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Transplant recipient renal function is donor renal mass- and recipient gender-dependent

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Abstract

The effect of both donor renal mass and gender on renal function, in both gender recipients, was examined. Qualifying consecutive living-donor renal transplants ($n = 730$) were stratified into 4 donor–recipient groups: female–female ($n = 177$), male–female ($n = 151$), female–male ($n = 240$), male–male ($n = 162$). Groups were equivalent in age, race, body mass index (BMI), match, ischemia time, operative time, and estimated glomerular filtration rate (eGFR). Female recipients had lower serum creatinine (Cr_s). Male recipients had higher Cr_s wherever they received a female allograft. Male recipients of male kidneys had a higher eGFR than all other groups for 3 years. Renal function of the recipient correlated with the renal mass of the donor within each group. Male and female kidneys functioned equivalently in the female-recipient environment. Large nephron-mass male donor kidneys function more poorly in female recipients. The male kidney loses 15–20 ml/min eGFR in the female host. The diminished graft function may be related to androgen deprivation. Female and male donor kidneys function equivalently in the male recipient if adjusted for renal mass transplanted. Female kidneys improve eGFR by 7–10 ml/min by being transplanted into a male environment. Donor renal mass and gender affect recipient graft function Expectations of ultimate recipient renal function should take into account both the gender and mass disparity of the donor–recipient pair.

Introduction

Long-term renal allograft function is dependent on a multitude of recipient-related factors and a few definable donor-related factors those represent the quality of the renal parenchyma being transplanted. Among the donor-related factors which have been suggested to contribute to the quality of the parenchyma are donor age, donor sex, donor race, kidney mass, donor hypertension, donor renal perfusion prior to recovery, warm ischemia time (WIT), and cold ischemia time. Because of the wide range of variables related to the donors and more related to the recipients, it is difficult to determine the influence of any one factor on the actual functioning of the allograft. Consequently, most analyses have been essentially correlation of putative factors with graft survival. Only very large deceased-donor renal transplant series could possibly account for all the variables to elucidate the effects on graft function. The marked increase in living-donor renal transplantation and the concomitant improvements in immunosuppression now allow series of living-donor renal transplants to be large enough for analysis. Living donation removes some of the confounding factors potentially affecting the renal parenchymal quality. For example, donor organ-related diseases are practically eliminated as a variable. Renal vascular perfusion is generally excellent pre-harvest. WIT time is shorter and cold ischemia time is very much shorter in the living-donor setting as opposed to the cadaver situation. Living-donor kidneys function much faster and those kidneys with

damaged renal parenchyma can be identified early. A live renal transplant is expected to have excellent initial graft function with vigorous and immediate urine output and a prompt normalization of serum creatinine (Cr_s) to 2.5 mg% by day 5. However, even in ideal living-donor grafts, renal function may vary between grafts on account of the donor-organ qualities that are measurable. This current study was undertaken to determine whether the renal function of live kidney transplants varies based upon donor gender disparities.

Materials and methods

After approval by the institutional review board (IRB), the medical records of 1000 consecutive living-donor renal transplant donor–recipient pairs were reviewed in order to evaluate the effect of gender on graft function. The donor kidneys were all harvested laparoscopically. Kidneys not achieving $Cr_s \leq 2.5$ mg%) by day 5 were removed from the analysis as confounding variables. These disqualified grafts carried the diagnosis of one of the following: not transplanted, primary graft nonfunction, delayed graft function, or slow graft function ($n = 226$). Kidneys with either a donor or recipient of the category of either <18 years ($n = 18$) or >70 years ($n = 26$) were removed from analysis because estimated glomerular filtration rate (eGFR) is not validated at the age extremes. The remaining 730 kidneys were stratified into four groups:

1. Female donor-female recipient (F»F) ($n = 177$)
2. Male donor-female recipient (M»F) ($n = 151$)
3. Female donor-male recipient (F»M) ($n = 240$)
4. Male donor-male recipient (M»M) ($n = 162$).

