The Effect of Donor Gender on Renal Allograft Survival

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ABSTRACT
Donor gender plays a role in the outcome of renal transplantation, but the mechanisms responsible for this effect are unclear. In this study, actuarial graft survival in 1049 recipients transplanted at Montefiore Medical Center between 1979 and 1994 was examined. It was found that donor gender had no influence on graft survival in recipients treated with pre-cyclosporine immunosuppressive agents. In contrast, graft survival time was greater in cyclosporine-treated recipients of male donor kidneys compared with female kidneys (P < 0.05). This survival time difference was evident in the early post-transplant period and was entirely accounted for by the survival advantage of kidneys from white male donors. There was no gender-related difference in graft survival time among recipients of African-American donor kidneys. Recent attention has focused on the hypothesis that a mismatch between female donor kidney nephron supply and male recipient functional demand results in hyperfiltration-mediated glomerular injury and that this is responsible for reduced survival time of female allografts. Any hypothesis purporting to explain gender-related differences in graft survival time must take into account this study's observations that the donor-gender effect was observed only in cyclosporine-treated recipients, was not seen in African-American donors, appeared soon after renal transplantation, and did not increase progressively with time. These observations are most consistent with the hypothesis that gender-related differences in graft survival time may reflect differences in susceptibility to cyclosporine nephrotoxicity or differences in the therapeutic response to cyclosporine.

Key Words: Cyclosporine, transplantation, chronic rejection, immunosuppression

It has been clearly established that donor gender influences renal allograft survival (reviewed in Reference 1). However, the mechanisms responsible for this effect remain controversial (1). In general, graft survival time is reduced in recipients of kidneys from female donors as compared with recipients of male donor kidneys (1). Several hypotheses have been advanced to explain the donor-gender effect, including gender-related differences in kidney HLA density and gender-related differences in donor kidney susceptibility to cyclosporine nephrotoxicity or in the therapeutic response to cyclosporine (2-11). More recently, attention has focused on the hypothesis that the diminished survival time of kidneys from female donors is the result of mismatch between the female donor's nephron supply and the male recipient's functional demand (12-14). Because women have smaller kidneys and have been postulated to have fewer nephrons than men, transplantation of a female kidney into a male recipient may be functionally inadequate for the needs of the recipient (12-14). Resultant hemodynamically mediated glomerular injury might then give rise to progressive loss of glomeruli and chronic graft failure.

If hyperfiltration-mediated glomerular injury were primarily responsible for gender-related differences in graft survival, then the survival advantage of male donor kidneys would not be expected to arise in the early post-transplant period because longer periods of time would be required to develop hyperfiltration-mediated renal injury. Moreover, gender differences in graft survival would progressively increase with time after transplantation. To evaluate these predictions, we examined renal graft survival in over 1000 recipients at Montefiore Medical Center who were transplanted between 1979 and 1994.

METHODS

From 1979 to December 1994, 1049 patients (695 men, 354 women) underwent renal transplantation at Montefiore Medical Center/Albert Einstein College of Medicine. Almost all donor kidneys were from cadaver sources (N = 933). Of the total number of patients, 651 (428 men and 223 women) received cyclosporine. One hundred forty-one cyclosporine-treated male recipients and 96 female recipients received kidneys from female donors. The immunosuppressive protocol has been described previously in detail and included the use of cyclosporine in the immediate postoperative period only if the serum creatinine level fell below 30% of initial levels in the first 24 h postoperatively (15). Azathioprine or antilymphocyte globulin were used in combination with prednisone in patients with delayed graft function. Acute rejection episodes were diagnosed by clinical parameters and were treated initially with three consecutive daily iv bolus doses of 500 mg methylprednisolone. Steroid-resistant graft rejection was confirmed by percutaneous renal biopsy and was treated with antilymphocyte globulin or muromonab-CD3.
In total, 1410 renal allograft biopsies were performed in 602 patients between 1979 and 1994. In addition to baseline histologic specimens obtained at the time of transplantation, clinical indications for allograft biopsy included proteinuria or a rise in serum creatinine level unresponsive to empiric antirejection therapy or reduced cyclosporine dosage. The percentage of sclerotic glomeruli in biopsy specimens was corrected for the degree of glomerulosclerosis present in baseline specimens, or where baseline studies were not obtained, by donor age at the time of transplantation according to previously described regression equations (16).

