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Gender Imbalance and Outcomes in Living Donor Renal Transplantation in The United States

Liise K. Kayler[a], Cynthia S. Rasmussen[b], Dawn M. Dykstra[b], Akinlolu O. Ojo[c], Friedrich K. Port[b], Robert A. Wolfe[d] and Robert M. Merion[a]

[a] *Department of Surgery, University of Michigan, Ann Arbor, MI*
[b] *University Renal Research and Education Association, Ann Arbor, MI*
[c] *Department of Internal Medicine, University of Michigan, Ann Arbor, MI*
[d] *Department of Biostatistics, University of Michigan, Ann Arbor, MI*
**Corresponding author: Robert M. Merion, MD, merionb@umich.edu*

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In living donor kidney transplantation there are disproportionately more female-to-male donations and fewer male-to-female donations. Given the rapid increase in living donor transplantation, we studied gender demographics and outcomes of these transplants.

We analyzed living donor kidney transplants in the Scientific Registry of Transplant Recipients (SRTR) database between 1990 and 1999.

There were 30 258 living donor transplants [26 510 (87%) biologically related; 2367 (8%) spousal; 1381 (5%) nonspousal unrelated]. Females comprised 68% of spousal and 56% of related and unrelated nonspousal donors ($p < 0.0001$). The distributions of gender pairings in nonspousal groups (related and unrelated) were significantly imbalanced ($p < 0.0001$). Opposite-sex pairs demonstrated more female-to-male donations among living related (64%, $p < 0.0001$), unrelated nonspousal (65%, $p < 0.0001$), and spousal pairs (68%). The higher incidence of end-stage renal disease among males and the slight predominance of females in the general population did not explain these gender disparities. Male recipients of male donor kidneys demonstrated significantly higher graft survival than other combinations ($p < 0.006$).

Gender disparities in living donor transplantation result from a higher proportion of wife-to-husband donations and disproportionate female-to-male donations among biological relatives and unrelated pairs. There appears to be a graft survival advantage for male recipients of male donor kidneys.

Key words: Gender, kidney transplant, outcomes

Abbreviations: HLA: human leukocyte antigen; OPTN: Organ Procurement and Transplantation Network; PRA: panel reactive antibodies; SRTR: Scientific Registry of Transplant Recipients.

Introduction

Many studies have evaluated the role of gender inequality in kidney transplantation (1–12). More than half of living donors are female, females are less likely than males to be on the organ transplant waiting list among chronic kidney failure patients, and wait-listed females are less likely to receive either a cadaveric or living renal transplant (1–12). This disparity not only exists among spouses, in which female-to-male donation rates represent 68–73% of cases (8,12), but also between biological relatives, with more mothers, daughters and sisters donating and more fathers, sons and brothers receiving kidney allografts (12). Although patterns of donation have not been well studied among unrelated nonspousal donations, such as from friends and in-laws, a recent single-center analysis of living kidney donors at the University of Michigan revealed a surprisingly high proportion of male donors in this group (12).

Separately, investigations on the potential impact of gender and renal transplant outcome have demonstrated, with few exceptions (13–15), superior graft survival in recipients of male donor kidneys, both after living and cadaveric renal transplants (16–20). The benefit of male over female donor kidneys is greater in the presence of risk factors for graft failure such as older donor age, prior recipient sensitization, poor HLA matching, and retransplantation (17–22). Enhanced graft outcome of male donor kidneys has also been demonstrated among haploidentical siblings (15,18,20) and parental donor first transplants (17,22). Donor gender, however, has not been shown to influence graft outcomes when the donor is young (e.g. 16–30 years of age) (15,18), when the recipient is a HLA-identical sibling (19,20), or when there is a combined zero or one antigen mismatch at the HLA-B and HLA-DR loci (19).

In this study, we examined national data to assess donor–recipient gender combinations in three types of living donor kidney transplants: (1) biologically living related, (2) living unrelated spousal, and (3) living unrelated nonspousal donor transplants. Additionally, we studied trends in gender disparities. Lastly, we performed graft survival analyses among gender pairs to identify advantages or disadvantages of existing patterns of donation.

Materials and Methods

Using data submitted to the Organ Procurement and Transplantation Network (OPTN) by all kidney transplant centers in the United States, the Scientific Registry of Transplant Recipients (SRTR) database identified 30 258 patients who received a living donor kidney transplant between January 1990 and December 1999, with follow-up available through October 2001. There were 27 315 first transplantations and 2943 patients who had had a prior kidney transplant.