eGFR was determined from the MDRD formula: eGFR (ml/min/1.7 m^2) = $186 \times (Cr_s)^{-1.154} \times age)^{-0.203} \times (0.742$ if female) $\times$ (1.21 if African-American (AA) [1]. Body surface area (BSA) was determined by the Dubois formula [2] ($BSA = 0.20247 \times Ht(m)^{0.725} \times Wt(kg)^{0.425}$). Ideal body weight (IBW) was determined by the Robinson formulae [3] (male = 52 kg + 1.9 kg per in. >5 feet, female = 49 kg + 1.7 kg per in. >5 feet). Data regarding whether grafts were re-transplants is not available. The number of grafts excluded from analysis was equivalent between groups. Data is expressed as ±SD and statistical significance assessed by the Student *t*-test or chi-squared test.

Results

Table 1 details the donor characteristics of the four groups. There are no statistically significant differences between the groups with regard to age, race, body mass index (BMI), degree of donor–recipient relationship, human leukocyte antigen (HLA) match, HLA AB mismatch, HLA DR mismatch, graft WIT, operative time, or eGFR. The male donors are significantly heavier, taller, and have a higher Cr_s .

Table 2 details the recipient characteristics of the 4 groups. There are no statistically significant differences between the groups with regard to age, race, or BMI. The male recipients are significantly heavier and taller.

Table 3 shows Cr_s values of the recipients for the four groups. Female recipients have a lower Cr_s regardless of the gender of the donor kidney. Male recipients have a significantly higher Cr_s if they received a female kidney than if they received a male kidney. These findings are stable from day 5–3 years post-transplantation.

Table 1. Living-donor characteristics.

	Female–female	Male–female	Female–male	Male–male
n	177	151	240	162
Donor age (years)	39.3 ± 11.3	41.0 ± 11.7	39.8 ± 11.2	38.6 ± 11.3
% AA race (%)	30.5	25.8	20.4	24.1
Donor Ht (in)	64.7 ± 2.5	70.1 ± 2.8†	64.9 ± 2.9	70.4 ± 2.7†
Donor Wt (kg)	74.3 ± 18.2	87.5 ± 14.8†	75.4 + 18.9	87.4 ± 14.6†
Donor BMI	27.3 ± 5.9	27.5 ± 4.3	27.8 + ±6.9	27.1 ± 4.1
HLA match (6)	3.0 ± 1.4	2.9 ± 1.7	2.7 ± 1.7	3.1 ± 1.6
HLA AB Mismatch	2.1 ± 1.9	2.3 ± 1.9	2.3 ± 1.8	2.3 ± 2.0
HLA DR Mismatch	1.1 ± 1.7	1.3 ± 1.6	1.2 ± 1.7	1.4 ± 2.0
1st degree relative (%)	72	60	50	72
2nd degree relative (%)	11	8	6	7
Unrelated (%)	17	32	44	21
WIT (s)	157 ± 73	191 ± 107	168 + 89	177 ± 85
OR time (min)	197 ± 49	217 ± 46	198 ± 46	202 ± 47
Cr_s (mg%)	0.79 ± 0.1	1.03 ± 0.1†	0.80 ± 0.1	1.03 ± 0.1†
eGFR(ml/min)	94.6 ± 25.0	92.2 ± 18 = 0.2	91.6 ± 21.00	92.9 ± 17.8

†$P < 0.001$ male versus females.

Table 2. Recipient characteristics.

	Female–female	Male–female	Female–male	Male–male
n	177	151	240	162
Age (years)	45.5 ± 12.4	45.3 ± 11.9	47.6 ± 12.2	46.7 ± 12.8
% AA race	29.9	25.8	20	24.7
Ht (in)	64.1 ± 3.1†	63.8 ± 3.1†	69.8 ± 3.7†	69.5 ± 3.6†
Wt (kg)	70.6 ± 20.5†	68.1 ± 18.1†	83.1 ± 19.3†	82.9 ± 17.6†
BMI	26.6 ± 6.7	26.1 ± 6.5	26.6 ± 19.3	26.8 ± 4.7

†$P < 0.001$ males versus females.

Table 3. Recipient serum creatinine.

