Maternal compared with paternal donor kidneys are associated with poorer graft outcomes after kidney transplantation

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Noninherited maternal human leukocyte antigens may be less detrimental on allograft outcomes after kidney transplantation compared with noninherited paternal antigens, but this association in the era of modern immunosuppression remains unknown. Here we determine the association between parental donor kidneys, acute rejection, and graft failure in primary live-donor parental kidney transplant recipients using data from the Australia and New Zealand Dialysis and Transplant Registry between 1997 and 2012. Of the 1139 recipients followed for a median of 7.2 years (8588 person-years), 652 received kidneys from maternal donors. Compared with paternal donor kidneys, maternal donor kidneys were associated with a significantly increased risk of acute rejection (adjusted odds ratio 1.54; 95% confidence interval [CI], 1.14–2.07) and significant overall graft loss. The latter was confined to recipients who have experienced acute rejection (adjusted hazard ratio 1.60; 95%CI, 1.05–2.43) but not in those who did not experience acute rejection. Thus, our study suggests that recipients of maternal donor kidneys have a greater risk of rejection and graft loss. Hence, clinicians and patients should be cognizant of this association when determining which of the 2 parental donors is most suitable for transplantation.

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Live-donor kidney transplantation is associated with superior graft survival compared with deceased-donor kidney transplantation, with projected graft half-lives of human leukocyte antigen (HLA)-mismatched grafts of 22 and 17 years, respectively.[1] Although there has been a proportional decline in live-donor kidney donation over the past 5 years, live-related kidney transplantation remains an important source of organ donors worldwide.[2] In Australia, parental donors accounted for 53% of overall live-related donors in 2012, with a similar proportion being observed in the United States and the United Kingdom.[3] Despite being older, parental donors are associated with equivalent graft survival compared with sibling and unrelated live donors.[4,5]

Highly sensitized individuals have been shown to induce a lesser immunogenic response, including the production of alloantibodies against noninherited maternal HLA antigen (NIMA) compared with noninherited paternal HLA antigen (NIPA), possibly through intrauterine-induced tolerance to NIMA resulting in the development of B-cell tolerance and regulatory T cells or a switch to T-helper 2 phenotypes (or both) on re-exposure to NIMA in later life.[6] In bone marrow transplantation, sibling transplants mismatched for NIMA and mother-to-child transplants were associated with significantly less acute and chronic graft-versus-host disease compared with sibling transplants mismatched for NIPA and father-to-child transplants, respectively.[7–9] A study in pregnant women showed that rhesus (Rh)-negative women whose mothers were Rh-positive were less likely to acquire anti-Rh antibody during pregnancy with an Rh-positive fetus compared with Rh-negative women of Rh-negative mothers.[10] In addition, adult individuals who had received multiple blood transfusions were less likely to form antibodies against NIMA compared with NIPA, suggesting that the exposure to maternal antigens *in utero* may induce a form of tolerance to maternal-derived HLA antigens in later life.[6] In kidney transplantation, there are conflicting reports on the clinical and biological implications of NIMA. Recipients of mismatched NIMA kidney transplants from deceased donors and sibling donors have superior graft survival compared with mismatched NIPA kidney transplants, suggesting that

donors expressing NIMA may be regarded as an acceptable HLA mismatch of no clinical significance.[11,12] In contrast, analyses using data from the Collaborative Transplant Study registry reported contradictory findings suggesting that maternal donor kidney transplants have reduced graft survival compared with paternal donor kidneys.[13] The aim of this study was to determine the differential impact of maternal and paternal living donor kidneys and graft outcomes in kidney transplantation and to determine whether rejection is a potential modifier between parental donor kidneys and outcomes.

RESULTS

Study population

Table 1 shows the baseline characteristics of the study population stratified by parental donors. There were 1139 kidney transplant recipients between 1997 and 2012 who had received kidneys from parental donors and were followed for a median of 7.2 years (interquartile range, 3.8–11.2 years) resulting in 8588 person-years. The majority of recipients from paternal donors were of white race (n = 995 [87.4%]). A total of 371 (32.6%) cases of all living parental donor transplantation was preemptive. Of these patients, 487 (42.8%) received donor kidneys from their fathers and 652 (57.2%) received kidneys from their mothers. A total of 374 (32.8%) recipients experienced acute rejection and 217 (19.1%) experienced graft loss within the follow-up period. Compared with recipients with kidneys from paternal donors, those who received kidneys from maternal donors were significantly older and more likely to be current or former smokers. There were similar proportions of father-to-son/daughter and mother-to-son/daughter transplants (64%/36% vs. 59%/41% respectively; $P = 0.11$).

