The Effect of Donor Gender on Graft Survival

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Abstract. Differences in actuarial graft survival according to donor gender have been reported for renal allografts and for cardiac and hepatic allografts, but for the latter in small series with limited biostatistical power. Using the large database of the Collaborative Transplant Study (CTS), this study is an evaluation of graft survival according to donor and recipient gender for renal ($n = 124,911$), cardiac ($n = 25,432$), and hepatic ($n = 16,410$) transplants. Confounders, such as calendar year, geographical area, race, donor and recipient age, HLA mismatch, cold ischemia time, and others, as well as interaction terms were taken into consideration. Death-censored actuarial renal allograft survival from female compared with male donors was less in female recipients and even more so in male recipients. The donor gender–associated risk ratio for graft loss was 1.15 in female recipients and 1.22 in male recipients. The age-gender interaction term was statistically significant, the gender effect being more pronounced for younger (16 to 45 yr) compared with older (>45 yr) donors. Serum creatinine concentrations 1 yr after transplantation were also higher for recipients with kidney grafts coming from female donors irrespective of recipient gender. For first cardiac transplants, graft survival was inferior when the donor was female and the recipient male, but no statistical difference according to donor gender was demonstrable in female recipients. For first hepatic transplants overall, no significant differences according to donor gender were noted. The proportion of recipients who had treatment for rejection crisis during the first year was higher for male recipients of kidneys from female donors compared with male donors. No difference according to donor gender was demonstrable in female recipients. For cardiac and hepatic grafts, no significant effect of donor gender on the proportion of patients treated for rejection episodes was noted. The data show that adverse effects of female donor gender for different organs is much less uniform than reported in the past. An important confounder is donor age. A gender effect on graft survival is also observed for cardiac allografts. Therefore, in addition to potential "nephron underdosing," further pathomechanisms must play a role, possibly differences in immunogenicity according to donor gender.

It has been noted for a considerable time that kidney transplants fare better in female than in male recipients (1,2). More recent studies also documented inferior short-term and long-term graft survival when female kidneys were transplanted into male patients (3–5). This phenomenon was also seen in combined kidney and pancreas transplantation (6). The findings have not been entirely consistent, however, presumably because of the small number of individuals assessed and the failure to account for confounding factors.

The observation of worse functional prognosis of female grafts is of interest in view of the fact that the renal prognosis in primary chronic renal disease is considerably better in female patients, as documented by experimental (7–10) and clinical observations (11–15). This has been ascribed to a protective effect of estrogens.

An intriguing hypothesis has been offered to account for the effect of donor gender on renal allograft outcome, *i.e.*, the postulate that female kidneys contain fewer nephrons (nephron underdosing) (16), thereby increasing the workload of the individual nephrons (16,17). The general concept that the total number of nephrons transplanted is a determinant of long-term graft outcome has been well illustrated by experimental studies, where, all other things being equal, graft outcome was better when two kidneys were transplanted (18,19). Preliminary evidence in humans also appears to point in the same direction (20,21).

We evaluated the problem of whether the above gender effect is specific for kidney grafts or whether it is more generally seen with other solid organ grafts as well. In the first case, gender-dependent differences in renal function and/or structure would be the most plausible explanation. In the latter case, organ-unrelated effects of donor gender on immune-recognition and/or immune effector mechanisms would be more logical candidates.

To address this issue, we compared long-term graft outcome for kidney as well as other solid organ grafts on the basis of the very large and complete database of the Collaborative Transplant Study (CTS).

Materials and Methods

Renal, cardiac, and hepatic transplants at centers participating in the CTS were analyzed: 464 renal transplant centers in 49 countries,

165 cardiac transplant centers in 29 countries, and 103 hepatic transplant centers in 25 countries. We assessed first renal transplants performed from 1985 to 2000, first orthotopic cardiac transplants from 1985 to 2000, and first hepatic transplants from 1988 to 2000. Transplants were included only when recipient and donor age were at least 16 yr at the time of transplantation. The age characteristics of the patients are summarized in Table 1. In addition to first cadaveric kidney grafts, 5716 kidney grafts between HLA-identical siblings were evaluated. Clinical follow-up information was obtained at 3, 6, and 12 mo after transplantation and yearly thereafter.