Cr_s (mg%)	Female–female*	Male–female*	Female–male*	Male–male*
Day 5	1.27 ± 0.4	1.27 ± 0.5	1.63 ± 0.4§	1.47 ± 0.4§
1 month	1.37 ± 0.6	1.26 ± 0.5	1.69 ± 0.7§	1.52 ± 0.8§
3 months	1.36 ± 0.5	1.28 ± 0.4	1.68 ± 0.5§	1.48 ± 0.4†
6 months	1.29 ± 0.4	1.32 ± 0.5	1.69 ± 0.6§	1.49 ± 0.4§
1 year	1.32 ± 0.4	1.36 ± 0.5	1.74 ± 0.6§	1.49 ± 0.4§
2 years	1.49 ± 0.7	1.47 ± 0.7	1.64 ± 0.5	1.59 ± 0.5
3 years	1.28 ± 0.4	1.28 ± 0.5	1.63 ± 0.4§	1.47 ± 0.4§

*$P < 0.01$ males versus females.
§$P < 0.01$ FM vs. MM.

Table 4. Recipient eGFR.

EGFR (ml/min)	Female–female	Male–female	Female–male	Male–male*
Day 5	58.1 ± 22.6	59.3 ± 23.1	56.3 ± 20.6	63.6 ± 21.6
1 month	54.5 ± 20.2	58.2 ± 19.4	55.0 ± 17.8	63.4 ± 20.0
3 months	53.9 ± 20.0	57.6 ± 21.0	54.0 ± 17.1	62.0 ± 17.0
6 months	56.8 ± 26.6	55.9 ± 9.4	54.6 ± 18.1	62.0 ± 19.6
1 year	54.9 ± 22.1	55.1 ± 22.0	52.5 ± 18.1	61.5 ± 19.1
2 years	51.5 ± 25.1	52.9 ± 23.2	55.1 ± 17.8	57.7 ± 20.4
3 years	49.1 ± 20.0	52.0 ± 33.7	52.3 ± 18.0	55.9 ± 17.5

*$P < 0.01$ M»M vs F»F, M»M vs M»F, M»M vs. F»M.

Table 4 shows the recipient eGFR for the 4 groups. Male recipients of male kidneys have a higher eGFR than male recipients of female kidneys and female recipients regardless of the gender of the donor kidney. These findings are stable from 5 days to 3 years post-transplantation. The eGFR for all groups decreases over time.

Graft survival is shown in Table 5. Grafts are more likely lost to death, not to rejection. At 1 year post-transplant 12 recipients had graft loss but were alive. A further 19 died with a functioning kidney. At 3 years, 27 recipients had graft loss and 4 died without kidney. A further 32 died with a functioning kidney.

The relationship to renal mass was examined. BSA was initially employed as a surrogate for renal mass [4]. The recipient/donor BSA ratio was correlated to the recipient eGFR. Recipient renal function correlates with the mass

Table 5. Graft survival.

	Female–female	Male–female	Female–male	Male–male
n	177	151	240	162
1 month (%)	99.4	98.6	100	99.4
3 months (%)	99.4	97.2	98.7	99.3
6 months (%)	97.5	97.1	96.8	97.9
1 year (%)	94.0	92.4	93.7	96.9
2 years (%)	86.9	89.1	88.6	93.4
3 years (%)	81.6	85.1	84.3	93.3

of the kidney being transplanted within each group. At 5 days for F»F grafts, $r = .39$, for F»M grafts $r = .32$, for M»F grafts $r = .19$, and for M»M grafts $r = .36$. At 1 month the correlations are: F»F grafts $r = .34$, F»M grafts $r = .27$, M»F grafts $r = .22$, and M»M grafts $r = .19$.

Table 6 shows the effects of donor gender on female recipient graft function. Male donor kidneys function equivalently to female donor kidneys in the female recipient environment. However, if adjusted for the larger male renal mass by any of the surrogate ratios, the male kidneys should be functioning much better. The M»F kidneys function significantly more poorly ($P < 0.01$) than M»M kidneys. The male kidney has approximately a 0.2 mg% higher Cr_s in the female environment. The male kidney loses on the order of 15–20 ml/min eGFR in the female host.

