EVALUATION OF RENAL FUNCTION IN A SPECIFIC POPULATION OF LIVING KIDNEY DONORS

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SUMMARY

Background: The increase in candidates for kidney transplant has led to growth in the number of living donor transplants. Therefore, studies that adequately evaluate the possible long-term consequences of elective transplant nephrectomy are needed.

Objective: To evaluate the possible long-term adverse effects of transplant nephrectomy on the renal function of living kidney donors.

Design: A cross-sectional study.

Participants: Thirty-three living kidney donors registered in the transplant programme of a centre in Alagoas, Brazil.

Measurements: Demographic characteristics, anthropometric measures, clinical data and biomarkers (creatinine, eGFR, microalbuminuria, cholesterol and triglycerides) were measured. Creatinine clearance was calculated using the Cockcroft-Gault and Modification of Diet in Renal Disease formulae.

Results: Of the 33 individuals, 63.63% were female, and the median age was 45 years. Additionally, 24.24% of these individuals had altered blood pressure, 39.39% had altered abdominal circumference (AC) and 36.36% were obese, with a body mass index $\geq$30. Furthermore, 33.33% of these individuals had elevated triglyceride levels. The average eGFR was 97.33 (33.03–175.9) ml/min/1.73 m^2 (CG) and 84.14 (29.4–131) ml/min/1.73 m^2 (MDRD). The microalbuminuria level was altered in 12.12% patients.

Conclusion: Kidney donation is unquestionably a safe procedure. However, a better understanding of the long-term consequences of living donor kidney transplantation is still needed. This knowledge may have important implications for the follow-up of these patients. Our study has demonstrated a non-negligible presence of an early marker of glomerular injury and a decrease in the GFR of some patients, thereby reinforcing the proposal for long-term follow-up of living kidney donors.

KEY WORDS **Chronic kidney disease • Kidney transplantation • Living donors**

BIODATA

Thalyta Rodrigues is a Physician who graduated at the Alagoas State University of Health Science. Her research focuses on investigating kidney donation and its long-term implications.

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INTRODUCTION

Kidney transplantation is considered the best therapeutic option for end-stage kidney disease (ESKD) (Abecassis *et al.* 2008). Kidney transplantation can be performed with living or deceased donors. Ideally, there would be no need for living donation if there were enough deceased donor kidneys of sufficient quality and quantity. Living donor transplantation should be chosen when the donor has HLA compatibility with the recipient. The shortage of deceased donors compared with the increase in transplant demand has led to a notable increase in kidney transplants involving living donors (Delanaye *et al.* 2012).

LITERATURE REVIEW

Studies have shown that at short-term follow-up, living donors recover a large portion of kidney function, with no accelerated loss of its function and the same incidence of Chronic kidney disease (CKD) as the general population (Siebels *et al.* 2003; Fehrman-Ekholm *et al.* 2011). A major concern has been the possible long-term consequences (Gossmann *et al.* 2005; Grams *et al.* 2016; Thiel *et al.* 2016). New research approaches are being developed to compare living kidney donors with healthy non-donors, and some studies have shown an increase in the risk of ESKD in the former (Mjoen *et al.* 2014; Muzaale *et al.* 2014).

Laboratory studies have demonstrated that a significant reduction in renal mass leads to glomerular hyperfiltration and progressive glomerular sclerosis, clinically expressed as proteinuria, azotaemia and hypertension. Higher rates of leptin, which are strongly associated with body mass index (BMI), also lead to proteinuria and glomerular sclerosis (Praga *et al.* 2000). There is also strong evidence of an association between cardiovascular disease and CKD, which is expressed as proteinuria or a reduced glomerular filtration rate (GFR) (Sarnak *et al.* 2003; Van der Velde *et al*. 2011). However, recent studies have not been able to confirm that there is a higher risk of cardiovascular events in living kidney donors compared with non-donors (Garg *et al.* 2012; Reese *et al.* 2014).

