathogenesis of ADPKD, the commonest mutations are in the genes *PKD1* and *PKD2* (encoding polycystin-1 and polycystin-2, respectively).[1] Polycystin-1 and polycystin-2 are located on the primary cilia (an apical antenna-like organelle with an important role in mechanotransduction), where they are believed to transmit information from the external environment internally to the cell.[1] Both polycystin molecules are expressed in organs that are integral to maintenance of glucose homeostasis outside of the kidney (eg, pancreas, liver, skeletal muscle)[28] and could be implicated in glycemic dysregulation. Mutation of *PKD1* has been shown to enhance glycolysis in cells in a mouse model of ADPKD and in kidneys from humans with ADPKD.[29] The work from Rowe et al[29] demonstrated a switch in glucose utilization to higher lactate production in murine *PKD1*^{-/-} renal cells and supports a role for ciliary components in cellular glucose metabolism. In fact, as many as two-thirds of the type 2 diabetes susceptibility genes have documented entries in the ciliary proteome database.[30] Therefore, a direct pathophysiologic link between ciliary dysfunction and susceptibility to PTDM could be postulated and requires further mechanistic investigation.

Paradoxically, there is some suggestion of *reduced* risk for diabetes among ADPKD individuals outside the setting of kidney transplantation but is limited to single-center experience. Pietrzak-Nowacka et al[31] observed a lower prevalence of transplant-unrelated diabetes after analyzing 291 questionnaire respondents from the Polish Registry of ADPKD patients (prevalent OR, 0.18; 95% confidence interval, 0.07-0.47; $P < 0.001$). However, this contradicts work from the same

TABLE 2.

Clinical outcomes of kidney transplant recipients stratified by ADPKD status

Variable	ADPKD	No ADPKD	*P*
Posttransplantation diabetes, n (%)	48 (19.4)	195 (14.9)	0.085
Postoperative stay (d), mean (SD)	11.6 (9.1)	11.5 (8.9)	0.875
1-y rejection, n (%)	14 (7.2)	68 (7.2)	1.000
1-y estimated GFR (mL/min), mean (SD)	49.4 (19.0)	51.4 (22.1)	0.296
3-y estimated GFR (mL/min), mean (SD)	52.3 (22.6)	50.5 (22.6)	0.474
5-y estimated GFR (mL/min), mean (SD)	51.0 (22.0)	49.2 (24.6)	0.510
Emergency readmission within 90 d, n (%)	95 (38.3)	475 (36.2)	0.565
Any cardiology admission, n (%)	5 (2.0)	41 (3.1)	0.418
Any CVA admission, n (%)	4 (1.6)	39 (3.0)	0.293
Any cancer admission, n (%)	15 (6.0)	59 (4.5)	0.327
Any infection admission, n (%)	59 (23.8)	256 (19.5)	0.142
Death-censored graft loss, n (%)	35 (14.1)	205 (15.6)	0.631
Death, n (%)	25 (10.1)	124 (9.5)	0.814