To answer the question of whether the female hormonal environment was toxic to the male kidney, a subset examination of the M»F recipient function was undertaken. Female recipients under the age of 40 years ($n = 57$), presumed to have pre-menopausal circulating estrogen levels [5], were compared to female recipients over age 50 ($n = 50$), presumed to be postmenopausal. There was no significant difference in either Cr_s or eGFR for 1 year following transplantation between these subsets.

Table 6 shows the effects of donor gender on male recipient graft function. Female kidneys function more poorly in the male recipient. However, female kidneys function equivalently to male kidneys in the male recipient when adjusted for the smaller renal mass transplanted. These F»M kidneys improve significantly compared to F»F kidneys ($P < 0.01$). The female kidney improves eGFR by 7–10 ml/min by being transplanted into a male environment and the improvement remains consistent for 1 year.

The relationship of recipient renal function to renal mass transplanted was further examined. The following ratios of recipient/donor were examined as surrogates for the renal mass transplanted: 1. Wt. 2. IBW. 3. BSA. The recipient/donor ratios for were:

Table 6. Recipient renal function adjusted for donor mass.

	Female–female	Male–female	Female–male	Male–male
Time	Cr_s/BSA ratio*	Cr_s/BSA ratio	$Cr_s \times$ BSA ratio*	$Cr_s \times$ BSA ratio
Day 5	1.32 ± 0.4	1.53 ± 0.6	1.48 ± 0.4	1.54 ± 0.4
1 month	1.35 ± 0.7	1.50 ± 0.6	1.18 ± 0.5	1.61 ± 0.9
3 months	1.36 ± 0.5	1.54 ± 0.6	1.52 ± 0.5	1.58 ± 0.6
6 months	1.34 ± 0.4	1.58 ± 0.6	1.52 ± 0.5	1.60 ± 0.6
1 year	1.37 ± 0.4	1.62 ± 0.7	1.58 ± 0.6	1.62 ± 0.8
	eGFR × BSA ratio*‡	eGFR × BSA ratio†‡	eGFR/BSA ratio*	eGFR/BSA ratio†
Day 5	55.5 ± 19.5	48.9 ± 18.5	61.3 ± 20.8	60.2 ± 18.2
1 month	52.0 ± 18.1	47.8 ± 16.9	60.5 ± 18.9	60.3 ± 18.6
3 months	50.0 ± 18.9	48.3 ± 18.2	59.6 ± 19.1	58.5 ± 17.2
6 months	54.5 ± 23.0	47.1 ± 17.1	60.4 ± 19.7	58.6 ± 18.3
1 year	52.9 ± 20.2	46.6 ± 19.1	58.6 ± 20.5	58.2 ± 18.7

*$P < 0.01$ F»F vs. F»M.
†$P < 0.00001$ M»F vs. M»M.
‡$P < 0.001$ F»F vs. M»F.

1. Wt. F»F = 1.01 ± 0.3 F»M = 1.15 ± 0.3 M»F =0.80 ± 0.2 M»M = 0.95 ± 0.2
2. IBW F»F = 0.99 ± 0.1 F»M = 1.28 ± 0.2 M»F = 0.74 ±.1 M»M = 0.97 ± 0.1
3. BSA F»F = 0.98 ± 0.2 F»M = 1.12 ± 0.1 M»F = 0.86 ± 0.1M»M = 0.96 ± 0.1

The Cr and eGFR data were examined using all surrogate ratios but no significant changes from the BSA ratio were seen (data not shown).

Discussion

Graft renal function is felt to be proportional to the mass transplanted [6]. The evaluation of the effect that donor renal mass has on recipient deceased-donor graft survival has been attempted both by weighing the kidneys *ex vivo* and by calculating the donor size/recipient size discrepancy [7–11]. Studies generally have not well separated the issues related to graft function versus graft survival. Evaluation of pediatric transplant function is generally a situation with too much renal mass, rather than too little. In evaluation of adult transplant function, the situation is about too little renal mass. Many studies have looked at the effect of renal mass on the ultimate long-term graft survival; most have shown that too little renal mass accelerates injury, which progresses to chronic allograft nephropathy. In deceased-donor transplantation, increasing donor age, female sex, and AA race have been shown to be poor prognostic factors for the development of chronic allograft nephropathy and graft survival [12–16]. However, the effect of these parameters on renal function, rather than on survival, is poorly delineated.