Some countries have made the clinical follow-up of living kidney donors mandatory (Rowinski *et al.* 2009). In Brazil, a national registry for kidney donors is still not available, which makes it impossible to evaluate the consequences of nephrectomy on the renal function of the remaining kidney and on the longevity of the donor at long-term follow-up (Medina-Pestana *et al.* 2011). Brazil also does not have any guidelines on the assessment and follow-up of living kidney donors; therefore, rates of follow-up among living kidney donors are unknown. In the Alagoas region, according to the Brazilian Association of Organ Transplantation (ABTO), between July 2004 and June 2015, 240 transplants were performed, 136 of which were performed with living kidney donors.

Therefore, studies that adequately evaluate the possible long-term consequences of elective transplant nephrectomy are needed. Longer follow-up periods, measures of glomerular filtration and microalbuminuria, and other clinical and laboratorial criteria must be taken into consideration when studying this specific population of patients.

AIM OF THE STUDY

The primary aim of this study was to evaluate the long-term consequences of kidney donation on living donor health.

METHODS

SETTING AND SAMPLE

This study was performed at a reference transplant centre located in Alagoas in northeast Brazil after local ethics committee approval was obtained (040662/2014). This observational and cross-sectional study included 33 living kidney donors registered in the transplant programme of the hospital. The donors were contacted and invited to participate in the study; all donors had to sign an informed consent form. Individuals who did not consent to undergo the additional clinical and laboratory tests were excluded from the study.

The kidney donors were separated into the following three subgroups, which were established using the time after the surgical procedure eligibility criterion: five years or less since transplantation (group I), between five and ten years since the procedure (group II) and at least 10 years since the surgery (group III).

PROCEDURES

All patients underwent a clinical evaluation that consisted of anthropometric measures such as weight (kg, kilogram) and height (m, metres), which were obtained by the same examiner using the same calibrated scale to calculate the body index mass (kg/m^2); blood pressure measurement using Korotkoff's auscultatory method; collection of demographic data such as gender (categorised as male or female), age (years) and ethnicity (White, Black or other); and an investigation of oedema or urinary

symptoms through clinical examination and assessment to evaluate the presence or absence of these symptoms.

In the biochemistry analysis, the following data were collected: plasma creatinine, which was used to evaluate renal function through the calculation of creatinine clearance using the Cockcroft-Gault [CG = (140-age) × weight × (0.85 if female)/ 72 × serum creatinine] and Modification of Diet on Renal Disease [MDRD = 186 × (serum creatinine)−1.154 × age−0.203 × 0.442 (if female) × 1.212 (if Black)] formulae. Although not ideal, they have been used with this group of patients before and seem to have the most accurate approximation to the GFR compared with other formulae (Issa *et al.* 2008; Macias *et al.* 2013). Data on the lipid profile (total cholesterol and its fractions and triglycerides) and fasting glucose, which were used to analyse the cardiovascular risk factors, and on microalbuminuria (defined as the excretion of small but abnormal amounts of albumin, 30–300 mg/g), which was used as an early marker of glomerular damage (National Kidney Foundation Kidney Disease Outcomes Quality Initiative 2002) were also collected.

The decision to use the estimated glomerular filtration rate (eGFR), rather than the 24 hour urine collection method, was based on the sample's socio-demographic characteristics. These patients were not receiving follow-up care at any health centre at the time of the study; therefore, we could not perform the 24 hour urine collection because we knew that most patients would not return for a second assessment. Therefore, all the data extracted for this study had to be collected on the same day.

In our study, the kidney donors were defined as hypertensive when their systolic blood pressure was above 140 mmHg or their diastolic pressure was higher than 90 mmHg (Malachias *et al.* 2016). The donors were classified as having dyslipidaemia, when their total cholesterol >200 mg/dl, LDL (low-density lipoprotein) >160 mg/dl, HDL (high-density lipoprotein) <40 mg/dl in men or <50 mg/dl in women and TG (triglycerides) >150 mg/dl (Xavier *et al.* 2013). All patients who had diabetes and patients with CKD were considered at high cardiovascular risk.