Multivariate Cox regression analysis (22) was used to explain the effects of the donor gender on graft survival time. Apart from donor gender, relevant explanatory variables with corresponding scaling were included in the Cox proportional hazards analysis: calendar year of transplantation, geographical area, recipient race, recipient age, recipient gender, donor age, HLA mismatch, cold ischemia time, original disease, body mass index, systolic BP (outpatient clinic), pretransplant cytotoxic antibodies, pretransplant blood transfusions, immunosuppressive therapy, and interaction terms. Graft and patient survival graphs were computed according to Kaplan Meier (23). Patients who died with functioning grafts were counted as graft failures. In the analysis of serum creatinine concentration, significance of the difference between groups was estimated with the classic χ^2 test of fourfold tables (24).

Results

Actuarial Graft Survival of Renal Transplants According to Donor and Recipient Gender

Actuarial survival of first cadaver renal transplants was consistently lower when the donor was female irrespective of whether the recipient was female or male. The univariate Kaplan-Meier estimates of graft or patient survival are given in the respective figure legends (Figures 1 and 2).

By multivariate Cox regression analysis, the donor gender-related risk ratio (female donors *versus* male donors) was 1.15 (95% CI [confidence interval], 1.07 to 1.23; $P < 0.0001$) when the recipient was female and even higher at 1.22 (95% CI, 1.16 to 1.29; $P < 0.0001$) when the recipient was male. The effect of donor gender is thus greater in male recipients than female recipients.

With respect to patient survival, the actuarial survival of the recipients of renal transplants was also slightly but significantly less if the donor of the renal graft was female, and this was true irrespective of whether the recipient was male or female (Figure 2). The magnitude of the effect was not sufficient to explain the difference of allograft survival according to donor gender. The so-called functional allograft survival was even numerically more adverse than the uncorrected actuarial graft survival. The donor gender–related risk ratio (female donors *versus* male donors) was 1.17 (95% CI, 1.08 to 1.27; $P = 0.0002$) when the recipient was female and 1.30 (95% CI, 1.22 to 1.39; $P < 0.0001$) when the recipient was male.

Influence of Donor Age on Actuarial Renal Graft Survival According to Donor Gender

The interaction term of donor gender/donor age was significant. Table 2 illustrates that the inferior actuarial graft survival in female recipients of kidneys from female donors was demonstrable only for younger female donors, *i.e.*, ≤45 yr. In addition, the risk ratio was higher when kidneys of younger female donors (16 to 45 yr) compared with kidneys from older female donors (>45 yr) were transplanted in male recipients.

Actuarial Graft Survival of HLA-Identical Sibling Renal Transplants According to Donor and Recipient Gender

As expected, early graft function was remarkably good for renal grafts from HLA-identical siblings. After several years, the tendency for lower actuarial graft survival of grafts from female donors became apparent. By Cox regression analysis, the risk ratio for the graft of a female donor relative to that of a male donor was 1.11 (95% CI, 0.98 to 1.26; $P = 0.0876$). The risk ratio of a graft transplanted into a female recipient relative to a male recipient was 0.82 (95% CI, 0.72 to 0.94; $P = 0.0030$) (Figure 3).

Actuarial Cardiac Graft Survival According to Donor and Recipient Gender

As shown in Figure 4, cardiac transplants from female donors had significantly inferior actuarial survival in male recipients, whereas no difference according to donor gender was demonstrable in female recipients. By Cox regression

Table 1. Age characteristics (yr) of the patients (first cadaveric kidney, heart, and liver grafts)[a]

| Graft | Specification | Male Recipient | | Female Recipient | |
		Male Donor	Female Donor	Male Donor	Female Donor
Kidney	n	47,436	26,559	27,880	17,320
	recipient age	44.2 ± 0.06	45.0 ± 0.08	43.7 ± 0.08	44.5 ± 0.10
	donor age	36.4 ± 0.07	41.7 ± 0.09	36.2 ± 0.09	41.7 ± 0.11
Heart	n	16,074	5199	1957	2202
	recipient age	49.6 ± 0.08	50.3 ± 0.16	46.8 ± 0.28	47.7 ± 0.26
	donor age	30.4 ± 0.09	35.8 ± 0.16	29.1 ± 0.24	35.1 ± 0.26
Liver	n	6560	3291	3228	3331
	recipient age	47.7 ± 0.13	47.7 ± 0.20	46.0 ± 0.23	47.2 ± 0.22
	donor age	36.0 ± 0.18	41.8 ± 0.24	33.8 ± 0.25	40.7 ± 0.24