Statistical analyses included descriptive and proportional comparisons based on donor source and relationship, age, and donor-to-recipient gender pairing. Among nonspousal donor-recipient gender proportions, adjustments for recipient panel reactive antibody (PRA) were performed using a logistic regression analysis. All analyses were performed using SAS software, version 8 (SAS Institute, Inc., Cary, NC). Statistical significance was identified by a p-value of less than 0.05.

Analyses were performed comparing observed and expected proportions of gender combinations. External standards for expected recipient proportions were calculated based on the published incidence of end-stage renal disease for males and females less than 65 years of age for the years 1996–99 (male 56%, female 44%) (23). Additionally, as the potential donor pool constitutes the entire population of the United States, expected proportions of donation were assumed to mirror the gender makeup of the general population (51.1% female, 48.9% male) (24). Thus, expected proportions of the donor–recipient pairings among nonspousal pairs were: 29% (0.489*0.56) male-to-male, 27% (0.511*0.56) female-to-male, 22% (0.489*0.44) male-to-female, and 22% female-to-female (0.511*0.44). Comparison of actual and expected proportions of donation were performed by chi-square analysis.

Graft survival was estimated using Cox proportional hazards regression with adjustment for the following potential confounders: donor and recipient age, gender (male vs. female), race (black vs. nonblack) and ethnicity (Hispanic vs. non-Hispanic), recipient body mass index (continuous); most recent PRA level, HLA B and HLA-DR combined mismatch (0, 1, 2, 3, 4), diagnosis (diabetes, hypertension, glomerulonephritis, other), dialysis modality (hemodialysis vs. peritoneal dialysis), time on dialysis, hospitalization status at time of transplant (hospitalized vs. outpatient), pretransplant transfusions (yes vs. no), prior kidney transplantation (yes vs. no), and year of transplant. Transplantation was considered successful if the recipient remained alive without reinstitution of chronic dialysis or retransplantation. Patients who died with functioning grafts were considered to have had graft failures.

Results

Among 30 258 living donor cases, 26 510 (87%) were biologically related and 3748 (13%) were unrelated. The majority of living unrelated transplantations were from spousal donors and constituted 8% (n = 2367) of the entire cohort. The remaining 5% (n = 1381) were nonspousal donors (e.g. friends and in-laws) (Figure 1). Recipient characteristics for living related and living unrelated transplants are shown in Tables 1 and 2. Spousal donors and recipients were 6–9 years older than the living related donors and recipients, respectively ($p < 0.0001$) (Table 3). More spousal allograft donors were female (68%) compared with the living related (56%) and living unrelated nonspousal donors (56%) ($p < 0.0001$). More spousal recipients were male (68%) compared with the living related (57%) and living unrelated nonspousal (57%) recipients ($p < 0.0001$).

Among the entire living donor cohort, the proportion of living donor transplants from living unrelated donors increased from 4.5% in 1990 to 23% in 1999 (Figure 2). However, the proportion of males and females among the living unrelated donors did not show any appreciable change over the 10-year study period (data not shown).

The distribution of the donor-recipient gender pairing combinations among the living related and living unrelated nonspousal cases were very similar (Table 4). In both groups, there were fewer male-to-female donations compared with the other gender pairs, even when compared with the expected number. We calculated the expected gender distribution for recipients using published incidence data for end-stage renal disease among adults aged younger than 65 years old (23) and using U.S. census data for donors (24). In both the living related and living unrelated nonspousal groups, the differences between the observed and expected proportions were statistically significant (Table 4). The differences primarily resulted from the lower than expected male-to-female and higher than expected female-to-male proportions in both groups.

We performed a sensitivity analysis in which same-sex pairs were excluded from the living related and living unrelated nonspousal groups to allow comparisons with the spousal transplants. The analysis of these opposite sex pairs demonstrated fewer male-to-female donations in all three groups of transplants, accounting for 36%, 35%, and 32% of living related, living unrelated nonspousal, and living unrelated spousal cases, respectively (Table 5). Within each group, the difference between the observed and expected proportions of gender pairs was statistically significant ($p < 0.0001$), again reflecting a lower than expected proportion of male-to-female and higher than expected proportion of female-to-male donations. In addition, the gender imbalance in the spousal group was significantly greater than in the living related group ($p < 0.0001$).

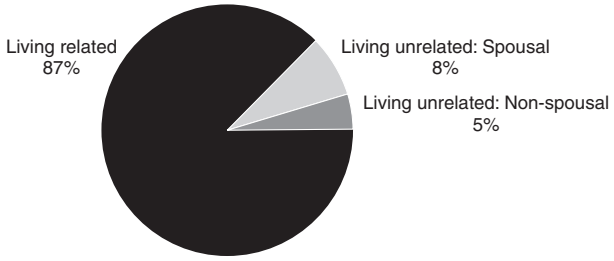

Figure 1: Donor type among 30 258 living donor transplants performed between 1990 and 1999.

