Donor-Recipient Gender and Size Mismatch Affects Graft Success after Kidney Transplantation

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BACKGROUND: Female recipients of male kidneys have an inferior graft survival, and patients receiving larger kidneys relative to their body size may have a graft survival advantage. Thus, graft survival may be affected by both gender and kidney size mismatches. The objective of this study was to analyze the possible confounding effect of body mass mismatch (body mass as proxy for kidney size) between female recipients of male donor kidneys.

STUDY DESIGN: A total of 668 kidney transplantations between 1996 and 2005 at our center were studied retrospectively. Graft and patient survival were determined by Kaplan-Meier estimation. Multivariate Cox proportional analyses were performed to determine the hazards of graft loss.

RESULTS: There were 146 female recipients of male kidneys. Compared with all other gender combinations, this group had the lowest unadjusted graft survival (86%, 79%, and 78% vs 92%, 88%, and 86% at 1, 2, and 3 years, respectively; log-rank $p = 0.01$). Donor body mass index (BMI) correlated with donor kidney size ($p < 0.001$). Male kidneys were a risk factor of graft loss for female recipients (hazard ratio [HR] 3.45, 95% CI 1.40 to 8.51, $p = 0.01$), but male donors with a larger BMI relative to female recipients' significantly reduced the risk (HR 0.19, 95% CI 0.05 to 0.67, $p = 0.01$).

CONCLUSIONS: The inferior graft survival for female recipients of male donor kidneys is mitigated by male donors with a larger BMI. (J Am Coll Surg 2010;210:718–727. © 2010 by the American College of Surgeons)

Although current registry data from the United Network of Organ Sharing report similar graft survival rates for males and females,[1] a 2005 systematic review on gender differences in kidney transplantation identified 14 studies with contradicting results.[2] More recently, an analysis from the Collaborative Transplant Study[3] demonstrated that female recipients of male donor kidneys had the worst graft survival after the first year and up to 10 years post-transplant.[4]

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The authors hypothesized that an alloimmune response mediated by H-Y minor histocompatibility antigens could be responsible. H-Y antigens have been associated with acute rejection in smaller gender mismatch investigations of bone marrow[5] and corneal and kidney transplants.[6-8]

Several investigations have suggested a graft survival advantage for recipients receiving larger kidneys relative to their body size.[9-11] Compared with males, females usually have smaller kidneys.[12-14] It has been theorized that when the recipient's metabolic demand exceeds the capacity of the smaller donor kidney, hyperfiltration from nephron underdosing could occur.[15,16] Larger donor kidney mass in relation to smaller recipient mass diminishes hyperfiltration injury, and subsequently, immune-mediated rejection.[9] Earlier studies of donor-recipient gender mismatch have not explored the possible confounding of body size mismatch between female recipients of male donor kidneys, which was the purpose of this study.

METHODS

Study participants

With Institutional Review Board approval, we conducted a retrospective chart review of 863 consecutive kidney transplantations performed between January 1996 and August

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Abbreviations and Acronyms

AR = acute rejection
BMI = body mass index
HLA = human leukocyte antigen
HR = hazard ratio
MDFR group = male donor to female recipient transplants
PRA = panel-reactive lymphocytotoxic antibody

2005 at Tulane University Medical Center. Cases were excluded if donor or recipient age, race, gender, height, and/or weight values were not documented. Six hundred sixty-eight subjects met the inclusion criteria. Missing information on graft status and/or death was obtained from the United Network for Organ Sharing and the National Death Index, respectively. A database for data entry and cleaning was created using Microsoft Access 2003. A quality check of the data entry was performed by randomly selecting 10% of the final sample for double entry. An individual was trained and assigned exclusively to perform the quality check. The discrepancy rate was less than 5%.

Immunosuppression therapy

Patients received standard triple immunosuppression: steroids, tacrolimus or cyclosporine, and mycophenolic acid. High risk patients, including those with a previous transplant, 6-antigen human leukocyte (HLA) mismatches, and/or a panel reactive antibody >20%, received induction therapy with the interleukin (IL)-2 receptor antagonist basiliximab. All patients received standard antifungal, antibacterial, and cytomegalovirus prophylaxis. Acute rejection (AR) was confirmed by kidney biopsy, and the severity was graded according to the Banff classification.[17]

Correlating donor body mass index and donor kidney size

Donor kidney surface area was calculated (kidney length × width) from measurements provided by Louisiana Organ Procurement Agency stored records. Univariate correlations between donor body mass index (BMI) and kidney size using Pearson's correlation coefficient were calculated for 205 male donors and 155 female donors.

Donor-recipient body mass index match and mismatch

BMI (kg/m^2) was calculated for donors and recipients. There is no consensus as to what constitutes a match of donor-recipient BMI. In this study, this concept was operationalized noting a match if the donor's BMI fell within ± 2 units of the recipient's BMI (Appendix 1). BMI values outside the designated parameters were categorized as mismatches.

Statistical method and outcomes analysis

Donor and recipient demographic and clinical parameters were stratified by gender. Significant differences between groups were ascertained by least squared means and maximum likelihood ratio for continuous and categorical variables, respectively, and subsequently for the male donor-female recipient group versus all others.

Kaplan-Meier estimates of graft and patient survival were calculated for donors and recipients by gender and for the male donor-female recipient group versus others. Subanalyses on survival were performed for living and deceased donor recipients by donor gender, recipient gender, and donor-recipient gender combination. Log-rank p value was used as a test of significance.

A multivariate Cox proportional hazards model ascertained independent associations of graft loss. Covariates for model adjustment included deceased donor and recipient age, deceased donor and recipient black race, hypertension, diabetes mellitus, number of HLA mismatches, cold and warm ischemia times, peak panel-reactive lymphocytotoxic antibody (PRA), previous kidney transplantation, donor type, 30-day acute rejection, donor BMI greater than 2 units compared with recipient BMI, and male donor-female recipient versus others. Estimates of risk were also calculated after censoring for death. A second regression model to assess the risk of graft loss was stratified by recipient gender and adjusted for previous covariates plus male donor BMI 2 units larger and male versus female donor.

All statistical analyses were performed using SAS 9.1.3, and p values less than 0.05 were considered statistically significant.

RESULTS

Donor-recipient demographics and baseline clinical characteristics

There were 146 male donor-to-female recipient transplants (MDFR group) and 213, 179, and 130 male-to-male, female-to-male, and female-to-female combinations, respectively. In this study, the latter 3 combinations were pooled for most analyses to form a single group (others) because no statistical differences in demographic characteristics or outcomes were identified in the exploratory analyses. Donor and recipient age, race, and BMI did not differ significantly between the MDFR group and others (Table 1). Compared with recipients among the others, recipients in the MDFR group had a higher prevalence of diabetes (31% vs 22%, $p = 0.03$) but were less sensitized (70% vs 65% for peak PRA < 50 and 30% vs 35%, for PRA ≥ 50, $p < 0.01$. Table 1, bottom panel).