ORIGINAL ARTICLE

Early glomerular filtration rate changes in living kidney donors and recipients: an example of renal plasticity

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ABSTRACT

Background. In living kidney transplantation there are two different individuals, a healthy donor and a renal transplant
recipient. This is an excellent human model to study factors that influence kidney function in the context of reduced
renal mass and the adaptation of two comparable kidneys to different metabolic demands.

Methods. We analyzed the changes in measured glomerular filtration rate (GFR, iohexol) from pretransplantation to 12 months after transplantation in 30 donor–recipient pairs. Each donor was compared with his/her recipient. We defined *a priori* three different groups based on GFR differences at 12 months: donor > recipient (Group A; 78 ± 8 versus 57 ± 8 mL/min), donor < recipient (Group B; 65 ± 11 versus 79 ± 11 mL/min) and donor ≈ recipient (Group C; 66 ± 7 versus 67 ± 7 mL/min). Other factors like donor/recipient mismatches in body mass index (BMI), surface area and gender were evaluated.

Results. In Group A donors were mostly male and recipients were female (75% each). Donors had a higher baseline weight than their recipients. During follow-up, weight remained stable in donors but increased 7% in recipients. In Group B donors were mostly female (60%) and recipients male. At baseline, donors had a lower weight than recipients. At 12 months, weight was stable in donors but increased in recipients. In Group C donors were mostly (75%) female and recipients male. At baseline, donors had a higher BMI than their recipients. At 12 months, BMI was stable in donors but increased 14% in recipients. In multivariable analysis, higher GFR at 12 months was associated with higher baseline weight and GFR in donors and with male gender and higher baseline weight in recipients.

Conclusions. Kidneys from living donors are more 'plastic' than originally thought and respond to metabolic demands and weight changes of their new host. These changes should be taken into account when assessing GFR outcomes in this population.

Keywords: body mass index, gender, glomerular filtration rate, kidney transplantation, living donors

INTRODUCTION

Living donor kidney transplantation is the best therapeutic option for patients with advanced renal disease [1]. It is associated with better graft and patient survivals compared with patients who receive a graft from deceased donors [1–3]. Potential healthy donors are rigorously screened and must meet strict eligibility criteria. An excellent health status must be proven and occult diseases must be ruled out. As expected, an accurate evaluation of renal function is mandatory to be certain that glomerular filtration rate (GFR) is above an acceptable cut-off value for donation.

Also, living donor kidney transplantation is a unique situation in which two different individuals end up with a single kidney of the same origin. Thus two optimal kidneys are located in different environments: a healthy subject and a patient with chronic kidney disease. During follow-up, several factors may affect renal function in donors and recipients. Some pertain to the recipient, i.e. allograft rejection, infections, nephrotoxicity and recurrent or *de novo* kidney disease. Others are common to donors and recipients, including smoking and metabolic syndrome factors, i.e. hypertension, hyperglycemia, dyslipidemia and obesity [4–7]. Thus living donation could be considered a clinical model to study the adaptive capacity of two comparable kidneys placed in different environments as well as the impact of risk factors for renal dysfunction in subjects with reduced renal mass.

Obesity is a risk factor for renal disease [8]. However, not all obese individuals are at risk: patients with obesity and metabolic syndrome may be those with the highest risk for chronic kidney disease (CKD) [9]. Also, reduced renal mass may play a role in obesity-related renal disease [10]. In fact, obesity is a major cause of proteinuria and renal function loss after a nephrectomy [11]. In renal transplantation, indirect markers of nephron mass, such as gender and body surface area (BSA) mismatch between donors and recipients, could negatively affect graft function in the long term [12–14]. Previous studies have indicated that females may in general have a lower renal mass and renal function compared with men [12]. Thus transplantation from a female donor to a male recipient has been considered by some researchers a factor with a possible negative impact on graft function in the long term. However, how the impact of renal endowment and gender mismatch in GFR changes over time in donors and recipients has not been completely elucidated.

In this study we evaluated the factors that influenced renal function changes in 30 pairs of living donors and recipients during the first 12 months after transplantation. GFR changes were analyzed in donors and their recipients to evaluate how both kidneys adapted to diverse environments and its changes over time.

MATERIAL AND METHODS

Patients and design

In this observational prospective study, we analyzed the evolution of renal function in 30 donor–recipient pairs during the first year after transplantation. GFR was measured by the plasma clearance of iohexol before transplantation in donors and 12 months after transplantation in donors and recipients.

Inclusion criteria were the following: ≥18 years of age, donor–recipient pairs studied for living kidney donation at the Nephrology Department of the Hospital Universitario de Canarias (HUC) and 12 months of follow-up after donation. Exclusion criteria were psychiatric disease that limits compliance with the protocol, inability to understand the protocol, paired-organ donation, allergy to iodine or contrast media and pregnancy or lactation. The protocol was approved by the Ethics Committee of the Hospital Universitario de Canarias (Tenerife, Spain).