Table 1: Descriptive characteristics of living related and unrelated recipients

Recipient characteristics	Living related n = 26 510 (mean or percentage)	Unrelated n = 3748 (mean or percentage)	p-value
Race or ethnicity			
Non-black	85.7%	89.4%	<0.0001
Black	14.3%	10.6%	<0.0001
Hispanic	11.8%	8.7%	<0.0001
Hospitalized at transplantation			NS
No	97.6%	97.3%	
Yes	2.4%	2.7%	
Prior blood transfusion	37.0%	32.0%	< 0.0001
Mean HLA BDR mismatch	1.4	2.8	<0.0001
PRA			
Not reported	6.6%	5.8%	NS
0–19%	87.1%	90.0%	<0.0001
20–79%	5.1%	3.8%	0.0006
80+ %	1.2%	0.4%	<0.0001
Previous kidney transplant	9.8%	9.5%	NS
Previous nonkidney transplant	1.1%	2.1%	<0.0001
Etiology of end-stage renal disease			
Hypertension	11.9%	12.9%	NS
Diabetes	19.6%	24.4%	<0.0001
Glomerulonephritis	33.0%	25.7%	<0.0001
Other	35.6%	37.0%	NS
Time on dialysis (years)	1.4	1.4	NS
No pretransplant dialysis	20.0%	21.1%	NS
Body mass index (kg/m^2)	30.5	27.0	NS

Table 2: Descriptive characteristics of spousal and non-spousal living unrelated recipients

Recipient characteristics	Unrelated spousal n = 2367 (mean or percentage)	Unrelated non-spousal n = 1381 (mean or percentage)	p-value
Race or ethnicity			
Non-black	90.5%	87.6%	0.007
Black	9.5%	12.4%	0.007
Hispanic	9.1%	8.0%	NS
Hospitalized at transplantation			NS
No	97.3%	97.4%	
Yes	2.7%	2.6%	
Prior blood transfusion	31.3%	33.2%	NS
Mean HLA BDR mismatch	2.8	2.7	0.018
PRA			
Not reported	5.8%	5.8%	NS
0–19%	90.8%	88.6%	0.026
20–79%	3.0%	5.1%	0.001
80+ %	0.4%	0.5%	NS
Previous kidney transplant	9.2%	10.1%	NS
Previous nonkidney transplant	2.1%	2.1%	NS
Etiology of end-stage renal disease			
Hypertension	12.4%	13.6%	NS
Diabetes	25.9%	21.9%	0.005
Glomerulonephritis	25.7%	25.7%	NS
Other	35.9%	38.8%	NS
Time on dialysis (years)	1.4	1.5	NS
No pretransplant dialysis	22.8%	18.2%	0.001
Body mass index (kg/m^2)	27.6	25.9	NS

Table 3: Gender and age of donors and recipients

	Living related n = 26 510	Unrelated non-spousal n = 1381	Unrelated spousal n = 2367	p-value
Age (years±SD)				
Recipients	37±16	43±14	46±11	<0.0001
Donors	38±11	39±10	44±10	<0.0001
Recipient gender				
Male	15,043 (57%)	789 (57%)	1,618 (68%)	<0.0001
Female	11,467 (43%)	592 (43%)	749 (32%)	
Donor gender				
Male	11,611 (44%)	604 (44%)	749 (32%)	<0.0001
Female	14,899 (56%)	777 (56%)	1,618 (68%)	

Direct analysis of PRA levels among candidates for living donor kidney transplantation was not possible, as fewer than 50% of the recipients of living donor transplants had been previously placed on the cadaveric waiting list, and this is where PRA data are recorded. However, each of the three types of living donor grafts displayed a higher level of sensitization among female recipients (Table 6). The level of sensitization was less than that found among wait-listed candidates for males as well as females, as expected.

Overall, the 1- and 5-year-adjusted living donor graft survival rates were 94% and 79%, respectively, and did not differ appreciably by donor or recipient gender. However, male recipients of male donor kidneys demonstrated significantly higher graft survivals compared with the other gender pairs (Table 7).

