

Sex Matching Plays a Role in Outcome of Kidney Transplant

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Abstract

Objectives: The effect of sex matching between donors and recipients was studied in 135 kidney transplant operations performed in our center between December 1998 and December 2007.

Materials and Methods: Patients were divided into 4 groups: group 1 (63 patients, male donor-male recipient), group 2 (25 patients, male donor-female recipient), group 3 (37 patients, female donor-male recipient), and group 4 (10 patients, female donor-female recipient). Except for donor age, recipient body mass index and donor-recipient sex matching, recipient, and donor characteristics, and the immunosuppression were comparable between the 4 groups.

Results: Acute rejection and the need for anti-thymocyte globulin. Pre-emptive rescue therapy were comparable between the donor-recipient combinations. Except for 1-year actuarial patient and graft survival, comparable hospital stay, and incidence of acute graft and slow graft function were comparable between the 4 groups. One death occurred, only, in groups 1 and 2; posttransplant complications being comparable. While 1-year graft survival (death censored and uncensored) were comparable, 1-year graft function (serum creatinine) showed that the worst graft function was seen in group 3 (female-to-male). Significant differences between the 4 patient groups also were seen in pretransplant and posttransplant hemoglobin levels as well as in posttransplant arterial hypertension and

high-density lipoprotein cholesterol and blood levels. Other metabolic indices were generally comparable between the 4 patients. **Conclusions:** The results revealed that sex mismatching (group 2, male donor to female recipient) had the best 1-year graft function but the same for patient and graft survival.

Keywords: Gender matching, Graft function, Immunosuppression, Kidney transplant

Introduction

While kidney transplant remains the treatment of choice in end-stage renal disease,^{1,2} the demand for suitable kidneys exceeds the supply of available organs, thereby resulting in progressively increased use of older donors (both deceased and living) and cross-sex kidney transplant.^{1,3} Improvement in short-term transplant outcomes has largely been due to the introduction of potent immunosuppressive regimens,⁴ whereas long-term graft survival remains suboptimal. This poorer graft function and survival is attributed to several reasons including senescence, greater susceptibility to ischemic injury, acute rejection episodes, and reduced nephron mass in the case of female-to-male transplant.^{3,5}

Many studies have evaluated the role of donor sex on renal transplant outcomes. Recent evidence has demonstrated that the sex of the donor influences several aspects of allograft outcome after kidney and other solid-organ transplants.⁶ This was highlighted by the findings that kidney transplants perform better in female than in male recipients,^{7,8} and poor graft survival was associated with male patients transplanted with female kidneys.^{8,9} Compared with males receiving a male kidney, and females receiving a female kidney, male recipients receiving a kidney from a female

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donor have been shown to have a reduced graft survival.^{3, 10, 11} In contrast, donor's sex did not affect patient or graft survival in female recipients.¹¹ Collectively, this suggests that sex should be considered as criteria in choosing donors and recipients in organ allocation.¹²

Several theories have proposed to explain the poor functional prognosis of female grafts, including the protective effect of estrogens, and the presence of fewer nephrons in female kidneys.¹³⁻¹⁵ However, this sex effect has not been confirmed in other studies,¹⁶ and an ethnic contribution to this phenomenon appears plausible. This necessitated the need for independent confirmation in populations of diverse ethnic backgrounds. In this study, we investigated the effects of sex matching on patient and graft survival and function in 135 Lebanese kidney transplant recipients.

Materials and Methods

Patient demographics

This was a retrospective study conducted between December 1998 and December 2007 at the St-Joseph Hospital (Baabda) and Middle East Institute of Health (Bsalim). Table 1 summarizes patient demographics. Patients were divided into 4 groups based on the sex of the donor and recipient: group 1 (n=63; male donor, male recipient), group 2 (n=25; male donor, female recipient), group 3 (n=37; female donor, male recipient), and group 4 (n=10; female donor, female recipient). Significant differences were seen in HLA-DR matching ($P < .001$), and previous transplants (5/2/1/0), multiple transfusions (5/2/1/0), multiple

pregnancies (0/3/0/2), and high panel-reactive antibody (PRA) score ($> 50\%$; 0/1/1/0) in groups 1, 2, 3, and 4; and a single case of multiple pregnancies + transfusions (group 2) and redo + transfusions (group 1) were noted. The ethics committee of the institution approved all protocols before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Indications for kidney transplant included chronic glomerulonephritis (9/1/1/1), chronic pyelonephritis (10/1/2/2), polycystic kidney disease (2/1/7/2), retransplant (0/1/1/0), focal segmental glomerulosclerosis (0/0/1/0), arterial hypertension (3/2/2/0), cardiovascular disease (3/2/1/1), interstitial nephritis (0/1/1/0), and diabetes (2/0/2/0) in groups 1, 2, 3, and 4. Recipient age, donor-recipient relationship (deceased, living-related, emotionally related), and blood grouping (identical, compatible) were comparable between groups ($P = NS$). Donor age ($P < .001$), recipient body mass index ($P = .03$), and duration of pretransplant dialysis ($P = .04$) were significantly different between the 4 patients groups, with preemptive dialysis done for 6, 2, 5, and 4 patients in group 1, 2, 3, and 4.