Demographic and clinical characteristics

Before transplantation we collected data on age, gender, weight, height, body mass index (BMI), BSA and laboratory analysis of donors and recipients. In particular, for donors we collected information on arterial hypertension, dyslipidemia, medications, smoking status and normal glucose metabolism based on glucose oral tolerance tests. Renal function was evaluated by measured and estimated GFR (mGFR, eGFR), serum creatinine, 24-h creatinine clearance and albuminuria. Total kidney volume was calculated as the sum of the right and left kidney volumes by a high-resolution CT scan using Vitrea software (Vitrea, General Electric, Milwaukee, WI, USA). Data on recipients included the

cause of renal disease, renal replacement therapy or preemptive transplant, human leukocyte antigen (HLA) compatibility, concomitant diseases (i.e. hypertension, dyslipidemia and diabetes) and cardiovascular events.

For donors, after transplantation we collected early surgical complications, acute kidney injury (AKI), weight changes and hypertension (*de novo* or previous), dyslipidemia, hyperglycemia and the use of medications. For recipients we analyzed early surgical complications, acute rejection, obstructive uropathy, delayed graft function, BK virus nephropathy, levels of immunosuppressants, anticalcineurin toxicity, AKI, weight changes, hypertension, dyslipidemia and post transplant diabetes mellitus (PTDM).

All data were stored in an online database designed ad hoc for the study using the web application provided by the RedCap Consortium (https://www.project-redcap.org/). Based on the Spanish law for data protection, all data were anonymized and the identification of patients was stored and was not accessible from Internet.

Measured GFR with the plasma clearance of iohexol using dried blood spots

The procedure has been described elsewhere [15, 16]. In brief, 5 mL of iohexol solution (Omnipaque 300, GE Healthcare, Chicago, IL, USA) is injected intravenously in a forearm vein over 2 min. Then, 120 min after the injection, capillary blood (10 μL) is taken by finger prick, collected by a capillary pipette and deposited on filter paper at 120, 150, 180, 210 and 240 min [15, 16]. If the subject has GFR values <40 mL/min, samples are taken at 120, 180, 240, 300, 360 and 420 min. Iohexol was measured in dried blood spots as previously described [15, 16] and iohexol clearance (mL/min) was calculated according to a one-compartment model and then corrected following Bröchner-Mortensen [17].

The plasma clearance of iohexol was performed in clinically stable patients, which means in the absence of acute episodes that may influence renal function, such as severe infectious disease, acute cardiovascular disease, AKI or other acute intercurrent conditions. GFR was unadjusted to analyze the impact of weight changes on GFR without the interference of the adjustment for BSA. The cut-off for donation in our center is 80 mL/min for donors >30 years of age and 90 mL/min for those younger [7, 18, 19]. All living donors in the HUC are selected based on mGFR and not eGFR.

Statistical analysis

This is an exploratory analysis. We aimed to analyze renal function changes in donors and recipients before and after transplantation. Each pair was evaluated individually and then grouped according to the evolution of mGFR. We foresaw *a priori* three different evolutions of renal function at 12 months in donors and their recipients: (Group A) mGFR higher in donors than recipients, (Group B) mGFR lower in donors than recipients and (Group C) mGFR comparable between donors and recipients. The cut-off for defining a GFR higher or lower in a donor compared with its recipient was 10 mL/min, which is three times the reproducibility of mGFR in our laboratory (3%).

Univariable and multivariable regression analysis was used to test the impact of factors on GFR changes during the first 12 months after donation/transplantation and diverse linear regression models were developed in donors and recipients. The outcome was the GFR at 12 months. Covariates included age, gender, weight, BMI and BSA at baseline and at 12 months, male

donors who donated to female recipients and female donors who donated to male recipients.

To evaluate the impact of renal endowment on renal function after donation, in a sensitivity analysis we evaluated the following groups: males who donated to females, females who donated to males, donors with a greater BSA than their recipients and donors with a lesser BSA than their recipients.

Comparisons between groups were performed with Mann–Whitney or chi-squared tests as determined by the characteristic of the variable. For analysis we used SPSS (version 25.0 (IBM, Armonk, NY, USA).

RESULTS

Pretransplant characteristics

The mean age of donors was 45 years [interquartile range (IQR) 40–53) and half of the subjects were female. The mean weight was 75.9 ± 12 kg, BMI 27 ± 3.4 kg/m^2 and BSA 1.85 ± 0.17 m^2 (Table 1). Eight subjects (26%) had hypertension and seven (23%) had dyslipidemia. Measured GFR before transplantation was 99 ± 14 mL/min (IQR 87–109). The average total kidney volume was 300 ± 38 cm^3. Left and right kidneys were comparable (data not shown).

The mean age of recipients was 42 years (IQR 33–46), 43% were female. The mean weight was 73.5 ± 17 kg, BMI 25 ± 4.3 kg/m^2 and BSA 1.84 ± 0.25 m^2 (Table 1). Most subjects were hypertensive, 15 (50%) had dyslipidemia and 4 (13%) had diabetes mellitus. Polycystic kidney disease was the main cause of renal disease [$n = 7$ (23%)], followed by glomerulonephritis [$n = 6$ (20%)] and diabetic nephropathy [$n = 3$(10%)]. Before transplantation, 60% of the recipients were on dialysis and 40% were in predialysis care. Half of the pairs were genetically related (53%), four were HLA identical (15%) and one was ABO incompatible (3%).