Discussion

This analysis of national data illuminates three notable patterns among living donor kidney transplants in the United States. First, females constitute a disproportionate majority of donors for kidneys utilized for biologically living related, spousal, and nonspousal living unrelated transplants. Second, as with cadaveric renal transplantation, males constitute the majority of recipients of all three types of living donor transplants. Third, the occurrence of male living donor to female recipient transplantation is much less common than with other gender combinations. This particular gender disparity is found among donations from biological relatives and nonbiologically related individuals, such as friends and in-laws, and is even more pronounced in spousal transplants.

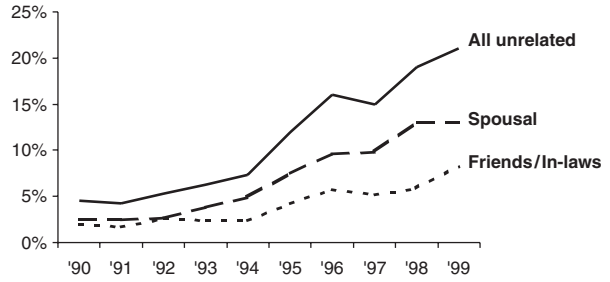

Figure 2: Living unrelated transplants by year as a proportion of all living donor transplants.

There are many potential reasons for the lower proportion of male donors. As the actual living donor candidate pool cannot be directly analyzed, we assumed it to mirror the general population of the United States, which has a slight female predominance (23). However, other potential imbalances between the donor pool and the general population are more difficult to assess directly. Whereas some investigators have shown that males may have a greater degree of ambivalence about donation compared with women (25), others suggest that men may be less available or less able to donate. The greater incidence of coronary artery disease and hypertension among males (1) may eliminate a greater proportion of males from the potential donor pool. It is also unknown to what extent

Table 4: Donor-recipient gender pairing in living donor transplants

	Living related n (%)	Living unrelated non-spousal n (%)
Observed proportions		
Female-to-male	8,036 (30%)	400 (29%)
Male-to-male	7,007 (26%)	389 (28%)
Female-to-female	6,863 (26%)	377 (27%)
Male-to-female	4,604 (17%)	215 (16%)
Expected proportions*		
Female-to-male	7,588 (29%)	395 (29%)
Male-to-male	7,258 (27%)	378 (27%)
Female-to-female	5,962 (22%)	311 (22%)
Male-to-female	5,703 (22%)	297 (22%)
Observed vs. expected		
Chi-square (d.f. = 3)	382.7	37.0
p-value	<0.0001	<0.0001

*Expected proportion of donation is based on incidence rates for end-stage renal disease by gender for patients <65 years during 1996–99 (23) and donor gender ratio corresponding to the general population of the United States (24).

Table 5: Comparison of opposite-sex pairs among living donor transplantations

	Living related n (%)	Living unrelated non-spousal n (%)	Living unrelated spousal n (%)
Observed proportions			
Female-to-male	8,036 (64%)†	400 (65%)	1,618 (68%)†
Male-to-female	4,604 (36%)	215 (35%)	749 (32%)
Expected proportions*			
Female-to-male	7,078 (56%)	344 (56%)	1,325 (56%)
Male-to-female	5,561 (44%)	270 (44%)	1,041 (44%)
Observed vs. expected			
Chi-square (d.f. = 1)	294.4	20.4	146.7
p-value	<0.0001	<0.0001	<0.0001

*Expected proportion of donation is based on incidence rates for end-stage renal disease by gender for patients <65 years during 1996–99 (23).
†$p < 0.001$.

Table 6: Living donor recipient and wait-listed candidate*: panel reactive antibody by gender

Group	Living related n = 26 510		Living unrelated non-spousal n = 1381		Living unrelated spousal n = 2367		Wait-listed candidates* n = 68 862	
PRA	Male	Female	Male	Female	Male	Female	Male	Female
Not reported	6.7	6.4	4.8	7.1	5.8	5.9	11.7	11.4
0–19%	89.4	84.1	90.1	86.5	92.0	88.4	76.9	63.5
20–79%	3.2	7.5	4.7	5.7	2.0	5.1	8.3	17.5
80+ %	0.7	2.0	0.4	0.7	0.3	0.7	3.1	7.6

*Includes all patients aged 18–64 years wait-listed for kidney transplant between 1996 and 1999.
PRA = panel reactive antibody.

males may be unavailable to donate as a result of military obligations or incarceration, both of which are very uncommon among females. The absence of a guaranteed system of reimbursement for lost wages for donors may impact both the recipient's and the donor's interest in having a primary breadwinner (statistically more often male in the USA) undergo donor nephrectomy. Efforts to increase living donation by offering employee leave time for living donation as proposed by an amendment to the Family and Medical Leave Act (26) may help to ameliorate the observed irregular topography of donation patterns.