ADPKD, autosomal dominant polycystic kidney disease; CVA, cerebrovascular accident; GFR, glomerular filtration rate.
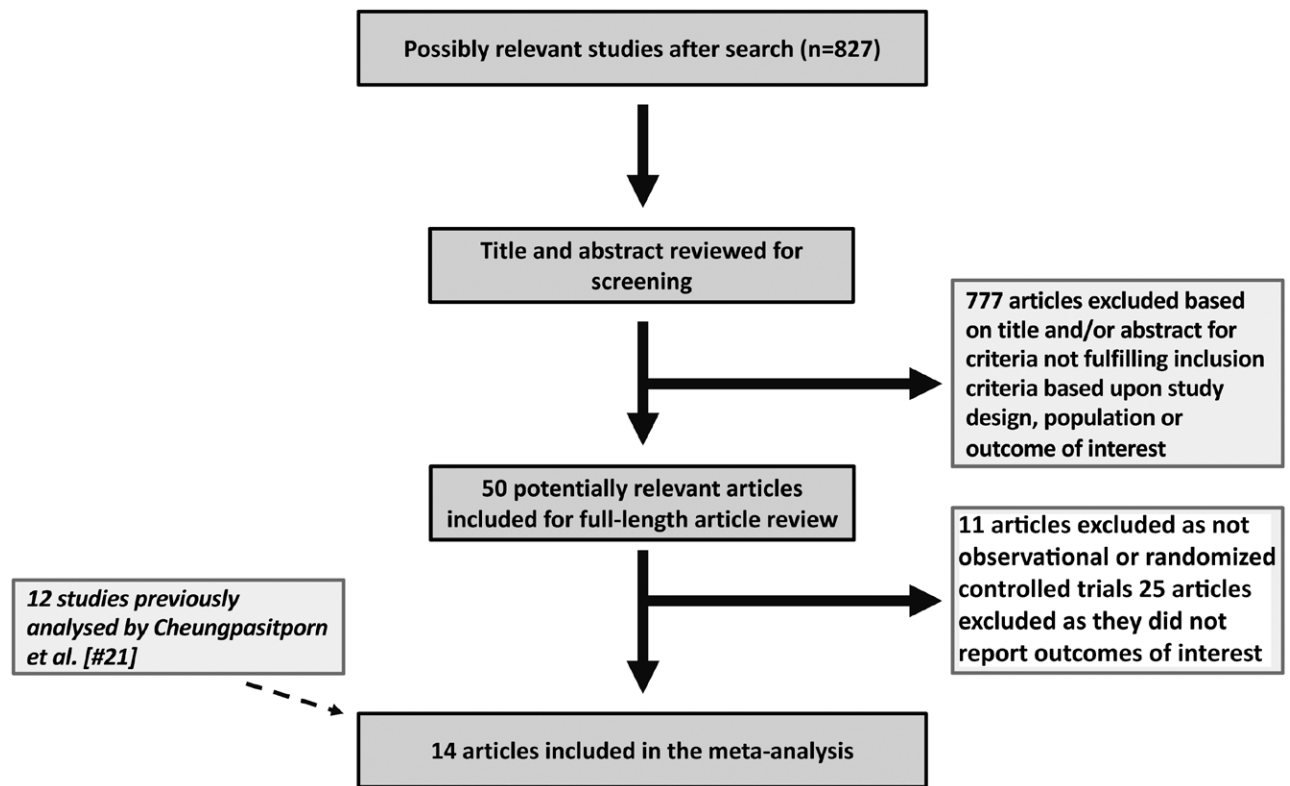
FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study inclusion and exclusion.

group showing higher prevalence of metabolic syndrome[31] and impaired β-cell function[26] in ADPKD individuals with normal renal function. It could be hypothesized that polycystic kidneys have suppressed gluconeogenesis and observed that hyperinsulinemia is due to slower insulin breakdown in the kidneys with the context of reduced renal function. More

TABLE 3.

Main characteristics of included studies

Study	Y	Country	Total no. of patients	Total no. of ADPKD patients	PTDM definition criteria	Valid PTDM diagnosis[6]
Ducloux et al[7]	1999	France	52	26	FPG >7.8 mmol/L OR need for insulin OR need for oral antidiabetic therapy	No
Gentil et al[8]	2002	Spain	354	42	Need for continuous use of insulin over ≥1 mo	No
de Mattos et al[9]	2004	United States	270	135 (matched cohort)	RPG >200 mg/dL on 2 consecutive measurement at least 1-d apart documented[a]	No
Hamer et al[10]	2007	United Kingdom	429	67	RPG ≥200 mg/dL on 2 separate d >6 wk after transplant	No
Pietrzak-Nowacka et al[11]	2008	Poland	196	98 (matched cohort)	2 FPG >126 mg/dL OR 2 RPG >200 mg/dL	Yes
Goncalves et al[12]	2009	Portugal	445	48	FPG >126 mg/dL OR need for hypoglycemic agents or insulin after transplant	Yes
Razeghi et al[13]	2010	Iran	90	6	FPG ≥126 mg/dL OR RPG ≥200 mg/dL on 2 occasions OR need for insulin therapy and/or hypoglycemic drugs[b]	Yes
Jacquet et al[14]	2011	France	5313	534	Not defined	No
Courivaud et al[15]	2011	France	2010	322	Need for insulin or oral antidiabetic therapy within the first 6 mo after transplant	No
Caillard et al[16]	2011	France	120	18	FPG >126 mg/dL on 2 occasions OR RPG >200 mg/dL OR 2-h glucose level of standard OGTT >200 mg/dL OR need for antidiabetic medication	Yes
Prakash et al[17]	2012	India	68	4	FPG ≥126 mg/dL OR symptom of diabetes plus RPG ≥200 mg/dL OR 2-h glucose level of standard OGTT >200 mg/dL on at least 2 occasions	Yes
Ruderman et al[18]	2012	Australia	502	79	RPG ≥200 mg/dL on 2 separate days OR 2 FPG levels ≥126 mg/dL at least 60 d after transplant OR A1C ≥6.5% or need for oral hypoglycemic medication or insulin	Yes
Alagbe et al[19]	2017	South Africa	111	11	FPG >7 mmol/L OR RPG >11.1 mmol/L	Yes
Roozbeh et al[20]	2018	Iran	201	101 (matched cohort)	FPG >126 mg/dL OR need for hypoglycemic agents or insulin after transplant	Yes