Posttransplant evolution

In Group A, including 12 donor–recipient pairs, measured GFR was 105 ± 12 mL/min at baseline and decreased to 78 ± 8 mL/min at 12 months in donors (Table 2; Figure 1, left panel). In contrast, in recipients, mGFR at 12 months was lower than in donors (57 ± 8 mL/min; P = 0.008) (Figure 1, left panel). At baseline, donors were older, mostly male (75%), with a higher weight (82 ± 12 versus 66 ± 15 kg; P = 0.007), BMI and BSA than recipients. Most recipients (75%) were female (Table 2). Compared with donors in Groups B and C, those of Group A had a higher weight and BSA. The average total kidney volume at pretransplant was 320 ± 26 cm^3, which was comparable to the volume of Group B and higher than that of Group C (P = 0.025) (Table 2).

During follow-up, recipients increased in weight, BMI and BSA, whereas donors remained stable (Figure 1, middle panel). This led to comparable BMI and BSA between donors and recipients at 12 months (27 ± 3 versus 26 ± 5 kg/m^2 and 1.91 ± 0.15 versus 1.80 ± 0.20 m^2, respectively; P = not significant in both cases). Two recipients (17%) developed PTDM. Finally, three recipients presented five relevant clinical complications. One patient had an acute rejection followed by an episode of calcineurin inhibitor (CNI) toxicity, another patient had an episode of obstructive uropathy followed by pyelonephritis and the third had an obstructive uropathy. The analysis excluding these three cases ($n = 9$) showed comparable mGFR values at 12 months for the complete group ($n = 12$): 57 ± 11 versus 57 ± 8 mL/min.

Group B, including 10 donor–recipient pairs, had a measured GFR in donors that changed from 98 ± 13 mL/min at

Table 1. Baseline characteristics of donors and recipients

Characteristics	Donors	Recipients
n	30	30
Age (years), mean (IQR)	45 (40–53)	42 (33–46)
Gender (female), *n* (%)	15 (50)	13 (43)
Size (cm), median ± SD	168 ± 8	170 ± 10
Weight (kg)	75.9 ± 12	73.5 ± 17
Body mass index (kg/m^2), median ± SD (range)	27 ± 3.4 (21–34.6)	25 ± 4.3 (18–35)*
Body surface area (m^2), median ± SD (range)	1.85 ± 0.17 (1.46–2.15)	1.84 ± 0.25 (1.38–2.38)
Recipients, *n* (%)		
ABO incompatibility	–	1 (3)
Genetically related	–	16 (53)
Identical HLA	–	4 (15)
Clinical conditions, *n* (%)		
Etiology of CKD		
Diabetic nephropathy	–	4 (13)
Polycystic kidney disease	–	7 (23)
Nephroangiosclerosis	–	1 (3)
Glomerulonephritis	–	6 (20)
Interstitial nephropathy	–	4 (13)
Unknown	–	5 (17)
Other	–	3 (13)
Dialysis *n* (%)	–	18 (60)
Predialysis care *n* (%)	–	12 (40)
Donors and recipients		
Concomitant diseases *n* (%)		
Arterial hypertension	8 (26)	26 (87)
Dyslipidemia	7 (23)	15 (50)
Diabetes	–	4 (13)
Smoker *n* (%)		
Never	15 (50)	19 (63)
Former	6 (20)	3 (10)
Active	9 (30)	8 (27)
Antihypertensive drugs *n* (%)		
ACE inhibitors	1 (3)	10 (33)
Angiotensin-receptor blockers	4 (13)	3 (10)
Calcium channel blockers	–	15 (50)
Diuretics	1 (3)	10 (33)
Beta-blockers	–	4 (13)
Alpha-blockers	–	5 (17)
Others	–	3 (10)
Lifestyle interventions only	3 (10)	–
Laboratory tests		
Hemoglobin (g/dL), mean (SD)	14.1 (1.4)	12 (1.3)
Total cholesterol (mg/dL), mean (SD)	187 (33)	156 (30)
Triglycerides (mg/dL), median (IQR)	103 (68–135)	114 (90–166)
HbA1c (%), mean (SD)	5.4 (0.27)	–
Serum creatinine (mg/dL), mean (SD)	0.89 (0.15)	5 (2.2–12)
Albuminuria (mg/24 h), median (IQR)	5 (3–7)	–
Measured GFR (mL/min), median (IQR)	99 (87–109)	–
Total kidney volume (cm^3), mean ± SD	300 ± 38	–

HbA1c: glycated hemoglobin; ACE: angiotensin-converting enzyme; SD: standard deviation. *P < 0.0001.

baseline to 65 ± 11 mL/min at 12 months (Table 2; Figure 1, right panel). In recipients, mGFR at 12 months was higher than in donors (79 ± 11 mL/min; P = 0.012) (Figure 1, right panel). At baseline, donors were mostly females (60%), with a lower weight (71 ± 12 versus 84 ± 15 kg; P = 0.005) and BSA than recipients (Table 2). Most of the recipients (90%) were males. The total kidney volume at pretransplant was 300 ± 44 cm^3, which was comparable to Groups A and C.