Immunosuppressive regimen

Induction therapy was instituted for 56 patients (88.9%) in group one, 23 patients (92.0%) in group two, 25 patients (67.6%) in group three, and 8 patients (80.0%) in group four ($P = .013$). This consisted of daclizumab given as 1 dose (24/8/8/6) or 2 doses (2/1/0/0), or as an intraoperative bolus of anti-thymocyte globulin Fresenius (20/8/14/2) or extended regimen (10/6/3/0) in groups 1, 2, 3, and 4. Maintenance immunosuppression comprised

Table 1. Characteristics of Study Subjects

	Group 1 (63)	Group 2 (25)	Group 3 (37)	Group 4 (10)	P Value
Recipient age (y)	44.1 ± 13.9	36.4 ± 15.3	42.4 ± 12.7	37.3 ± 9.6	NS
Donor age (y)	30.7 ± 8.4	29.5 ± 7.5	41.8 ± 8.7	45.1 ± 8.2	< .001
Recipient BMI (kg/m ²)	25.1 ± 3.9	22.8 ± 4.8	26.1 ± 3.9	21.6 ± 4.8	.03
Donor-recipient relationship					NS
Deceased-donor	4	0	4	2	
Living-related	7	5	25	7	
Emotionally related	52	20	8	1	
Blood groups					NS
Identical	58	19	29	9	
Compatible	5	6	8	1	
Dialysis					
Pretransplant (mo)	16.0 ± 18.0	20.4 ± 14.7	14.6 ± 16.0	29.8 ± 39.5	.048
Preemptive (pts)	6	2	5	4	

Abbreviations: BMI, body mass index; NS, not significant

triple therapy in which cyclosporine (N), tacrolimus (F), or rapamycin (R) was combined with an antimetabolite (mycophenolate mofetil [C] or azathioprine [A] and prednisone [P]). These consisted of NAP (2/1/2/1), NCP (31/9/20/4), FAP (0/1/0/0), FCP (17/10/6/0), N/FCP (8/2/6/3), N/RCP (1/0/2/1), and F/NCP (2/2/0/0) were given to group 1, 2, 3, and 4 patients ($P = NS$). One patient in group 4 received quadruple therapy (FRCP), and another in group 3 received F/NRCP.

Statistical analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 13.0, IBM Corporation, Armonk, New York, USA). Data are expressed as percentages of total (categorical variables) or as means \pm SD (continuous variables). The t test was used to determine differences in means, and the Pearson chi-square or Fisher exact test was used to assess intergroup significance. Values for P less than .05 were considered statistically significant.

Results

Main transplant outcomes

The main transplant outcomes are summarized in Table 2. Acute rejection occurred in eight patients in group 1, six in group 2, two in group 3, and one in group 4 ($P = NS$), and the need for anti-thymocyte globulin (ATG-F) rescue therapy was comparable between the 4 groups ($P = NS$). Excellent 1-year graft survival was seen in the 4 groups (6/63, 0/25, 2/37, and 1/10), and slow graft function (6/63, 0/25, 2/37,

and 0/10), and slow graft function (7/63, 1/25, 1/37, and 1/10) rates were comparable between the 4 patient groups ($P = NS$). Comparable hospital stays (d) also were recorded for group 1 (13.3 ± 6.2 d), group 2 (11.7 ± 2.8 d), group 3 (13.5 ± 5.9 d), and group 4 patients (10.9 ± 2.2 d) ($P = NS$).

