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ORIGINAL ARTICLE

The impact of donor-to-recipient gender match and mismatch on the renal function of living donor renal graft recipients

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Abstract

Introduction: *Donor-to-recipient gender match and mismatch may be a potential prognostic factor for living donor renal graft function.* **Methods:** *A retrospective review of donor-to-recipient pairs undergoing living donor kidney transplantation was done. They were classified according to gender match as: male-to-male, female-to-female, male-to-female, and female-to-male. Serum creatinine was recorded during one year for donors and for up to four years for recipients. Renal function was evaluated by estimating the glomerular filtration rate with the Chronic Kidney Disease-Epidemiology Collaboration formula. A comparative statistical analysis was performed.* **Results:** *The analysis included 217 donor-to-recipient pairs. No significant differences across the four groups in estimated glomerular filtration rate and serum creatinine at any cut-off time point except at day one serum creatinine were found. Recipients had a significant difference in serum creatinine up to the first year of follow-up, with higher values for male recipients; no significant differences were found during the second through fourth year of follow-up. A significant difference was observed in estimated glomerular filtration rate throughout all follow-ups among the four groups, favoring female recipients of male kidneys.* **Conclusions:** *Donor-recipient mismatch may have a deleterious effect over long-term graft function. Female recipients of male kidneys have the best prognosis.* (Gac Med Mex. 2016;152:579-83)
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Introduction

Renal transplantation is the ideal treatment for end-stage renal disease. It provides better quality of life compared to other alternatives of renal replacement therapy. It replaces the need for dialysis, which is a complex and expensive therapy[1]. Kidney graft survival rates have improved during the last decades due to advances in immunosuppression and transplant management[2]. However, several variables may affect graft function. Donor-to-recipient gender matching has recently gained attention as a prognostic factor; for example, kidneys in women weigh 10-20% less than in men[3]. On the other hand, testosterone has been proven to influence kidney functions[4]. Consequently, the

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kidneys of males, females, and females receiving testosterone show different morphology[5]. This evidence supports the need to investigate the influence of donor-to-recipient gender matching on renal graft function.

The objective of this study is to compare the impact of donor-to-recipient gender matching on the function of renal grafts obtained from living donors.

Materials and methods

A retrospective, comparative, and analytic study was designed. We reviewed our institutional database of renal transplantation procedures approved by our local Commission of Ethics in Research. Renal donor-to-recipient pairs undergoing living donor kidney transplantation from January 2005 to December 2012 were included in the analysis. They were classified according to gender match as: male-to-male, female-to-female, male-to-female, and female-to-male. Renal function was evaluated by estimating the glomerular filtration rate (eGFR) with the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula[6]. Serum creatinine (SCr) was recorded during one year after surgery for donors and for up to four years in recipients. A comparative statistical analysis between gender match groups was performed considering demographic and clinical variables using ANOVA and Kruskal Wallis test. The SPSS (Statistical Package for Social Sciences®, v17.0, SPSS Inc., Chicago, IL, USA) software was employed. A two-tailed $p < 0.05$ was considered as significant.

Results

Data from 217 donor-to-recipient pairs were analyzed. Donor characteristics are depicted in table 1, including serum creatinine and eGFR. Table 2 shows similar data from recipients.

Donors

Donor characteristics are described in table 1. They had a mean age of 36.0 ± 10.27 years and a body mass index (BMI) of 25.11 ± 2.6 kg/m^2. A total of 116 nephrectomies were performed with laparoscopic hand-assisted technique and 97 with conventional open nephrectomy. There were 198 left nephrectomies and 19 right ones. Warm ischemia time was 3.35 ± 2.24 minutes. Donors had no significant differences in age, nephrectomy technique employed, nephrectomy side, or warm ischemia time. Preoperative SCr was 0.81 ± 0.18 mg/dl, and then turned into 1.31 ± 0.28 mg/dl at day 1; 1.18 ± 0.24 mg/dl at month 1; 1.13 ± 0.25 mg/dl at month 6; and 1.12 ± 0.23 mg/dl at month 12. Average values for eGFR were 96.6 ± 21.1, 55.6 ± 16.1, 62.4 ± 17.7, 65.8 ± 18.7, and 66.8 ± 18.8 mg/dl/1.73 m^2 at corresponding cut-off time points. There were no significant differences in eGFR and SCr at any cut-off time point except in day 1 SCr follow-up across the four proposed groups.