[a] Mean ± SEM.
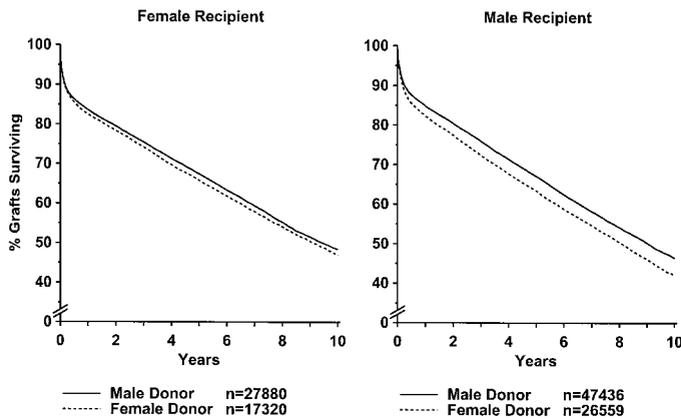
Figure 1. First cadaveric kidney transplants (1985 to 2000); actuarial graft survival. In female recipients, the 10-yr Kaplan-Meier estimate was 48.4 ± 0.4 yr for male donors and 46.9 ± 0.6 yr for female donors ($P = 0.0020$). In male recipients, it was 46.5 ± 0.3 yr for male donors and 42.1 ± 0.5 yr for female donors ($P < 0.0001$).
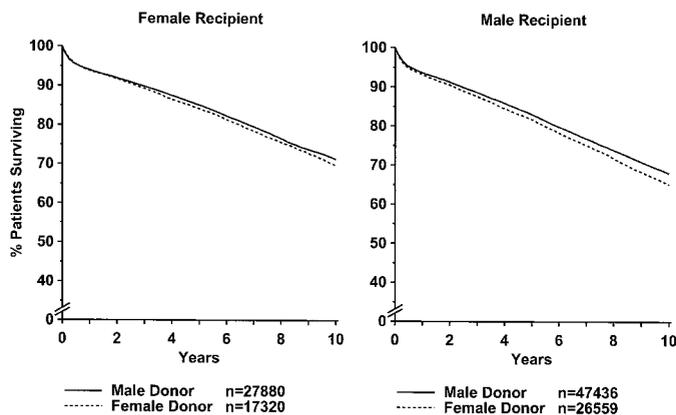

Figure 2. First cadaveric kidney transplants (1985 to 2000); actuarial patient survival. In female recipients, the 10-yr Kaplan-Meier estimate was 71.3 ± 0.4 yr for male donors and 69.7 ± 0.6 yr for female donors ($P = 0.0191$). In male recipients, it was 68.0 ± 0.3 yr for male donors and 65.2 ± 0.5 yr for female donors ($P < 0.0001$).

analysis, the risk ratio for the graft of female donors was 1.13 (95% CI, 1.08 to 1.19; $P < 0.0001$) in male recipient, but it was not significantly different from 1.0 for grafts of female

donors transplanted into female recipients compared with grafts from male donors.

Actuarial Hepatic Graft Survival According to Donor and Recipient Gender

Overall there were no significant differences of actuarial graft survival according to donor gender (Figure 5). By Cox regression analysis, the risk ratio related to donor gender (female donors *versus* male donors) was 0.94 (95% CI, 0.87 to 1.03; $P = 0.1782$) when the recipient was female and 1.07 (95% CI, 0.99 to 1.15; $P = 0.0731$) when the recipient was male.

Separate analysis according to geographical area showed that worse actuarial survival rates were found in North American centers when livers of female donors were transplanted to male recipients (risk ratio, 1.22; 95% CI, 1.04 to 1.44; $P = 0.0149$), whereas no such difference was seen in Western Europe.