To explain the paucity of male-to-female donations, it has been suggested that the greater level of lymphocytotoxic antibodies among females may provide a barrier to transplantation in this group, particularly from some males. In addition to the sensitizing effects of pregnancy, blood loss associated with menstruation may contribute to greater blood transfusion requirements among females, in turn leading to more allosensitization. Elevated PRA is a barrier to cadaveric kidney transplantation regardless of gender. Moreover, a report on cadaveric transplant rates by Wolfe *et al.* demonstrated that the 14% lower transplant rates among females compared with males was largely explained by adjustment for recipient PRA, suggesting that sensitization is a critical factor responsible for recipient gender disparities (27). In the setting of spousal transplantation, wives may be specifically sensitized to

Table 7: Adjusted* short and long-term graft survival among gender pairs

Gender pairs	n	1-year survival (%)	5-year survival (%)	p-value	Hazard ratio	95% confidence interval
Male-to-male	7396	95	81.2	Reference	1.0	Reference
Female-to-female	7240	93.8	79	0.006	1.12	1.03–1.21
Female-to-male	10 054	93.8	78.9	0.0002	1.17	1.08–1.27
Male-to-female	5568	93.7	78.3	0.0001	1.19	1.09–1.30

*Adjusted for donor and recipient age, gender, race, ethnicity, recipient body mass index, most recent PRA level, HLA B and HLA-DR combined mismatch, diagnoses, dialysis modality, time on dialysis, hospitalization status at time of transplant, pretransplant transfusions, prior kidney transplant, and year of transplant.

their husbands as a result of exposure to parental antigens during pregnancy, thus providing an immunologic contraindication to organ acceptance (1).

In contrast to the findings of our recent single-center report (12), this study of national data did not find a higher proportion of male donors among nonspousal living unrelated transplantations. In fact, the distribution of donor–recipient gender pairings among the living unrelated nonspousal cases was identical to that found among the living related pairs, with 56% of the donors being female. These observations stand in contrast to the spousal transplants, where 68% of the donors were the recipients' wives.

Graft survival rates are excellent among all living donor recipients. In concert with reported findings, graft survival analysis of this living donor cohort revealed significantly higher graft survival rates among male-to-male transplantations, which may reflect sufficient functional donor nephron adequacy (28–30). Female kidneys are smaller and have fewer glomeruli than males (31). When transplanted into a large recipient, the smaller female donor kidney responds with greater hypertrophy and enhanced hyperfiltration, ultimately achieving normal renal function in the larger recipient within weeks of the transplant (32). However, this physiological adaptation may additionally induce a functional overload leading to hyperfiltration injury (32). Based on experimental evidence, Hostetter and colleagues proposed that hemodynamically mediated glomerular injury results in progressive loss of glomeruli and graft failure (32). Proteinuria and histopathologic evidence of focal glomerular sclerosis may be the hallmark of this glomerulopathic process (32). These findings have been noted after transplantation of small pediatric kidneys into adult recipients (33), in adults after surgical removal of 75% of functioning renal mass (34), and in children with solitary kidneys (35) In addition to the potential for hyperfiltration injury, the smaller kidney must withstand the trauma of the donor procurement, preservation, the transplant surgery itself, cyclosporine toxicity, delayed graft function, and possible rejection episodes, all of which may reduce effective nephron mass. While the concepts of nephron under-dosing and hyperfiltration injury are compelling and lend a rational basis to our findings of improved graft survival in male-to-male grafts, these paradigms do not explain the absence of comparative or even higher graft survival among male-to-female grafts. The potential influence of gender on renal transplantation outcomes has been the subject of many experimental and clinical investigations and may include differential effects of sex hormones on immunologic responsiveness (36–38), drug metabolism (39–42), and hemodynamic responses (43–45).

The results of our study show that even after the exclusion of gender-imbalanced spousal donations, females are significantly less likely to be recipients and more likely to be donors of renal allografts in living renal transplants. In particular, there is a paucity of male-to-female donations among all groups of living donor transplantations. These disparities are not explained by the greater proportion of males within the potential recipient pool. Higher PRA levels may be an important barrier to transplantation of wives using their husband's kidneys, but the lack of availability of PRA data on the pool of potential living donor transplant candidates precludes direction examination of this issue. Epidemiological or prospective clinical studies that include data on insurance, income, matching, comorbidities, preformed lymphocytotoxic antibody status, patient preferences, health attitudes, and beliefs are necessary to further delineate the precise factors that contribute to this apparent barrier to transplantation for females, particularly from male donors.

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