Measurements of blood pressure obtained during follow-up clinic visits were available for analysis in 464 recipients, 316 of whom received grafts from male donors. Nearly all patients were treated with antihypertensive agents. Measurements of plasma cyclosporine levels obtained during follow-up clinic visits were available for analysis in 422 recipients, 286 of whom received kidneys from male donors. The mean number of plasma cyclosporine measurements obtained during the first 6 months post-transplantation was 7.4 ± 0.7 and 7.4 ± 0.8 in recipients of male and female donor kidneys, respectively. Additional plasma cyclosporine measurements made during the remainder of the follow-up period were available for analysis in a total of 422 recipients, 286 of whom received grafts from male donors.

Graft survival time was measured by using the cumulative life table method. Patients were dropped from follow-up 3 months after return to dialysis. Nine-year follow-up data is presented, after which time the number of survivors became small. Statistical significance was determined by the log rank test for the differences in graft survival time. Significance was defined as a P value below 0.05. Differences between categorical data were compared by using chi-squared test with Yates correction. Differences between numerical data were compared by using the t test for unpaired data or analysis of variance with Scheffe's correction. Methods described by Snedecor (17) to compare the slopes of two or more curves by using the t test and analysis of covariance were used to compare the slopes of cumulative curves and regression lines. Graft survival time was analyzed by using Cox's proportional hazards modeling with graft survival time as the dependent variable and the following as covariates: cause of death, recipient age, donor age, disease etiology, recipient gender, donor gender, HLA and DR mismatch, transplant number, and sensitization. These data are expressed as relative risk with 95% confidence intervals (CI). Computations were performed with the SPSS software package, Version 6.1.2 (Chicago, IL, 1995).

RESULTS

There was no difference in graft survival time between male (N = 267) and female (N = 131) donor kidneys transplanted into recipients of either sex who were not treated with cyclosporine (Figure 1). In contrast, in patients treated with cyclosporine, graft survival time was greater for male donor kidneys (N = 428) as compared with female donor kidneys (N = 223) (P < 0.05) (Figure 1). Figure 2 shows the difference in graft survival time between male and female donor kidneys at the indicated time points. At 24 months, 276 male and 120 female functioning donor kidneys remained at risk. Differences in graft survival time between male and female donor kidneys increased progressively with time to peak at 24 months post-transplantation (P < 0.025), but showed no further increase thereafter. Accordingly, there was no significant difference in the rate of decline in graft survival time between cyclosporine-treated recipients of male and female donor kidneys beyond the first 24 months post-transplantation. As shown in Figure 3, survival time of female kidneys transplanted into cyclosporine-treated males was no worse or better than the female kidneys transplanted into cyclosporine-treated women (P = not significant [NS]). Thus, in cyclosporine-treated recipients, survival time of female kidneys was generally poor, regardless of recipient gender. In contrast, in patients treated with non-cyclosporine immunosuppressives, the best graft survival time tended to be in the female-to-female group (P = NS) (Figure 3).

The following covariates were found to influence the risk of graft failure on the basis of a Cox proportional hazards model [relative risk (95% CI), P value]: donor race and gender—white male donor [0.82 (0.71 to 0.95), P = 0.03], regrafted recipient [1.43 (1.06 to
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Figure 3. Graft survival stratified by donor and recipient gender in cyclosporine-treated allograft recipients (top 4 curves) and in non-cyclosporine-treated allograft recipients (bottom 4 curves).

1.94), P = 0.02, HLA antigen mismatch (1.14 (1.04 to 1.24), P = 0.004). The proportion of grafts lost as a result of acute rejection did not differ between recipients of male and female donor kidneys (26.5 versus 27.7%, P = NS).

There was no significant difference in the prevalence of poorly controlled hypertension (average level exceeding 140/90 mm Hg) between recipients of male and female donor kidneys (36.1 versus 36.9%, P = NS) or in the average post-transplantation blood pressure (135 ± 1/84 ± 1 versus 134 ± 1/84 ± 1 mm Hg, P = NS). There was no significant difference between recipients of male and female donor kidneys in the average dose of prednisone (11 ± 1 versus 12 ± 1 mg/day). The mean plasma cyclosporine level also did not differ between the groups (6-month data: 389 ± 27 versus 334 ± 28 ng/mL, P = NS; data for the entire follow-up period: 196 ± 22 versus 204 ± 24 ng/mL, P = NS). For the group as a whole, allograft survival time was not correlated with mean plasma cyclosporine level (P = NS, Cox regression model). However, after stratification for donor gender, we found that allograft survival time correlated with the average plasma cyclosporine level measured during the first 6 months post-transplantation in recipients of male donor kidneys (N = 119), but not in recipients of female kidneys. The regression coefficient for recipients of male donor kidneys was -0.0023 (P = 0.014).