Proportion of Renal Graft Recipients with Serum Creatinine Concentrations <130 µmol/L

As shown in Table 3, the proportion of patients who had low (< 130 µmol/L) serum creatinine concentrations was lower for recipients of grafts from female donors. Men have on average higher serum creatinine concentrations than women; separate analyses according to recipient gender were therefore performed. In either recipient gender, there was a highly significant difference between recipients of grafts from female compared with male donors. The relative difference (%) was highest after 1 yr and decreased thereafter, possibly because of progressive dropout of individuals with the highest serum creatinine values.

Proportion of Recipients of Different Organ Grafts Requiring Treatment for Acute Rejection According to Donor and Recipient Gender

The salient feature of Table 4 is the finding that the proportion of male recipients of renal allografts who received organs from female donors and who required antirejection therapy was greater than the proportion of male recipients who had received an organ from a male donor.

A difference according to donor gender was not found in recipients of heart or liver grafts. In contrast among recipients

Table 2. Risk ratio of female donor *versus* male donor according to age of donor[a]

Recipient	Donor Age	Risk Ratio	95% CI of Risk Ratio		P
			Lower	Upper	
Female	16 to 45	1.08	1.04	1.12	0.0003
	>45	0.96	0.92	1.02	0.1719
Male	16 to 45	1.16	1.12	1.19	<0.0001
	>45	1.05	1.01	1.09	0.0206

[a] The table does not give absolute rates, but indicates by how much kidneys of female donors do worse than kidneys from male donors (and vice versa).
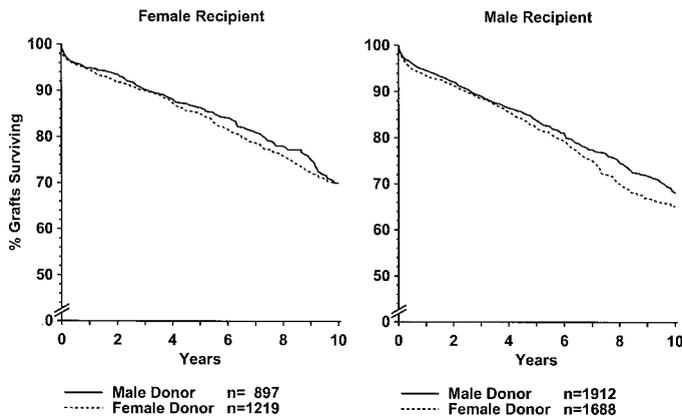
Figure 3. Kidney transplants (1985 to 2000); actuarial graft survival in HLA-identical siblings. In female recipients, the 10-yr Kaplan-Meier estimate was 70.1 ± 2.5 yr for male donors and 70.1 ± 2.1 yr for female donors ($P = 0.4684$). In male recipients, it was 68.1 ± 1.7 yr for male donors and 65.2 ± 1.8 yr for female donors ($P = 0.1191$).
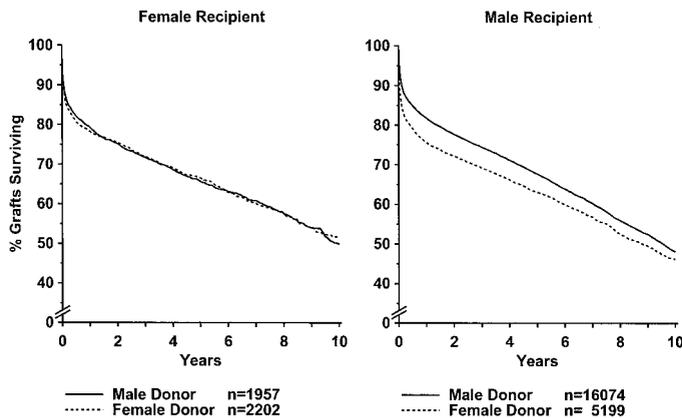

Figure 5. First liver transplants (1988 to 2000); actuarial graft survival. In female recipients, the 5-yr Kaplan-Meier estimate was 63.4 ± 0.9 yr for male donors and 63.4 ± 1.0 yr for female donors ($P = 0.4331$). In male recipients, it was 61.5 ± 0.7 yr for male donors and 59.3 ± 1.0 yr for female donors ($P = 0.0258$).