During follow-up, recipients increased weight, BMI and BSA, whereas donors remained stable (Figure 1, right panel). Five subjects (50%) developed PTDM. BMI and BSA at 12 months were greater in recipients compared with donors (Table 2). Finally, few cases presented relevant clinical complications.

Group C, including eight donor–recipient pairs, had measured GFR values of 93 ± 14 mL/min at baseline, which decreased to 66 ± 7 mL/min at 12 months in donors (Table 2, right panel). Renal function at 12 months in recipients was similar to that of donors (67 ± 7 versus 66 ± 7 mL/min) (Figure 1, right panel). Donors were older (45 ± 5 versus 35 ± 12 years; P = 0.035), mostly female (75%), with a similar weight and BSA as recipients (72 ± 4 versus 71 ± 19 kg and 1.80 ± 0.08 and 1.81 ± 0.30 m^2), but a higher BMI (27 ± 3 versus 24 ± 4; P = 0.025) at

Table 2. Characteristics at baseline and 12 months after transplantation of three different groups of donors and recipients

Characteristics	GFR higher in donors than their recipients (Group A)			GFR lower in donors than their recipients (Group B)			GFR similar in donors and their recipients (Group C)		
	Donor	Recipient	P-value	Donor	Recipient	P-value	Donor	Recipient	P-value
n	12	12		10	10		8	8	
Age (years)	44 ± 8	36 ± 11	0.07	49 ± 11	45 ± 7		45 ± 5	35 ± 12	0.035
Gender (female), n (%)	3 (25)	9 (75)		6 (60)	1 (10)		6 (75)	3 (37)	
Size (m)	171 ± 6	165 ± 9		166 ± 10	176 ± 8	0.007	165 ± 8	170 ± 13	
Weight (kg)	82 ± 12*	66 ± 15	0.007	71 ± 12	84 ± 15	0.005	72 ± 4	71 ± 19	
BMI (kg/m²), mean ± SD (range)	28 ± 4 (21–34)	24 ± 5 (18–35)	0.023	26 ± 3 (21–30)	27 ± 3 (24–34)		27 ± 3 (21–30)	24 ± 4 (19–31)	0.023
BSA (m²)	1.94 ± 0.15**	1.72 ± 0.20	0.041	1.78 ± 0.19	2.0 ± 0.20	0.013	1.80 ± 0.08	1.81 ± 0.30	
Dislipidemia, n (%)	2 (17)	6 (50)		3 (30)	5 (50)		1 (12)	4 (50)	
Cholesterol (mg/dL)	190 ± 26	149 ± 30		186 ± 35	150 ± 36		183 ± 42	147 ± 37	
Triglicerides (mg/dL)	112 ± 44	108 ± 43		93 ± 35	126 ± 76		83 ± 49	129 ± 65	
Glucose (mg/dL)	90 ± 8	153 ± 55***		85 ± 6	94 ± 9		86 ± 8	87 ± 8	
Hypertension, n (%)	2 (17)	10 (83)		2 (20)	10 (100)		0	6 (75)	
mGFR (mL/min)	105 ± 12	–		98 ± 13	–		93 ± 14	–	
TKV (cm³)	320 ± 26			300 ± 44			274 ± 33		
Weight (kg)	79 ± 11	70 ± 16		69 ± 10	91 ± 20	0.005	74 ± 5	81 ± 21	
Delta 0–12 m (%), median (IQR)	–2 (–12–1)	7 (0.05–16)		–1 (–4–3)	5 (–1–12)		4 (–2–7)	14 (6–22)	
BMI (kg/m²)	27 ± 3	26 ± 5		25 ± 2	29 ± 5	0.022	27 ± 10	28 ± 5	
Delta 12 m (%), median (IQR)	–2 (–12–1)	7 (0.05–16)		–1 (–4–3)	5 (–1–12)		4 (–2–7)	14 (6–22)	
BSA (m²)	1.91 ± 0.15	1.80 ± 0.20		1.77 ± 0.18	2.07 ± 0.24	0.005	1.82 ± 0.08	1.91 ± 0.3	
Delta 0–12 m (%), median (IQR)	–0.8 (–5–0.5)	2.9 (0.02–6.6)		–0.5 (–2–1)	3.6 (0.12–5)		1.5 (–0.7–3)	5.7 (2.5–8.7)	
Dislipidemia, n (%)	3 (25)	3 (25)		6 (60)	5 (50)		2 (25)	0	
Cholesterol (mg/dL)	187 ± 21	180 ± 31		204 ± 36	189 ± 43		185 ± 36	164 ± 30	
Triglicerides (mg/dL)	100 ± 51	112 ± 40		110 ± 40	140 ± 61		111 ± 62	96 ± 34	
Glucose (mg/dL)	91 ± 10	85 ± 18		87 ± 9	97 ± 15		88 ± 8	90 ± 12	
PTDM, n (%)	–	2 (16)		–	5 (50)		–	0	
Hypertension, n (%)	3 (25)	6 (50)		2 (20)	10 (100)		0	4 (50)	
mGFR (mL/min)	78 ± 8	57 ± 8	0.008	65 ± 11	79 ± 11	0.012	66 ± 7	67 ± 7	
Delta 0–12 m (%), median (IQR)	–25 (–32 to –20)			–34 (–37 to –31)			–31 (–34 to –23)		
Albuminuria (mg/g), median (IQR)	2.0 (2.0–3.35)	4.0 (2–53.29)		2.0 (2.0–2.0)	6.96 (2–30.36)		2.0 (2.0–2.0)	4.85 (2–8.23)	
Tacrolimus levels (ng/mL), median (IQR)	–	8.1 (7–9)		–	8.7 (7–9)		–	8.4 (8–9)	
Acute rejection, n (%)	–	1 (8)		–	1 (10)		–	1 (12)	
BK virus nephropathy, n (%)		0			0			0	
Pyelonephritis, n (%)		1 (8)			0			0	
CNI toxicity, n (%)		1 (8)			0			0	
Obstructive uropathy, n (%)		2 (17)			0			0	