Complications

Death occurred in 1 patient in group 1 due to cardiac dysrhythmia, which occurred 7 months after the transplant; and in 1 patient in group 2, which occurred 6 months after the transplant after cardiac surgery. Posttransplant infection rates were similar among the 4 groups, with a total of fifty-three infectious episodes in 29 patients in group 1, twenty-one infectious episodes in 15 patients in group 2, thirty-one infectious episodes in 18 patients in group 3, and nine episodes in 7 patients in group 4, which translated into 1.83, 1.40, 1.72, and 1.29 episodes/infected patients in the 4 groups ($P = NS$). The majority of the infections were bacterial (46/53) (7/21, 28/31, and 6/9), followed by viral infections in groups 1, 2, 3, and 4. Two cases of fungal infections were detected in each of group 1 and group 4 patients. Surgical complications comprised renal artery stenosis (2 and 2), ureteral stenosis (2 and 1), and lymphocele (1 and 1) in group 1 and group 3 patients, hematoma (two in group 2, one in group 3), and a single case of ureteral leak in group 1, and 1 case of renal vein compression in group 2.

Graft function

The graft survival rates (death censored and uncensored) were comparable among the 4 groups.

Table 2. Main Outcomes¹

	Group 1 (63)	Group 2 (25)	Group 3 (37)	Group 4 (10)	P Value
Acute rejection, (%)	18 (28.6) ²	6 (24)	9 (24.3)	1 (10)	NS
Needs for ATG-F, (%)	5 (27.8)	2 (33.3)	2 (22.2)	1 (100)	NS
Infections					
Patients	29 (46.0)	15 (60.0)	18 (48.6)	7 (70.0)	NS
Episodes	53	21	31	9	NS
Hospital stay (d)					
Mean \pm SD	13.3 \pm 6.2	11.7 \pm 2.8	13.5 \pm 5.9	10.9 \pm 2.2	NS
Range, (d)	6-48	6-19	8-41	7-15	
SGF, number (%)	7 (11.1)	1 (4.0)	1 (2.7)	1 (10.0)	NS
DGF, number (%)	6 (9.5)	0 (0.0)	2 (5.4)	0 (0.0)	NS
Graft survival (%)	96.8	92	100	100	NS
Graft survival-censored (%)	98.4	96	100	100	NS
Death	1	1	0	0	NS
Patient survival (%)	98.4	96	100	100	NS

Abbreviations: ATG-F, anti-thymocyte globulin Fresenius; DGF, delayed graft function; NS, not significant; SGF, slow graft function

¹The t test was used for continuous variables, and the Fisher exact test was used for categorical variables.

²Number (percentage of total)

Graft function (serum creatinine) showed a significant difference among the 4 groups, with group 1 (male-to-male) and group 4 (female-to-female) showing the best improvement in 1-year graft function (Table 3). Compared with the other groups, group 3 (female-to-male) had the worst graft function, with no difference in serum creatinine levels 1 year after discharge (Table 3), while group 2 (male-to-female) had marginal improvement in graft function.

Metabolic effects

Table 4 summarizes the metabolic profile in the 4 groups. Pretransplant and posttransplant serum glucose and cholesterol, and 1-year posttransplant low-density lipoproteins and triglyceride levels were comparable between the 4 patient groups. While posttransplant hemoglobin levels were lower than pretransplant levels, significant differences were found between the 4 patient groups regarding pretransplant ($P = .037$) and posttransplant ($P = .011$) hemoglobin levels. Other metabolic indices were generally comparable between the 4 patient groups.

Discussion

Several reports have demonstrated that both short-term and long-term kidney allograft survival was dependent on the sex of the donor, being worse when kidneys from female donors were transplanted into male recipients, compared with other donor/recipient combinations.^{8, 10, 11, 17} These results suggest that sex should be considered as one of the key criteria in the choice of donor and recipients in organ allocation.¹⁷ Similar conclusions also have been reached regarding heart and liver⁶ allografts, where transplant outcome was worse when the graft came from female donors.

The results of this study are consistent with studies in heart and cadaver-donor kidney transplants, but with notable differences. We demonstrated that sex mismatch does not affect 1-year graft survival. This was reminiscent of earlier studies in heart,¹⁰ Tunisian,¹⁶ and Iranian¹¹ studies where sex mismatch did not affect 1-year allograft survival. While not addressed here because of our study design (short-term allograft survival and function),

Table 3. Graft Function in Creatinine Level

	Group 1 (n=25)	Group 3 (n=37)	Group 4 (n=10)	P Value ²
Upon discharge	156.1 ± 44.2	132.6 ± 53.0	114.9 ± 61.9	< .001
Postdischarge				< .001
1 mo	123.8 ± 44.2	141.4 ± 53.0	114.9 ± 44.2	
3 mo	114.9 ± 35.4	132.6 ± 53.0	123.8 ± 35.4	
6 mo	104.9 ± 35.4	132.6 ± 53.0	106.1 ± 35.4	
1 y	96.1 ± 17.7	132.6 ± 53.0	97.2 ± 35.4	

Values are serum creatinine ± SD (μmol/L).
NS, not significant; P, analysis of variance.