The primary variables studied were serum creatinine, eGFR, microalbuminuria, oedema and urinary symptoms. Secondarily, the following variables were examined: sex, age, ethnicity, blood pressure, time post-donation, BMI, glycaemia, and serum total cholesterol, LDL, HDL and triglycerides.

DATA ANALYSIS

A descriptive statistical analysis was performed by calculating the percentage within a confidence interval of 95%. The data were stored, tabulated and analysed using the BioEstat program (5.0 version).

All data were evaluated as the means and standard deviations, when the variables were quantitative and normally distributed or as medians when the distributions were not Gaussian. The Kolmogorov-Smirnov test was used to examine normality. Qualitative variables were evaluated as frequencies and expressed as percentages. To assess the possible correlations between the variables, the Spearman test was applied. $p < 0.05$ was considered significant.

RESULTS

In this study, 33 individuals were included as living kidney donors. Of those individuals, 12 (36.36%) were male, and 21 (63.63%) were female. Their median age was 45 (range: 28–71) years, and the median time since donation was 64 (range: 6–249) months.

All study participants were separated into groups according to the amount of time since their unilateral nephrectomy. Specifically, 15 participants (45.45%) were in group one, 11 (33.33%) were in group two and 7 (21.21%) were in group three.

The descriptive statistics of the variables sex, age, time since donation, eGFR, creatinine, microalbuminuria, systolic and diastolic blood pressure (SBP, DBP), fasting glucose, LDL and HDL cholesterol, triglycerides, weight, BMI, abdominal circumference (AC) and symptomatology are shown by group in Table 1.

Analysing renal function using the CG and MDRD formulae, it was observed that the average eGFR scores were 97.33 (33.03–175.9) ml/min/1.73 m^2 and 84.14 (29.4–131) ml/min/ 1.73 m^2, respectively. The eGFR per group according to these equations is also shown in Graph 1.

For hypothesis testing, the Spearman test was employed to examine the correlation between the eGFR as calculated by the

Variables	GROUP 1	GROUP 2	GROUP 3
Sex			
Female	10 (66.67%)	7 (63.63%)	4 (57.1%)
Male	5 (33.33%)	4 (36.36%)	3 (42.85%)
Age (years)	41 (28–59)	40 (29–51)	58 (48–71)
Time post-uninephrectomy			
Months	24 (6–48)	96(62–120)	148 (121–249)
Years	2 (0.5–4)	8(5.16–10)	12.3 (10.08–20.75)
SBP(mmHg)	120 (90–140)	120(100–130)	130 (110–145)
DBP (mmHg)	77.14 ± 9.74	79.09 ± 6.64	79.57 ± 7.04
Weight (kg)	73.50 (48–89)	72.60 (53–105)	73.70 (54–82)
BMI (kg/m^2)	24.70 (18.98–39.5)	26.70 (23.51–33.47)	27.28 (20.83–32.76)
AC (cm)	88 (65–115)	86 (71–106)	93(80–102)
Oedema	2 (6%)	2 (6%)	0
Glycaemia (mg/dl)	84(70–129)	86 (74–104)	88(76–113)
LDL (mg/dl)	108 (86–372)	108 (76–313)	130 (91–226)
HDL (md/dl)	67.8 (26–133)	56.6 (7.8–178)	89 (32–168)
Triglyceride (mg/dl)	93.66 ± 20.16	97 ± 20.3	69 ± 26.28
Creatinine (mg/dl)	0.9(0.6–1.13)	0.8(0.7–1.38)	1.1 (0.8–1.8)
eGFR-CG (ml/min)	94.32(66.03–159.13)	109.2 (66.04–175.9)	77.24(33.03–107.1)
eGFR-MDRD (ml/min/1,73 m^2)	87.70 (53.4–131)	84.6 (62.8–126.6)	76.1 (29.4–93.6)
Microalbuminuria (mg/g)	8(2–37)	7(2–18)	11 (3–70)

Table 1: Descriptive statistics from a sample of living kidney donors in a transplant centre in Alagoas, Brazil.