Values are presented as mean ± SD unless stated otherwise. Results comparing donors between three Groups: *P = 0.014 versus donors in Group B and ªP = 0.016 versus donors in Group C; **P = 0.012 versus Group B and P = 0.025 versus Group C; ***P = 0.002 versus donors in Group B and P = 0.001 versus Group C; ᶜP = 0.025 versus Group A

Events in recipients of Group A: 5 events in three different patients: one patient with acute rejection had CNI toxicity; one patient had obstructive uropathy and pyelonephritis and one patient had obstructive uropathy alone.
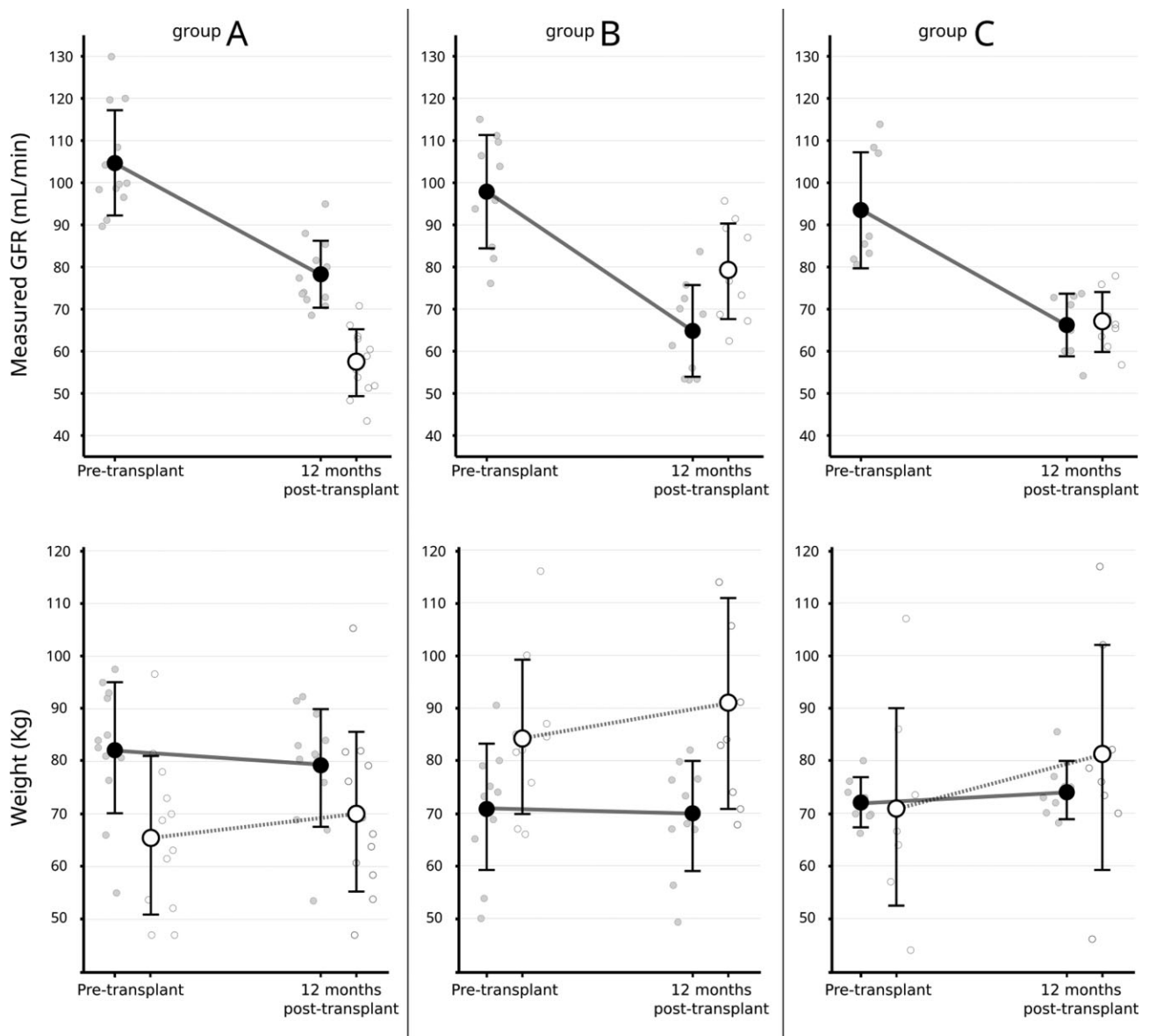
FIGURE 1: Measured GFR and weight changes in donor-recipient pairs grouped according to the difference in GFR at 12 months after transplantation. (Left panel) Group A: GFR higher in donors than recipients. (Middle panel) Group B: GFR lower in donors than recipients. (Right panel) Group C: mGFR comparable between donors and recipients. Donors: black circles; recipients: white circles.