Table 4. Metabolic Profile of Study Subjects

	Group 1 (n=63)	Group 2 (n=25)	Group 3 (n=37)	Group 4 (n=10)	P Value
Pretreatment glucose, mmol/L	5.4 ± 1.3	4.9 ± 0.6	4.8 ± 1.8	4.8 ± 0.7	NS
Pretreatment diabetes, No. (%)	5 (7.9)	0 (0.0)	2 (5.4)	0 (0.0)	NS
Posttreatment glucose, mmol/L	6.0 ± 1.8	5.1 ± 0.9	5.7 ± 2.3	4.4 ± 0.4	NS
Pretreatment HBP, No. (%)	34 (54.0)	11 (44.0)	28 (75.7)	6 (60.0)	NS
1-y Posttreatment HBP, No. (%)	35 (55.6)	10 (40.0)	25 (67.6)	3 (30.0)	.042
Pretreatment cholesterol (mmol/L)	4.8 ± 1.3	5.2 ± 1.3	4.8 ± 1.3	4.1 ± 1.3	NS
1-y Posttreatment cholesterol (mmol/L)	4.8 ± 1.2	5.3 ± 1.2	5.4 ± 1.4	5.7 ± 1.4	NS
1-y Cholesterol ¹ (mmol/L)	0.85 ± 0.87	0.55 ± 0.63	0.79 ± 1.07	1.65 ± 1.0	.024
1-y Posttreatment HDL, (mmol/L)	1.2 ± 0.2	1.4 ± 0.4	1.2 ± 0.2	1.6 ± 0.2	< .001
1-y Posttreatment LDL, (mmol/L)	3.2 ± 1.0	2.9 ± 1.1	3.4 ± 1.1	3.0 ± 0.9	NS
Pretreatment triglyceride (mmol/L)	2.5 ± 1.4	1.9 ± 1.0	2.2 ± 1.1	1.4 ± 0.8	.043
1-y Posttreatment triglyceride (mmol/L)	2.3 ± 1.1	2.1 ± 1.2	2.2 ± 1.4	2.3 ± 1.2	NS
Posttreatment Hb blood level (g/L)	108 ± 16	104 ± 13	110 ± 17	94 ± 19	.037
Posttreatment Hb blood level (g/L)	75 ± 18	64 ± 14	77 ± 18	64 ± 12	.011
Hb blood level ² (g/L)	33 ± 15	40 ± 14	33 ± 16	30 ± 15	NS
Need for posttreatment transfusion, units (patients)	30 (12)	18 (7)	22 (9)	4 (2)	NS

Abbreviations: Hb, hemoglobin; HBP, high blood pressure; NS, not significant

¹Difference between pretreatment and 1-y posttreatment cholesterol blood levels

²Difference between pretreatment and 1-y posttreatment hemoglobin blood levels

this may not necessarily hold true in long-term follow-up. For example, the 5-year kidney survival was markedly reduced (75.12%) in male patients transplanted with a female kidney, compared with the other combinations, in which graft survival ranged from 83.16% to 85.72%.¹⁰ Ben Hamida reported poor 5- and 10-year graft survival rates for male (76.8% and 70.0%) and female recipients (76.9% and 53.6%) receiving grafts from female donors.¹⁶ Whereas female-male transplants are associated with poor long-term survival, a recent Iranian study reported that the donor's sex did not affect patient or graft survival among female recipients.¹¹

While the 1-year graft survival was not affected by sex, graft function (creatinine clearance) was worse in female-male transplants. Some hypotheses have been proposed to explain why a female kidney allograft functions poorly in a male recipient. These included "nephron underdosing,"¹³ which centers on the fewer nephrons being present in female than male kidneys (typically 17% less),^{15, 17, 19} which in turn increases the workload of individual nephrons. Another possibility is the immunogenicity of female allografts, as was proposed.²⁰ This hypothesis is consistent with increased incidence of early acute rejection episodes in female kidney transplants.¹⁰ Our study supports the notion that donor sex does affect 1-year graft function, but not survival.

There are several limitations to our study. It was a retrospective, single-center study, with a limited number of patients with a short-term follow-up. In addition, the reasons for the high rate of this study was survival, which is attributed to the short follow-up. A large, long-term multicenter study is needed to address these concerns. Despite these limitations, our study recommends inclusion of donor sex as a key determinant of the success of kidney transplant.

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