Recipients

Recipient characteristics are shown in table 2. They had a median age of 32.0 ± 11.6 years and a BMI of 23.2 ± 3.6 kg/m^2. Recipients shared two haplotypes with their donors in 23 pairs, one haplotype in 115 pairs, and none in 75 pairs. No significant differences in age, BMI, or shared haplotypes were found across the groups. The SCr and eGFR values are depicted before surgery and at day 1, month 1, 6, 12, and year 2, 3, and 4 of follow-up. Median serum creatinine values were 10.6 ± 4.78 before surgery, 2.68 ± 1.86 at day 1, 1.19 ± 0.50 at month 1, 1.25 ± 0.62 at month 6, 1.27 ± 0.50 at month 12, 1.42 ± 1.38 at year 2, 1.40 ± 0.74 at year 3, and 1.59 ± 1.48 mg/dl at year 4. Mean eGFR was 6.24 ± 6.96 before surgery, 37.4 ± 29.1 at day 1, 67.3 ± 23.7 at month 1, 63.35 ± 22.8 at month 6, 61.7 ± 22.8 at month 12, 59.3 ± 23.7 at year 2, 59.8 ± 25.1 at year 3, and 59.5 ± 27.7 at year 4, according to each cut-off time point. There was a significant difference in SCr up to the first year of follow-up, with numerically higher values for male recipients; no significant differences were found during the second through fourth year of follow-up. A significant difference was observed in eGFR throughout all follow-ups among the four groups, with a numerically superior function favoring female recipients of male kidneys, then female recipients of female kidneys, and male recipients last.

Discussion

There were no significant differences regarding donor baseline age, BMI, nephrectomy technique employed (laparoscopic vs. open), or side among the four proposed gender match donor groups. We expected to find higher SCr levels for male donors. Although there were some numerical differences favoring higher male SCr levels during donor follow-up, they were not constant and no significant differences were found. Male donors usually have higher levels as creatinine is

Table 1. Donor characteristics

		Total (n = 217)	Male-to-male (n = 50)	Female-to-female (n = 49)	Male-to-female (n = 45)	Female-to-male (n = 73)	p
Age (years)		36.0 ± 10.27	36.2 ± 11.2	36.8 ± 11.1	36.6 ± 10.1	34.9 ± 9.1	0.72
BMI (kg/m^2)		25.11 ± 2.6	24.9 ± 2.6	24.9 ± 2.9	25.5 ± 2.5	25.0 ± 2.4	0.62
Nephrectomy technique (n)	Op	97	23	19	23	32	0.72
	Lap	116	25	29	21	41	
	Conv	4	2	1	1	0	
Nephrectomy side (n)		L 198 R 19	L 44 R 6	L 45 R 4	L 40 R 5	L 69 R 4	0.58
Warm ischemia time (minutes)		3.35 ± 2.24	3.50 ± 2.38	3.56 ± 2.38	3.03 ± 1.54	3.31 ± 1.83	0.69
SCr preoperative (mg/dl) (n = 211)		0.81 ± 0.18	0.80 ± 0.20	0.78 ± 0.14	0.84 ± 0.17	0.82 ± 0.18	0.58
eGFR preoperative ($ml/min/1.73\ m^2$) (n = 211)		96.6 ± 21.1	99.7 ± 21.7	99.2 ± 17.8	91.5 ± 20.1	95.7 ± 22.9	0.22
SCr day 1 (mg/dl) (n = 170)		1.31 ± 0.28	1.26 ± 0.28	1.22 ± 0.25	1.36 ± 0.26	1.36 ± 0.30	**0.05**
eGFR day 1 ($ml/min/1.73\ m^2$) (n = 170)		55.6 ± 16.1	58.4 ± 16.9	58.9 ± 16.	52.8 ± 15.32	53.4 ± 15.5	0.17
SCr month 1 (mg/dl) (n = 123)		1.18 ± 0.24	1.14 ± 0.22	1.16 ± 0.26	1.20 ± 0.26	1.21 ± 0.25	0.38
eGFR month 1 ($ml/min/1.73\ m^2$) (n = 123)		62.4 ± 17.7	60.8 ± 16.7	64.0 ± 16.5	57.2 ± 13.7	65.9 ± 13.7	0.24
SCr month 6 (mg/dl) (n = 128)		1.13 ± 0.25	1.16 ± 0.24	1.07 ± 0.19	1.13 ± 0.20	1.15 ± 0.31	0.58
eGFR month 6 ($ml/min/1.73\ m^2$) (n = 128)		65.8 ± 18.7	63.0 ± 14.9	66.3 ± 14.9	65.4 ± 18.5	67.4 ± 22.1	0.80
SCr month 12 (mg/dl) (n = 129)		1.12 ± 0.23	1.09± 0.22	1.10 ± 0.22	1.17 ± 0.25	1.12 ± 0.24	0.64
eGFR month 12 ($ml/min/1.73\ m^2$) (n = 129)		66.8 ± 18.8	67.9 ± 19.11	66.9 ± 16.9	62.6 ± 17.32	68.4 ± 20.9	0.64