baseline (Table 2). Most of the recipients (63%) were males. During follow-up, recipients showed a relevant increase in weight and BMI (from 24 ± 4 to 28 ± 5 kg/m^2), whereas donors did not have significant changes (Figure 1, right panel). No recipient developed PTDM. Accordingly, BSA at 12 months was greater in recipients compared with donors (Table 2). During follow-up, only one patient showed an episode of acute rejection, which was treated and resolved.

Linear regression analysis

In univariable analysis in recipients, older age and higher weight, BMI and BSA at baseline or at 12 months as well as male gender and females who donated to male recipients were factors associated with higher GFR at 12 months after transplantation (Supplementary data, Table A1). In multivari-

able analysis, weight, BMI and BSA were not introduced simultaneously to avoid colinearity and gender was not introduced with these anthropometric variables since male recipients showed greater weight and BSA (Supplementary data, Table A2). Age, greater weight and greater BSA both at baseline and 12 months after transplantation were associated with higher GFR at 12 months (Supplementary data, Table A3). Also, male gender and females who donated to male recipients were associated with higher GFR at 12 months.

In univariable analysis in donors, higher pre-donation GFR and greater weight and BSA at baseline or at 12 months as well as male gender were factors associated with higher GFR at 12 months postdonation (Supplementary data, Table B1). In multivariable analysis, weight, BMI and BSA were not introduced simultaneously to avoid colinearity. Higher GFR and greater weight predonation were independently
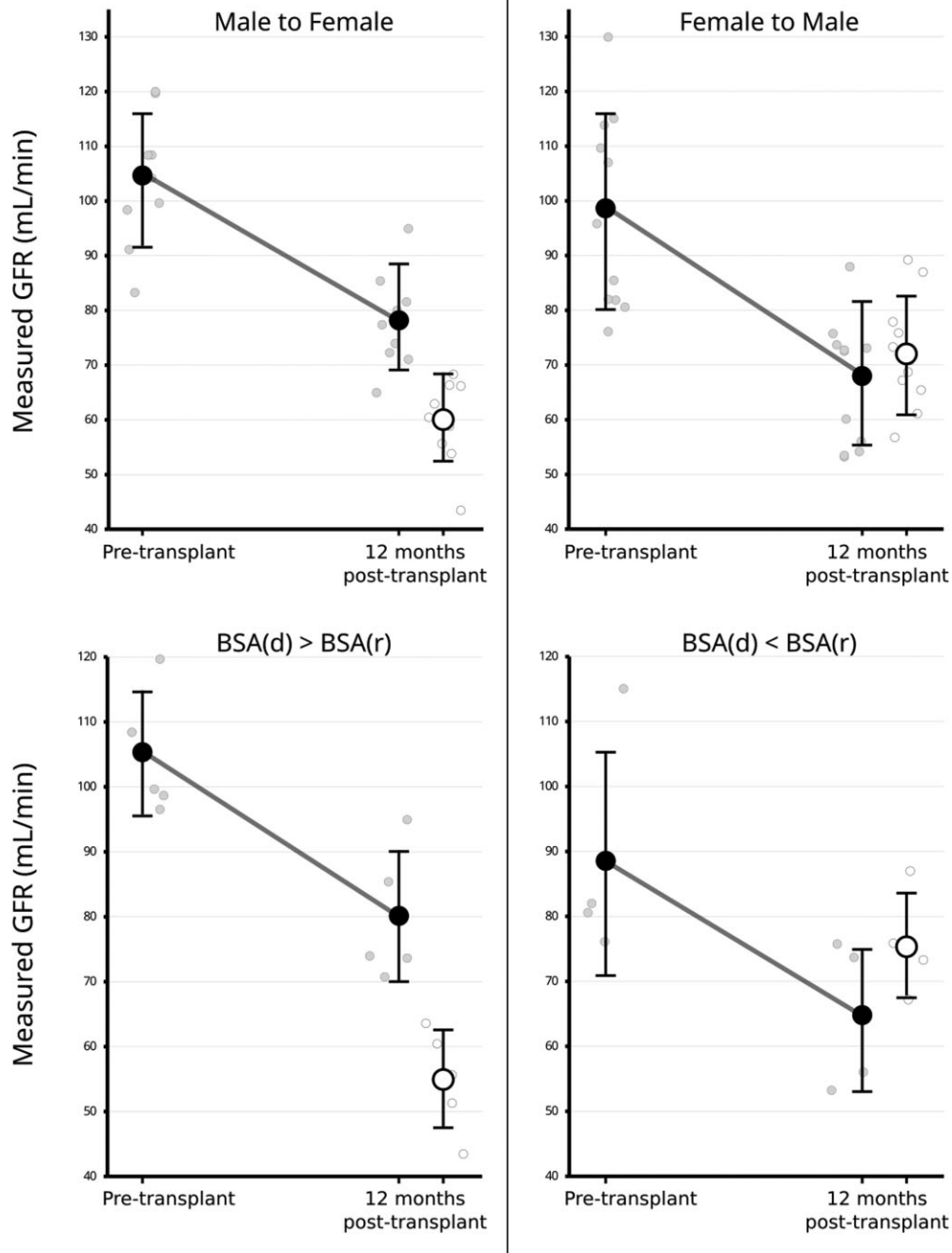
FIGURE 2: Measured GFR changes in donor-recipients pairs grouped by males who donated to females and females who donated to males. (Upper panels) Donors with greater BSA than their recipients. (Lower panels) Donors with lower BSA than their recipients. Donors: black circles; recipients: white circles.