[a]At least 30 d after an acute rejection episode.
[b]For at least 2 wk during 6-mo follow-up.
A1C, glycated hemoglobin; ADPKD, autosomal dominant polycystic kidney disease; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PTDM, posttransplantation diabetes mellitus; RPG, random plasma glucose.
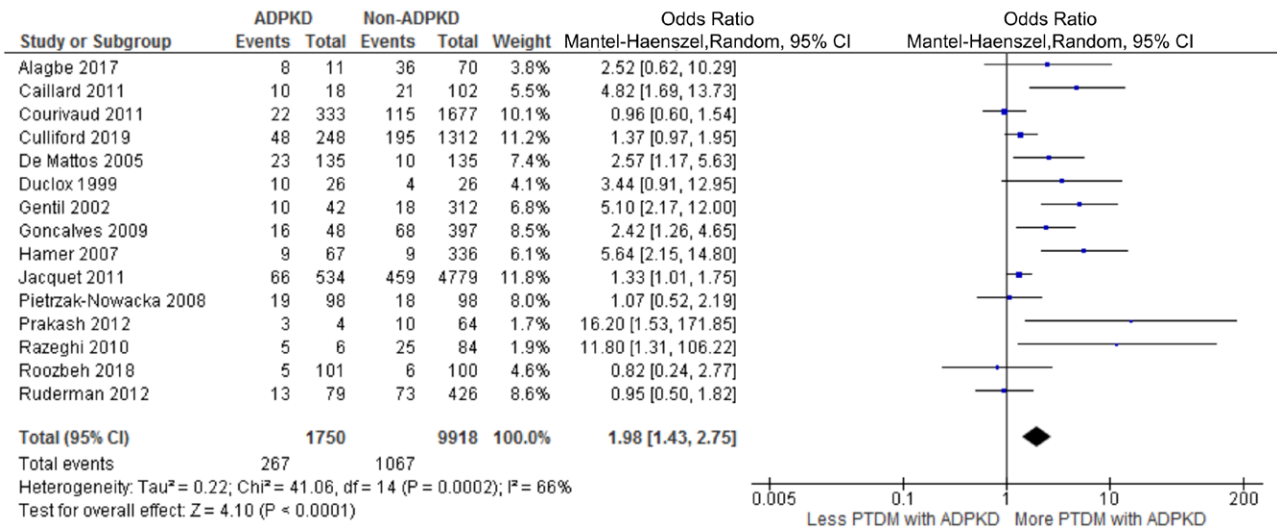
Study or Subgroup	ADPKD Events	Total	Non-ADPKD Events	Total	Weight	Odds Ratio Mantel-Haenszel,Random, 95% CI
Alagbe 2017	8	11	36	70	3.8%	2.52 [0.62, 10.29]
Caillard 2011	10	18	21	102	5.5%	4.82 [1.69, 13.73]
Courivaud 2011	22	333	115	1677	10.1%	0.96 [0.60, 1.54]
Culliford 2019	48	248	195	1312	11.2%	1.37 [0.97, 1.95]
De Mattos 2005	23	135	10	135	7.4%	2.57 [1.17, 5.63]
Duclox 1999	10	26	4	26	4.1%	3.44 [0.91, 12.95]
Gentil 2002	10	42	18	312	6.8%	5.10 [2.17, 12.00]
Goncalves 2009	16	48	68	397	8.5%	2.42 [1.26, 4.65]
Hamer 2007	9	67	9	336	6.1%	5.64 [2.15, 14.80]
Jacquet 2011	66	534	459	4779	11.8%	1.33 [1.01, 1.75]
Pietrzak-Nowacka 2008	19	98	18	98	8.0%	1.07 [0.52, 2.19]
Prakash 2012	3	4	10	64	1.7%	16.20 [1.53, 171.85]
Razeghi 2010	5	6	25	84	1.9%	11.80 [1.31, 106.22]
Roozbeh 2018	5	101	6	100	4.6%	0.82 [0.24, 2.77]
Ruderman 2012	13	79	73	426	8.6%	0.95 [0.50, 1.82]
Total (95% CI)		**1750**		**9918**	**100.0%**	**1.98 [1.43, 2.75]**
Total events	267		1067			