A greater proportion of kidney transplant recipients who received maternal donor kidneys experienced early acute rejection episodes (27.6% and 19.7%, respectively; $P < 0.01$), late acute rejection episodes (9.5% and 7.4%, respectively; $P = 0.21$), any rejection episode (37.1% and 27.1%, respectively; $P < 0.001$), and multiple rejection episodes (14.0% and 7.4%, respectively; $P < 0.01$) compared with recipients of kidneys from paternal donors. The proportion of recipients who experienced overall graft loss (21.3% and 16.0%, respectively; $P = 0.02$) and death-censored graft loss (DCGL) (19.2% and 14.8%, respectively; $P = 0.05$) over the follow-up period was higher in recipients who received maternal donor kidneys compared with paternal donor kidneys.

Table 1 | Baseline characteristics of kidney transplant recipients who received kidneys from parental donors (N = 1139)[a]

Variable	Paternal Donor (n = 487)	Maternal Donor (n = 652)	*P* Value
Demographics			
Age (yr, mean, SD)	22.3 ± 10.4	25.5 ± 10.9	<0.001
Male (n, %)	312 (64.1)	387 (59.4)	0.106
Race (n, %)			0.110
White	418 (85.8)	577 (88.5)	
Indigenous	25 (5.1)	18 (2.8)	
Asian/others	44 (9.1)	57 (8.7)	
Preemptive (n, %)	146 (30.0)	225 (34.5)	0.107
Diabetes (n, %)	13 (2.7)	30 (4.6)	0.091
Coronary artery disease (n, %)	8 (1.6)	14 (2.1)	0.540
Former/current smoker (n, %)	82 (16.9)	145 (22.4)	0.034
Cause of ESRD (n, %)			0.204
Glomerulonephritis	201 (41.3)	275 (42.2)	
Diabetes	11 (2.3)	20 (3.1)	
Cystic disease	17 (3.5)	40 (6.1)	
Waiting time (yr)	0.85 ± 1.31	0.82 ± 1.17	0.650
Donor			
Age (yr, mean ± SD)	52.1 ± 9.3	53.2 ± 10.2	0.178
Immunology/transplant			
HLA-ABDR mismatches (mean ± SD)	2.29 ± 0.79	2.35 ± 0.76	0.183
Peak PRA (%)	7.18 ± 18.10	6.03 ± 14.68	0.238
Ischemic time (h, mean ± SD)	2.46 ± 1.83	2.34 ± 2.20	0.328
Induction (n, %)	266 (54.6)	367 (56.3)	0.575
Initial prednisolone (n, %)	472 (96.9)	630 (96.6)	0.782
Initial CNI (n, %)	403 (82.8)	589 (90.3)	0.366
Initial antimetabolite (n, %)			0.578
None	36 (7.4)	46 (7.1)	
MMF	408 (83.8)	559 (85.7)	
Azathioprine	43 (8.8)	47 (7.2)	
Transplant era (n, %)			0.848
1997–2000	112 (23.0)	149 (22.9)	
2001–2004	119 (24.4)	173 (26.5)	
2005–2008	136 (27.9)	180 (27.6)	
2009–2012	120 (24.6)	150 (23.0)	
Outcomes (n, %)			
Acute rejection (n, %)			
First 6 months	96 (19.7)	180 (27.6)	0.002
Late rejection	36 (7.4)	62 (9.5)	0.207
Any	132 (27.1)	242 (37.1)	<0.001
Multiple	36 (7.4)	91 (14.0)	<0.001
Total rejection episodes	0.39 ± 0.76	0.59 ± 0.98	<0.001
Graft failure (n, %)	78 (16.0)	139 (21.3)	0.024
Death-censored graft failure (n, %)	72 (14.8)	125 (19.2)	0.053

CNI, calcineurin inhibitor; ESRD, end-stage renal disease; HLA, human leukocyte antigen; PRA, panel reactive antibody; MMF, mycophenolate.
[a]Data expressed as number (proportion) or as mean ± SD.

Parental donors and the timing of acute rejection

In the unadjusted logistic regression model, maternal donor kidneys were associated with an increased risk of any acute rejection (unadjusted odds ratio [OR], 1.59; 95% confidence interval [CI], 1.23–2.05) and early rejection (unadjusted OR, 1.55; 95% CI, 1.17–2.06). In the adjusted model, recipients of maternal donor kidneys had a significantly higher risk of any rejection (adjusted OR, 1.59; 95% CI, 1.22–2.08) and early rejection (adjusted OR, 1.54; 95% CI, 1.14–2.07) compared with recipients of paternal donor kidneys (Figure 1 and Table 2). There were no associations between parental donor kidneys and risk of late rejection (adjusted OR, 1.37; 95% CI, 0.88–2.13), with a similar finding when restricted to the era between 2004 and 2012 (Table 2). Age at transplantation was an effect modifier between parental donors and early rejection in the adjusted logistic regression model ($P < 0.01$). When stratified by age, maternal donors were associated with a higher risk of early acute rejection in adult recipients