associated with a higher GFR at follow-up (Supplementary data, Table B2).

Sensitivity analysis

Gender mismatch between donors and recipients. In males who donated to females ($n = 9$), baseline mGFR was 103 ± 12 mL/min and decreased to 78 ± 9 mL/min at 12 months after transplantation (Figure 2, upper panels). In females who donated to males ($n = 11$), baseline mGFR was 98 ± 18 mL/min and decreased to

67 ± 12 mL/min at 12 months (Figure 2, upper panels). Finally, 12 months after transplantation, female recipients with a male donor had an mGFR of 60 ± 8 mL/min, whereas male recipients with a female donor had an mGFR of 72 ± 10 mL/min (Figure 2, upper panels).

BSA mismatch between donors and recipients. In donors, a BSA ≥ 1.9 m^2 was large and ≤ 1.8 m^2 was small. The cut-off points were based on exploration of the dataset and reflect extreme values of BSA. Donors with a large BSA who

donated to recipients with small BSA ($n = 5$) had an mGFR at baseline of 104 ± 10 mL/min, which decreased to 80 ± 10 mL/min (-23%) at 12 months (Figure 2, lower panels). Donors with a small BSA who donated to recipients with a large BSA ($n = 4$) had a baseline mGFR of 88 ± 18 mL/min that decreased to 65 ± 12 mL/min (-26%) at 12 months (Figure 2, lower panels). Finally, 12 months after transplantation, recipients with a lower BSA than their donors had an mGFR of 55 ± 8 mL/min, whereas those with a larger BSA than their donors had an mGFR of 76 ± 8 mL/min (Figure 2, lower panels).

DISCUSSION

We evaluated factors that may influence renal function after donation/transplantation and found that a higher GFR at 12 months in both donors and recipients was associated with a higher pretransplant weight. Also, in recipients, changes in weight during follow-up were associated with higher renal function at 12 months. Finally, BSA and gender mismatch between donors and recipients influenced GFR evolution in both groups.

We investigated the impact of metabolic factors in GFR changes in pairs of donors and recipients, considering them a clinical model of reduced renal mass. To avoid the error of eGFR by formulas, we measured GFR with the plasma clearance of iohexol. Also, renal function was not adjusted by BSA since it artificially reduces GFR in obese subjects and increases GFR in lean subjects [20]. Finally, GFR changes were compared in each donor and the corresponding recipient.

We observed that at 12 months after transplantation, recipients could have higher, lower or similar GFR values than their donors and tried to evaluate the factors related with these changes. A GFR higher in recipients than in their donors seems counterintuitive (Group B). A lower GFR in donors could not be attributed to borderline GFR predonation, reduced renal volume or adverse events that could have affected renal function after donation. All donors had excellent levels of renal function evaluated with a gold standard procedure (98 ± 13 mL/min; Group B: Table 2) and the average decrease in GFR after donation was about 25–30%, which is in line with the change reported in the literature [21, 22]. However, the main characteristics of this group of donors were reduced weight and BSA compared with their recipients and the lack of weight increase after donation. Also, recipients were mostly males (90%), with greater weight and BSA predonation, and importantly, experienced a further increase in weight after transplantation. This finding was confirmed in a multivariable analysis showing that in recipients, a higher GFR at 12 months was associated with male gender, greater weight and BSA at pretransplant and at 12 months. Finally, in the subanalysis of recipients larger than their donors (BSA mismatch) or those males who received a kidney from a female donor (gender mismatch), recipients had a higher GFR at 12 months. Thus, in this group the grafts were exposed to different factors that can increase GFR. First, kidneys were implanted in patients with a larger metabolic demand (high body weight and BSA). Second, recipients experienced a major increase in weight and 50% of them developed PTDM, two factors related to glomerular hyperfiltration during follow-up.