Heterogeneity: Tau² = 0.22; Chi² = 41.06, df = 14 (P = 0.0002); I² = 66%
Test for overall effect: Z = 4.10 (P < 0.0001)

FIGURE 2. Forest plot of odds ratio for posttransplantation diabetes mellitus (PTDM) comparing autosomal dominant polycystic kidney disease (ADPKD) vs non-ADPKD kidney transplant recipients (all studies). CI, confidence interval.

studies are clearly required to investigate any underlying metabolic susceptibility to diabetes for ADPKD individuals, especially considering increased mortality is observed for patients with both ADPKD and type 2 diabetes in the context of moderate chronic kidney disease.[32] However, existing literature that has been published remains limited, heterogenous, and conflicting, which prohibits any firm conclusions.

This is an important issue to investigate because identifying kidney transplant candidates at increased odds for developing PTDM is aligned with internal consensus recommendations.[6] PTDM is a leading concern for kidney transplant recipients[33] and is associated with adverse posttransplant complications.[34] Risk awareness is important for patient counseling and can help reinforce the importance of lifestyle modification, which has recently been shown to reduce the risk of some adverse clinical metabolic outcomes.[35] Kidney transplant recipients with ADPKD could be considered for adapted immunosuppression regimens to prevent the risk of PTDM, if deemed to be low-immunologic risk, but this strategy needs to personalized based on individualized risk. For example, meta-analyses of randomized controlled trials show steroid withdrawal and/or avoidance reduces the risk for PTDM but increases the risk for rejection,[36] although risk for rejection may be attenuated with tacrolimus-based immunosuppression.[37]

However, the largest clinical trial of steroid maintenance versus withdrawal did not show any difference in PTDM incidence after 5 y post-kidney transplantation.[38] Torres et al[39] have also shown tacrolimus, mycophenolate mofetil, and steroid maintenance to be the optimal immunosuppression for achieving a PTDM/rejection balance in metabolically high-risk kidney transplant candidates. Although mammalian target of rapamycin inhibitors (eg, sirolimus and everolimus) were briefly considered beneficial at reducing cyst volume for ADPKD individuals,[40] subsequent randomized controlled trials have shown it to be ineffective and/or harmful.[41-43] Additionally, in a kidney transplantation setting, the use of the mammalian target of rapamycin inhibitor sirolimus has been associated with increased risk for PTDM[44] and non–cancer-related mortality,[45] thereby limiting its potential utility posttransplantation.[46] Finally, belatacept has limited data in the setting of kidney transplantation for recipients with ADPKD and its link to development of PTDM in clinical trials is unclear.[47] Therefore, in line with PTDM Consensus recommendations,[6] it is important even for ADPKD patients that posttransplant immunosuppression is tailored with long-term patient and graft survival as the primary focus, with secondary focus on minimizing potential side effects and/or immunosuppression-related complications. Although strength of our analysis was the same
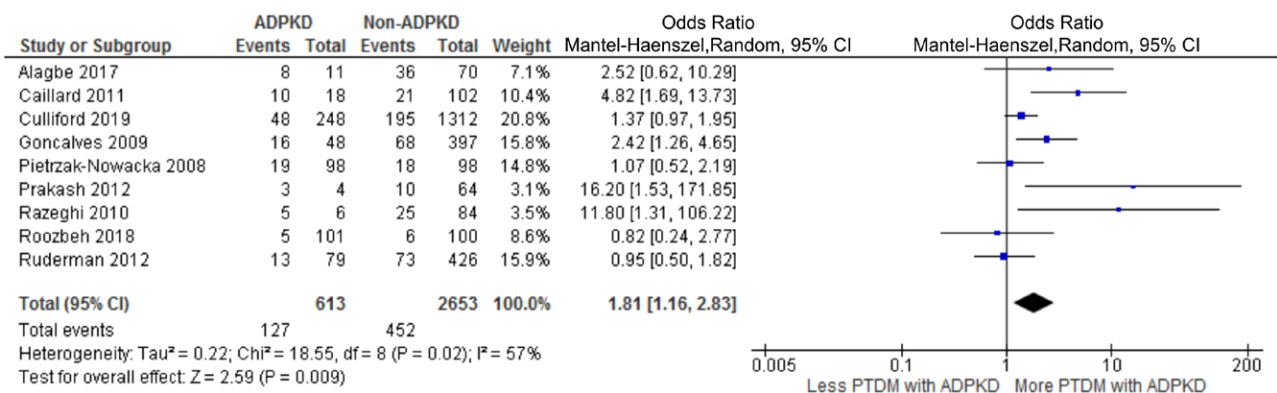
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Culliford 2019	48	248	195	1312	20.8%	1.37 [0.97, 1.95]
Goncalves 2009	16	48	68	397	15.8%	2.42 [1.26, 4.65]
Pietrzak-Nowacka 2008	19	98	18	98	14.8%	1.07 [0.52, 2.19]
Prakash 2012	3	4	10	64	3.1%	16.20 [1.53, 171.85]
Razeghi 2010	5	6	25	84	3.5%	11.80 [1.31, 106.22]
Roozbeh 2018	5	101	6	100	8.6%	0.82 [0.24, 2.77]
Ruderman 2012	13	79	73	426	15.9%	0.95 [0.50, 1.82]
Total (95% CI)		**613**		**2653**	**100.0%**	**1.81 [1.16, 2.83]**
Total events	127		452			