BMI: body mass index; Conv: conventional open nephrectomy; eGFR: estimated glomerular filtration rate; Lap: laparoscopic; L: left; Op: open; R: right; SCr: serum creatinine.

a surrogate of muscular mass. Moreover, when considering eGFR during follow-up, there were no significant differences between the four groups.

Recipient characteristics showed no differences in baseline age and BMI among the four gender-match groups. Furthermore, the number of shared haplotypes with the donors and warm ischemia time were no different either.

When analyzing renal function parameters at follow-up, there was a significant difference in SCr values, favoring higher levels for male recipients during the first year of follow-up, as was expected, considering muscle mass. When evaluating eGFR, there was a clear significant tendency in favor of female recipients of male kidneys, followed by female recipients of female kidneys. Interestingly, male recipients had the lower eGFR across the four groups. This tendency was maintained during the four years of follow-up. We expected a favorable behavior of female recipients of male kidneys. However, the notorious differences in female donor to female recipient from male donor to male recipient are unexpected.

Previous reports are mixed. Zeier, et al., in a large study of 124,911 renal transplants, found decreased

Table 2. Recipient characteristics

		Total (n = 217)	Male-to-male (n = 50)	Female-to-female (n = 49)	Male-to-female (n = 45)	Female-to male (n = 73)	p
Age (years)		32.0 ± 11.6	31.8 ± 11.5	32.7 ± 12.4	33.0 ± 12.0	31.2 ± 11.1	0.82
BMI (kg/m^2)		23.2 ± 3.6	22.8 ± 2.9	23.4 ± 3.7	23.2 ± 4.4	23.4 ± 3.4	0.85
Shared haplotypes (n)*	0	75	17	18	18	26	0.66
	1	115	27	27	22	35	
	2	23	5	5	3	11	
SCr preoperative (mg/dl) (n = 213)		10.6 ± 4.78	11.82 ± 4.71	7.96 ± 4.71	8.88 ± 4.35	12.59 ± 4.72	**0.01**
eGFR preoperative (ml/min/1.73 m^2) (n = 213)		6.24 ± 6.96	5.5 ± 7.6	7.81 ± 4.92	7.4 ± 6.5	4.9 ± 7.69	0.84
SCr day 1 (mg/dl) (n = 83)		2.68 ± 1.86	3.31 ± 2.01	1.44 ± 0.88	1.93 ± 0.96	3.33 ± 2.09	**0.01**
eGFR day 1 (ml/min/1.73 m^2) (n = 83)		37.4 ± 29.1	29.4 ± 25.3	60.6 ± 26.3	43.9 ± 24.7	27.0 ± 18.6	**0.01**
SCr month 1 (mg/dl) (n = 205)		1.19 ± 0.50	1.30 ± 0.66	1.13 ± 0.59	0.91 ± 0.21	1.31 ± 0.33	**0.01**
eGFR month 1 (ml/min/1.73 m^2) (n = 205)		67.3 ± 23.7	60.1 ± 20.1	73.6 ± 24.5	86.0 ± 23.0	56.5 ± 17.0	**0.01**
SCr month 6 (mg/dl) (n = 177)		1.25 ± 0.62	1.50 ± 1.13	1.08 ± 0.30	1.02 ± 0.29	1.33 ± 0.25	**0.01**
eGFR month 6 (ml/min/1.73 m^2) (n = 177)		63.35 ± 22.8	55.5 ± 23.5	72.7 ± 25.1	76.2 ± 21.9	53.8 ± 12.6	**0.01**
SCr year 1 (mg/dl) (n = 163)		1.27 ± 0.50	1.43 ± 0.72	1.17 ± 0.42	1.06 ± 0.46	1.38 ± 0.29	**0.02**
eGFR year 1 (ml/min/1.73 m^2) (n = 163)		61.7 ± 22.8	54.2 ± 18.7	68.0 ± 26.3	77.4 ± 24.5	52.2 ± 12.8	**0.01**
SCr year 2 (mg/dl) (n = 122)		1.42 ± 1.38	1.42 ± 0.44	1.90 ± 2.63	1.03 ± 0.30	1.55 ± 1.05	0.14
eGFR year 2 (ml/min/1.73 m^2) (n = 122)		59.3 ± 23.7	53.9 ± 21.3	61.1 ± 29.0	77.0 ± 29.0	50.0 ± 13.9	**0.01**
SCr year 3 (mg/dl) (n = 93)		1.40 ± 0.74	1.53 ± 0.56	1.63 ± 1.42	1.03 ± 0.43	1.44 ± 0.35	0.05
eGFR year 3 (ml/min/1.73 m^2) (n = 93)		59.8 ± 25.1	50.9 ± 20.3	63.9 ± 35.8	77.5 ± 22.8	51.4 ± 15.0	**0.01**
SCr year 4 (mg/dl) (n = 70)		1.59 ± 1.48	1.70 ± 0.87	1.82 ± 2.42	1.48 ± 1.81	1.43 ± 0.27	0.84
eGFR year 4 (ml/min/1.73 m^2) (n = 70)		59.5 ± 27.7	50.3 ± 23.6	67.7 ± 35.4	74.5 ± 31.6	49.3 ± 11.0	**0.01**