Because it has been suggested that kidneys from African Americans have fewer nephrons than those from Caucasians (13,14,18), we examined the interaction between donor race and donor gender on graft survival time in cyclosporine-treated recipients. Donor kidneys from white males (Caucasian and Hispanic) (N = 188) showed a greater survival time than kidneys from white females (Caucasian and Hispanic) (N = 137) (P < 0.05) (Figure 4). This survival time difference was evident soon after transplantation and peaked at 24 months post-transplantation. The survival curves of kidneys from male (N = 117) and female African Americans (N = 29) were virtually superimposable (not shown). Donor kidneys from white males (N = 188) had a better graft survival time than kidneys from African-American males (N = 117) (P < 0.05) (Figure 5). Differences in graft survival time increased progressively after 24 months.

The number of sclerotic glomeruli in biopsy specimens was analyzed as an index of hyperfiltration-mediated injury in both the cyclosporine and pre-cyclosporine eras. There were no significant differences between recipients of male and female donor kidneys in the slopes of the regression lines describing the percentage of glomeruli with segmental or global sclerosis versus time post-transplantation.

**DISCUSSION**

Previous studies have shown that kidneys from female donors have poorer 1-yr graft survival than do kidneys from male donors (2.4–6.9,11,19–34). In recipients of first cadaver transplants, the shorter survival time of female donor kidneys is observed primarily when the donor is over 30 years of age (2–5,11,28). In striking contrast, kidneys from young female donors have a first-graft survival rate equivalent to that of kidneys from young males (2–4,11,35). Similar observations have been made in living related-donor transplants involving HLA nonidentical siblings and in parental-donor kidney grafts (2,3,6,11,19,21,33,34,36,37).

Terasaki and coworkers (12,38) and Brenner et al. (13,14) have suggested that the diminished long-term survival of kidneys from female as compared with male donors may be explained by a mismatch between the donor's nephron supply, reflected by donor kidney weight, and the recipient's functional demand, reflected by recipient body weight (12–14). Because females have smaller kidneys and have been postu-
Other factors that may contribute to the donor-gender effect include the possibility that kidneys might be more susceptible to ischemic injury, immunologic rejection, or cyclosporine nephrotoxicity than male kidneys (3,8,11,35,49). This hypothesis and the nephron mismatch hypothesis are not mutually exclusive and do not preclude a role for diminished donor kidney nephron supply in enhancing renal injury after an insult to the kidney. For example, were female kidneys to have fewer nephrons, a reduced nephron reserve might give rise to greater susceptibility to a given immunologic, ischemic, or nephrotoxic injury. The fact that grafts from female donors are less likely to survive after a rejection episode than are male donor kidneys has been attributed to a smaller nephron reserve (2,4,5,7). It has also been suggested that female kidneys may be more antigenic than male kidneys and therefore elicit an enhanced immune response (3,8,11,35,49). However, no convincing experimental data exist to support this hypothesis.

In the study presented here, we analyzed graft survival time in over 1000 recipients over a period of 9 yr in an attempt to elucidate the mechanisms responsible for differences in graft survival time related to donor gender. We found that the donor-gender effect was observed only in cyclosporine-treated recipients, was not seen in African-American donors, appeared soon after transplantation, and did not increase with time beyond 24 months post-transplantation.

Although not a universal observation, previous studies have also found that the lower 1-yr survival of grafts from older female donors most often results from graft failure in the very early post-transplant period (2,3,5,11,24,38,50,51). In many of these studies, the decreased survival time of female donor kidneys was already evident within 3 to 6 months post-transplantation (12,52). However, most of these studies did not carefully analyze long-term graft survival to determine if this trend continued. Feduska and Cecka (51) analyzed data from 48,541 cadaveric renal allografts performed between 1987 and 1994. The survival curves for male and female donor kidneys diverged after 3 to 6 months. The difference in graft survival time between male and female donors was 4% at 1yr but did not increase further at 4yr post-transplantation. If hyperfiltration as a result of nephron mismatch were responsible for donor gender-related differences in graft survival time, we would not expect this difference to arise within 3 to 6 months after transplantation because longer periods of time would be required for the development of hyperfiltration-mediated glomerular injury. It is conceivable, however, that an additional insult, such as acute rejection or cyclosporine nephrotoxicity, may reduce nephron number to a degree that might exaggerate gender-related differences in nephron mass and greatly accelerate progression to end-stage renal failure. In addition, the mismatch hypothesis predicts that graft loss would increase steadily with increasing duration of exposure to hyperfiltration. This predic-