Heterogeneity: Tau² = 0.22; Chi² = 18.55, df = 8 (P = 0.02); I² = 57%
Test for overall effect: Z = 2.59 (P = 0.009)

FIGURE 3. Forest plot of odds ratio for posttransplantation diabetes mellitus (PTDM) comparing autosomal dominant polycystic kidney disease (ADPKD) vs non-ADPKD kidney transplant recipients (restricted studies). CI, confidence interval.

immunosuppression protocol for all kidney transplant recipients, this means we are unable to ascertain the impact of different immunosuppressants on risk for PTDM in our cohort.

It is important to appreciate the other limitations of this analysis for correct interpretation of the data. Our data are likely to underestimate the incidence of PTDM because some kidney transplant recipients are repatriated back to their referral hospitals within 3 mo posttransplant. In contrast, it is possible that some recipients with preexisting diabetes before kidney transplantation were not appropriately identified and, therefore, led to inclusion in our analyzed cohort as an overestimate. Missing data are an inherent bias in epidemiologic analyses such as this, although long-term hospitalization and survival data are complete for the entire cohort because of record linkage with national data resources. There are confounders that have an impact on PTDM kidney transplantation that we are unable to appreciate (eg, lifestyle factors, family history of diabetes) and the lack of patient-level data precludes any detailed assessment of potential confounders which could impact upon risk for PTDM in our meta-analysis. Our single-center cohort is underpowered to determine true difference in PTDM incidence and justified our methodologic approach to pool data with other cohort studies. However, we are still not able to ascertain with clarity whether the observed PTDM risk for ADPKD kidney transplant recipients is independent of competing risk factors. We lacked mechanistic insight into this association, and further investigation exploring metabolic physiology parameters (eg, insulin sensitivity and insulin secretion) would be of interest. Finally, our retrospective study was of short duration to robustly assess difference in survival outcomes and further maturing of this database in the long term should provide more definitive answers.

To conclude, our retrospective, single-center study did not identify an association between ADPKD and PTDM, but after pooling our data with published cohort studies, we demonstrated increased odds for developing PTDM among kidney transplant recipients with ADPKD. We believe that these data are important because ADPKD is a common indication for kidney transplantation and PTDM is a common medical complication posttransplantation. Confirming ADPKD as a risk factor for PTDM should facilitate targeted patient counseling pretransplantation to encourage lifestyle modification. However, further studies are warranted to investigate the mechanism linking ADPKD and abnormal glucose metabolism, which may shed light on pathophysiologic pathways for both ADPKD and PTDM, respectively. This may allow future risk stratification and tailored immunosuppression for ADPKD kidney transplant candidates to minimize risk for PTDM while still optimizing patient and allograft outcomes.

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