In contrast, some recipients had lower GFR than their donors (Group A). This could not be explained by adverse events in recipients or donors. Three recipients in this group had episodes of acute rejection, calcineurin toxicity and AKI. However, the differences in GFR compared with the donors persisted after the exclusion of these patients. In contrast, in this group, recipients were mainly females with lower weight and BSA than

their donors and without relevant weight change after transplantation. Moreover, donors were mainly males, had the highest weight and BSA than the other groups and higher GFR and renal volume than subjects in Group C. In the multivariable analysis in donors, a higher GFR at 12 months was associated with male gender and greater weight and BSA at pretransplant and at 12 months. This finding was supported by the subanalysis of donors larger than their recipients (BSA mismatch) or males who donated a kidney to a female (gender mismatch). Thus, opposite to the previous groups, the grafts were not exposed to a larger metabolic demand or to a major increase in weight during follow-up. The lack of these stimuli may have determined the lower GFR in recipients at 12 months compared with their donors.

In a wide range of mammals, including humans, there is a direct relationship between body size and metabolic rate [23]. From a physiological perspective, the kidney contributes to the excretion of metabolic waste products, so the increased metabolic demand of a large body will induce an increase in GFR. It is known from renal physiology that metabolic demand sets GFR [23]. It may be plausible that the kidneys of small donors grafted in large recipients adapted to the higher metabolic demands by increasing GFR. This adaptive capacity may depend on renal endowment, renal reserve and baseline GFR. Renal reserve was not measured in our study, but we might assume that renal endowment was acceptable, as reflected by the excellent level of GFR before donation. Renal reserve may indicate a better capacity to adapt to a major reduction of nephron mass, i.e. nephrectomy. However, some studies have indicated that renal reserve has no or minimal impact on renal function in the long term [24]. In any case, the scarce studies in the field preclude definitive conclusion. Interestingly, donors in Group C showed lower total kidney volume and GFR than donors in Group A, which may reflect a lower renal endowment even in subjects with excellent GFR. However, these kidneys adapted well to the change in weight of their recipients, as reflected in a comparable mGFR at 12 months between both groups. On the other hand, kidneys from large donors transplanted into small recipients may have down regulated GFR to the lower metabolic demands of a smaller body size. This could also be considered an adaptive capacity of the graft. The relevance of metabolic demand in living kidney donors deserves attention in future studies.

Clearly the adaptation to metabolic demand is not the only factor that can influence renal function in donors and recipients. Obesity is associated with metabolic changes like hyperglycemia, diabetes, dyslipidemia, hyperinsulinemia, insulin resistance and increased levels of angiotensin-converting enzyme and aldosterone [25–28]. In the kidney, these factors promote changes that may increase GFR, i.e. proximal sodium reabsorption, changes in the macula densa, resetting of tubular-glomerular feedback, imbalance of the afferent and efferent arterioles and others. All of the above may explain, at least in part, the increase in GFR in recipients who gained weight and developed PTDM after transplantation, as in the case of recipients in Group B. This may be considered a case of relative glomerular hyperfiltration in patients with reduced renal mass. On the other hand, in donors, overweight may determine the decrease in renal reserve after donation, a fact that may reduce the capacity of single kidneys to adapt to a new environment [29].

In any case, it can be difficult to separate the effect of metabolic demands and obesity in GFR. However, not all the recipients in our study were under the influence of a high metabolic demand. Recipients from Group C showed low BMI at

transplantation but experienced a large increase in weight on follow-up (from 24 to 28 kg/m^2 on average). So in this group, the GFR increase could be attributed only to obesity-induced GFR changes. Taken together, these results seem to indicate that kidneys from living donors with excellent pre-transplant GFR are more plastic than expected, showing the capacity to respond to stimuli like metabolic rate and obesity. The long-term impact of this phenomenon is worth investigating.

Previous studies evaluated the impact of BSA and gender mismatch in living kidney donors and recipients. Tent *et al.* [12], in an elegant study, analyzed almost 300 donor-recipient pairs at baseline and 88 during follow-up with mGFR before and after transplantation. In line with our study, recipients larger than their donors showed an increase in GFR over time and those smaller than their donors showed a mild decrease in GFR, which may reflect the adaptation of the kidney to metabolic demands. Contrary to our results, the authors categorized pairs into those with greater or lesser BSA between donors and recipients using a BSA ratio >1 or <1. The mGFR was not different among groups. Cases with a ratio around 1, i.e. 1.1 or 0.9, may not represent major differences in BSA, a fact that may have minimized possible differences in mGFR between groups. We preferred to analyze donor-recipient pairs based on the observed GFR at 12 months and to select extreme cases of BSA mismatches. So we individualized a subgroup of donors and recipients in whom a greater effect of BSA and weight changes on GFR is expected. Other studies have evaluated renal function in terms of BSA or gender mismatch among donors and recipients but used eGFR, in general adjusted by BSA, which precludes comparison of these studies with ours [30].

This study has limitations. First, it is an exploratory analysis with a limited number of cases. However, the results are in line with other publications, which seems to support the validity of our results [12]. In any case, our results must be tested in larger groups. Second, this is a short-term study, so longer follow-up is needed to analyze the impact of early GFR changes beyond 12 months.

CONCLUSION

In conclusion, in living kidney donation, kidneys are more plastic than expected and suffer the impact of metabolic demands and weight changes of their new host. The long-term consequences of this finding deserve special attention in *ad hoc* designed studies. Furthermore, the observed differences should be taken into account when assessing GFR outcomes in this population.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

A.O. is the CKJ Editor-in-Chief.

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