*2 cases were missing.
BMI: body mass index; eGFR: estimated glomerular filtration rate. L: left; R: right; SCr: serum creatinine.

graft survival of male recipients from female donors[7]. On the other hand, Csete, et al. found better graft function at one and 10 years after transplantation among recipients of male donor organs[8]. Kwon, et al. found decreased graft survival in female-to-male transplants and also described that this effect was more evident in older recipients[9]. The series previously described also confirm the concept that female recipients of male donors have the best graft function; noteworthy, they do not reproduce the behavior of male recipients in our series, which, regardless of donor gender, have the lowest eGFR compared to female recipients of female kidneys.

The effect of gender mismatching on kidney transplantation may be explained by physiological, hormonal, and immune interactions. Jacobs, et al. interestingly described the behavior of gender mismatched and matched grafts[10]. They found that a male kidney loses 15-20 ml/min of glomerular function in the female host, while female kidneys improve by 7-10 ml/min when transplanted into a male environment. Female and male donor kidneys functioned equivalently in the male recipient when adjusted for renal mass. These findings are contrary to those of other authors and suggest that androgens may influence kidney function. Furthermore, testosterone improves inulin clearance in males, and renal mass is testosterone-dependent in rats, dogs, and humans[11]. Our results do not support this hypothesis, as male kidneys in female recipients are not superior to female kidneys in female recipients.

Hyperfiltration is a possible physiological explanation for the decreased function of female-to-male grafts[12], where smaller female grafts may represent an inadequate nephron "dose" for a man. Different indexes have been proposed to measure this relationship. Nicholson, et al. created the allograft size to recipient body weight ratio[13]. They found that extreme mismatching between allograft and recipient size significantly affected SCr levels in the first five years after transplantation. Another index is the donor to recipient body surface area ratio, which has shown mixed results[14,15].

Zukowski, et al. found that female recipients of male kidneys have a greater risk of early graft loss, suggesting that sensitization may play a role in this phenomenon[16].

Our data confirms most of the information found in the literature and places male kidneys in female recipients as the best gender-matching selection. At this point, we cannot explain the lower than expected behavior of male kidneys in male recipients, and further investigation is warranted.

We identified weaknesses in our study. First, we used eGFR calculated with the best available formula, although it is not the gold standard. The ideal method would be measured creatinine clearance. Second, our sample is relatively small and follow-up must be extended to determine long-term behavior.

Conclusions

Donor-recipient mismatch may have a deleterious effect on long-term graft function. Gender matching affects kidney graft behavior. Female recipients of male kidneys have the best prognosis. A low function in male receptor of male kidneys was unexpectedly found. Further studies are required to determine the causes of differences among the groups. Hormonal and immune interactions may be the best-suited targets.

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