There is no ideal way to measure the functioning renal mass transplanted. Even weighing the kidney *ex vivo* before implantation has serious potential for error. In this study, many surrogates for renal mass were examined and the large numbers for each group allowed all methods to statistically discriminate well. The BSA ratio is shown, because BSA has been reported to be the most accurate predictor of renal mass [4]. Recently renal volume calculation by reconstruction of magnetic resonance imaging (MRI) [11] or CT [10] images has been successfully used to approximate renal mass.

However, renal mass alone does not explain gender differences entirely. The kidney is a sexually dimorphic organ [17–25]. Dr John Lattimer in 1942 showed that exogenous testosterone (T) improved inulin clearance in males [24]. He further showed that renal mass was T-dependent in rats, dogs, and humans. He also showed that T augmented by 10% the compensatory hypertrophy seen in the 1 kidney rat and human. Many renal functions are androgen-dependent [17–22,25]. These functions would be expected to work better in a male recipient environment. Our data show that the both male- and female kidney function, taken individually, is superior in male host. Male renal failure patients have low serum testosterone (T_s) [26–28]. Following renal transplantation, the hypothalamic–pituitary–testicular axisreturns toward normal, but the recovery is slow and erratic [29–36]. It is possible that donor kidneys are faced with suboptimal T_s in the male recipient environment, and with castrate T_s in female recipient environment. Besides renal failure, other factors irregularly affecting T_s in the male recipient include age, concomitant diseases, concomitant medications, and importantly immunosuppressive regimens [37–40]. To complicate the picture even further, male kidneys are more susceptible to injury [41–44] and T_s mediates accelerated progression

of nephropathy from hypertension [43–45]. While T_s may augment some renal metabolic processes, T_s may actually in some cases decrease ultimate graft survival [46,47].

Male kidneys placed in a female environment function most poorly. When adjusted for renal mass, the male donor kidneys lose more function than just the excess renal mass they started with. It does not appear that female sex steroids are toxic to the male kidneys.

Little is known about the female kidney placed in a male environment. Kouli *et al.*, in a series of 83 deceased-donor grafts, showed that creatinine clearance was lower for F»F, F»M, and M»F grafts but did not adjust for renal mass [48]. In the current study, female donor kidneys had an equivalent eGFR in the male recipient when adjusted for the lower renal mass. The female kidneys appear to express the molecular determinants to respond to T_s.

This study shows that ultimate allograft function is influenced by donor-related variables. Among those variables are renal mass and gender. Nephron mass, indirectly assumed by donor size or kidney mass, of female donors when transplanted into significantly larger male recipients results in comparatively inferior renal clearance, but actually higher eGFR on a mass basis. Contra-intuitively, large nephron-mass male-donor kidneys do not live up to their potential in smaller female recipients. This poorer graft function may also be related to the male kidney being relatively androgen-deprived. Potentially graft eGFR could be raised by androgen supplementation in female recipients or in hypogonadal male recipients. We plan to further explore the effects of androgens on graft function by obtaining androgen levels pre- and post-transplant in a series of living-donor recipients.

Outcomes of living-donor renal transplantation are excellent. However, disparity in the numbers of deceased donors and potential recipients continues to escalate. Past concentration on the identification of a highly matched live donor has been superseded by efforts to locate any single medically suitable donor. To this end, efforts in gender and/or BSA-matched individuals should be sought when multiple donor options are available. Furthermore, expectations of ultimate recipient renal function should take into account both the gender and mass disparity of the donor–recipient pair.

Authorship

SCJ designed the study, performed the study, collected the data, analyzed the data, and wrote the paper. JMN collected the data, designed the study, and wrote the paper. MWP collected the data. STB designed the study. MC collected the data, designed the study, analyzed the data and wrote the paper.

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