Figure 4. First orthotopic heart transplants (1985 to 2000); actuarial graft survival. In female recipients, the 10-yr Kaplan-Meier estimate was 49.9 ± 1.7 yr for male donors and 51.8 ± 1.7 yr for female donors ($P = 0.9581$). In male recipients, it was 48.0 ± 0.6 yr for male donors and 46.2 ± 1.0 yr for female donors ($P < 0.0001$).

of heart grafts, a significantly higher frequency was found in females irrespective of donor gender, and a similar trend, although not statistically significant, was noted in recipients of liver grafts.

Discussion

From single-center studies (4,5), it had been known that short-term and long-term graft survival was worse when kidneys from female donors were transplanted to male recipients. On the basis of results in small series it has also been claimed that graft outcome was worse for heart and liver allografts coming from female donors (33-38).

Our analysis concerned the large CTS registry comprising more than 100,000 kidney transplantations from 1985 to 2000. Inferior graft outcome was documented when kidneys of female donors were transplanted into male recipients compared with kidneys
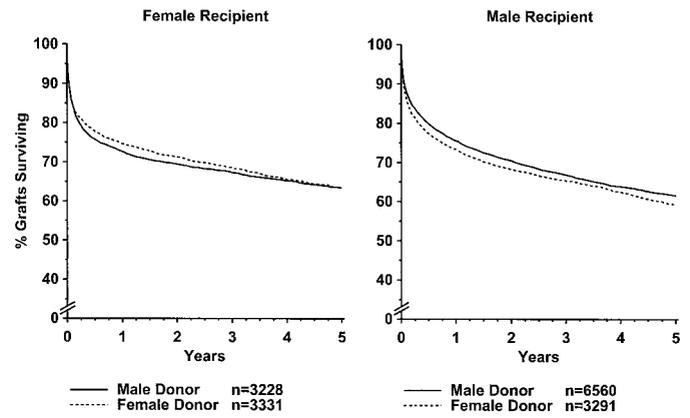
from male donors transplanted into female or male recipients (Figure 1). A similar difference according to donor gender was found for patient survival: survival was consistently better for female recipients of kidneys of male donors compared with male recipients of kidneys of female donors (Figure 2). The same dependency of graft survival on donor gender was even observed in HLA-identical siblings (Figure 3). It was also seen in cadavaric graft recipients on immunosuppression with calcineurin inhibitors or without (data not given). Such an effect of donor gender was obvious not only when graft survival but also when graft function was considered. After 1, 3, and 10 yr after transplantation, the proportion of recipients with a serum creatinine concentration below 130 μmol/L was higher in patients who received their renal allografts from a male donor irrespective of recipient gender (Table 3).

A proposal to explain earlier observations (4,5,40,41) of a worse outcome of kidney grafts coming from female donors was the idea of nephron underdosing (18-20). Experimental (17,18) and clinical studies (19-21) underline an adverse effect of nephron underdosing. In one study (25), long-term graft function was better when two kidney grafts were transplanted as compared with one. In allogeneic or syngeneic transplantation, a reduction of nephron mass had an adverse effect on graft function and morphology (26). There is also some clinical evidence that long-term graft function is better when two kidneys are transplanted into one recipient (20,21). The evidence is not perfectly consistent, however; Vianello (27), found that an imbalance of the donor and recipient kidney/body weight ratio had no major effect on kidney graft function and survival after 4 yr.

What is the evidence for fewer nephrons in kidneys of females? Anatomic studies have documented larger kidney weight in men (28), but the results were inconsistent when the kidney size was corrected for body surface area (16,28). In animals, kidney size and weight is greater in males (7,29), even when corrected for body weight (29,30). Information on the number of glomeruli in the two genders is also conflicting:

Table 3. Proportion of renal allograft recipients with serum creatinine < 130 μmol/L according to donor and recipient gender

Recipient	Donor	1 Yr after TX		3 yr after TX		10 yr after TX	
		Rate	P	Rate	P	Rate	P
Female	Female	54.9%	<0.0001	52.1%	<0.0001	50.6%	0.0032
	Male	64.8%		59.4%		57.8%	
Male	Female	30.7%	<0.0001	31.8%	<0.0001	34.8%	<0.0001
	Male	44.4%		43.8%		44.9%	

Table 4. Proportion of recipients of different organ grafts for whom treatment of acute rejection during the first year after transplantation has been reported

Recipient	Donor	Kidney ($n = 42,978$)		Heart ($n = 8144$)		Liver ($n = 1821$)	
Female	Female	26.3%	26.4%	54.2%	52.4%[b]	32.4%	33.2%
	Male	26.5%		50.9%		34.0%	
Male	Female	27.9%[a]	26.6%	44.1%	45.7%[b]	29.4%	29.1%
	Male	26.0%[a]		46.2%		28.9%	

[a] $P = 0.0006$ difference between female *versus* male donors in male recipients.
[b] $P < 0.0001$ difference between male and female recipients irrespective of donor gender.