Figure 5. Graft survival in cyclosporine-treated white male donor kidneys (solid line) and African-American male donor kidneys (dashed line)
ton is contrary to our observations and to those of Feduska and Cecka (51). However, we cannot exclude the possibility that only a subgroup of female donor kidneys are at risk because of nephron mismatch and that all these grafts fall within the first 1 to 2 yr post-transplantation.

Previous studies have demonstrated that African-American donor kidneys have a lower survival rate than kidneys from white donors, particularly when transplanted into white recipients (51,53-56). In these studies, the donor-race effect was observed as early as 3 months post-transplantation and was most prominent in the early post-transplant period (51). It has been suggested that kidneys from African Americans have fewer nephrons than kidneys from Caucasians and that this smaller nephron supply may account for the lower survival rate of grafts from African-American donors (13,14,18,57). In this context, we found an equivalent survival rate for kidneys from male and female African-American donors. These survival rates were significantly lower than the graft survival rate of kidneys from white male donors. Although our observations on the interrelationships between donor race and gender fail to clarify the mechanisms responsible for the donor gender effect, they do indicate that the survival advantage of donor kidneys from white males entirely accounts for donor gender-related differences in graft survival time. To our knowledge, there are no anatomical studies comparing nephron number or glomerular size in African-American males versus African-American females.

Another striking finding in our study is the absence of a donor-gender effect in transplants performed before the introduction of cyclosporine. Similarly, recipients treated with tacrolimus rather than cyclosporine also fail to show a donor-gender effect (R. Shapiro, personal communication). Our observations on the primary role of cyclosporine are in accord with those of previous investigators (2-5,11,19,21,22,28). In fact, donor gender was first recognized as a significant factor influencing graft survival time in the early to mid-1980s, corresponding in time to the introduction and widespread use of cyclosporine (2,4,5). Among cyclosporine-treated recipients, graft survival rates are lower in those receiving older female kidneys than in those receiving male kidneys (2-5,11,19,21,22,28). However, with non-cyclosporine immunosuppressive therapy (azathioprine and corticosteroid), graft survival time is comparable irrespective of gender (3).

Gender-related differences in therapeutic response to cyclosporine may help explain these observations. In this context, we observed a direct correlation between allograft survival time and mean cyclosporine levels only in recipients of male donor kidneys. Whereas cyclosporine increases the survival time of young female donor kidneys to the same extent as male donor kidneys, cyclosporine does not increase the survival time of older female kidneys (3,8,10). Enhanced susceptibility of older female kidneys to the nephrotoxic effects of cyclosporine may contribute to the survival advantage of male donor kidneys (2-6, 8,9,11). Kidneys from older female donors have a higher incidence of cyclosporine nephrotoxicity than kidneys from male or younger female donors (9). The explanation for this observation is unclear. Both race and gender-related differences in the distribution and pharmacokinetics of cyclosporine have been described in renal allograft recipients (58-60). However, no data exist that assess differences in cyclosporine tissue levels in kidneys from male versus female donors. Also, higher total doses of cyclosporine are administered to male recipients, who generally weigh more than females (4-6). It is not known whether or not this dosing pattern translates into greater renal accumulation of cyclosporine in female donor kidneys that are transplanted into male recipients (61).

The equivalence of graft survival time between male and female donor kidneys in non-cyclosporine-treated recipients suggests that a mismatch between nephron supply and donor functional demand leading to hyperfiltration-mediated glomerular injury is alone insufficient to explain the adverse effect of female donor gender observed in cyclosporine-treated recipients. The absence of an effect of donor gender in non-cyclosporine-treated recipients suggests that the gender-related differences in susceptibility to cyclosporine nephrotoxicity or in therapeutic response to cyclosporine, perhaps related to differences between the sexes in drug dosing, tissue accumulation or cellular metabolism, may contribute to the shortened graft survival time of female donor kidneys in cyclosporine-treated recipients.

REFERENCES