Nyengard (31) and MacLachlan (32) found similar numbers of glomeruli in males and females, but larger glomerular volumes. In the renal ablation model, larger glomerular volumes were found in male animals in some (7,32) but not all studies (7,8).

Although we cannot discount an effect of nephron under-dosing, the observation that a similar dependence of graft outcome on donor gender is found for nonrenal allografts as well, *i.e.*, heart grafts, strongly suggests that other mechanisms must also play a role.

Our observations are in line with smaller series, which showed earlier onset of allograft rejection (33,34) in recipients of hearts from female donors and more pronounced vascular intimal hyperplasia by intravascular ultrasound (35).

For liver transplants, the reported results were even more striking. Kahn (36) reported that no less than 60% of livers from female donors failed in male recipients, corresponding to a 3.7-fold higher risk of graft failure. Data from the UNOS registry (37) and several other series confirmed inferior graft and patient survival in males receiving the liver from a female donor (38). Our data confirm this effect in North American centers, but for unknown reasons, no such effect was seen in Western Europe.

In the search for alternative mechanisms involved in the donor gender effect, we considered immunologic factors. The importance of immune factors may be indirectly assessed by the number of episodes necessitating antirejection therapy.

Indeed, a significantly higher proportion of patients had required antirejection treatment by 1 yr after transplantation when kidneys from female donors had been transplanted into male recipients, compared with kidneys from male donors transplanted into male recipients (Table 4). Our observation is in line with the recent single-center experience of Vereerstraten

(5), who saw a higher incidence of acute rejection episodes (but also more technical problems) in male recipients of kidney grafts from female donors. This finding contrasts with some small earlier studies.

Animal experiments suggest that kidneys of females express more HLA antigens and are more antigenic (39,40). This hypothesis is supported by the finding that survival of kidney grafts coming from female compared with male donors is particularly poor in highly sensitized recipients (41). HLA matching does not completely abrogate the donor gender effect in first cadaver renal transplants and living related donor transplants (42,43). But a gender effect was demonstrable in our study, even in HLA-identical siblings, possibly pointing to an additional role of non-HLA factors.

A further possibility to consider would be an influence of chromosomal sex or sex hormones on vascular endothelial cells, one potential interface relevant for allograft recognition (44). Indeed, sex hormones influence some endothelial cell indices, *e.g.*, androgen exposure increases mononuclear cell adhesion to vascular endothelial cells (45), and both androgens and estrogens affect endothelial cell proliferation (46).

In contrast to previous reports (4,5,41) that female gender and older donor age are associated with an increased risk of graft failure, the analysis of the CTS database showed an increased risk for kidneys from younger (16 to 45 yr) female donors (Table 2). One hypothesis to explain our results might be a gender-related difference of the density of dendritic cells in the kidney.

Our results contrast with the findings of Meier-Kriesche (47), who examined a large database ($n = 73,477$) and found a higher risk of acute rejections for female recipients but a higher risk of chronic rejection in males. This may be ex-

plained by more intense stimulation of the immune system in a high-estrogen environment, as suggested by some experimental and clinical studies (48). Apart from the recipient's hormonal status, the hormonal status of donor may also be important.

A further consideration would be gender differences in the susceptibility to ischemia reperfusion injury with delayed resumption of graft function or technical problems. Whether kidneys of female donors are more susceptible to ischemia/reperfusion injury is controversial. According to our study, at any given duration of cold ischemia, kidney and heart transplants coming from female donors had consistently worse graft survival compared with male donors. Consequently, differences in the duration of ischemia do not explain the worse outcome for kidneys grafted from female donors, but this observation does not exclude that there are differences in susceptibility of grafts to ischemia/reperfusion injury according to donor gender.

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