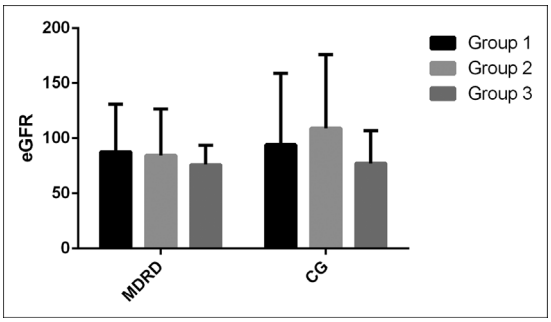
Estimated Glomerular Filtration Rate according to Cockcroft-Gault formula (eGFR-CG); estimated Glomerular Filtration Rate according to Modification of Diet on Renal Disease formula (eGFR-MDRD); systolic blood pressure (SBP); diastolic blood pressure (DBP); low density lipoprotein (LDL), high density lipoprotein (HDL); Body Mass Index (BMI); abdominal circumference (AC).

CG and MDRD formulas with time since uninephrectomy and/or current age. A statistically significant result was obtained with current age only, as shown in Table 2.

The same test was used to compare the variables of time since renal donation and current age as well as eGFR-CG and eGFR-MDRD with the variables SBP, DBP and microalbuminuria. A statistically significant relationship was found between current age and SBP only (rs = 0.3703) (p = 0.0369).

Microalbuminuria prevalence was 12.12% in our sample. When observing cardiovascular risk factors, there was a prevalence of 24.24% of individuals with systolic and diastolic pressure alterations. Additionally, 39.39% of patients had an AC in the obesity class. Of those patients, 55% were female, and 16.66% were male. Furthermore, 33.33% of the patients had elevated triglyceride levels, 6% of patients had above-normal LDL-C values and only 1 (3%) woman had a below-normal HDL-C value. Finally, according to BMI standards, 36.36% of the individuals were obese. Additionally, 2 (6%) patients had diabetes.

A correlation analysis between these variables and eGFR-CG and eGFR–MDRD was performed, which revealed that significant relationships existed between eGFR and HDL-C (rs = 0.38, p = 0.0268); weight and eGFR-CG (rs = 0.4703, p = 0.057); and BMI and eGFR-CG (rs = 0.3974, p = 0.0220).



Graph 1: Estimated glomerular filtration rate (eGFR) per group according to the MDRD and CG formulas.

Variable	eGFR-CG	eGFR-MDRD
Current age	rs = −0.6407	rs = −0.3661
	p = <0.0001	p = 0.0361
Time post-donation	rs = 0.2608	rs = 0.3291
	p = 0.1425	p = 0.0614

Table 2: Correlation between renal function, current age and time post-renal donation in a tranplantation centre in Aiagoas, Brazil.

Spearman Coefficient (rs); estimated Glomerular Rate using Cockcroft-Gault equation (eGFR-CG); estimated Glomerular Filtration Rate using Modification of Diet on Renal Disease formula (eGFR-MDRD).

DISCUSSION

The aim of this study was to evaluate the long-term outcomes of kidney donation on living donor health. The major concern associated with the surgical ablation of 50% of renal mass for donation purposes relates to the possibility of an additional damaging effect caused by compensatory hyperfiltration and haemodynamic changes that can lead to the progressive deterioration of renal function (Ibrahim *et al.* 2006).

The present study showed the presence of microalbuminuria in 12.12% of the sample. It has recently been demonstrated that nephrectomy in kidney donors increases the occurrence of microalbuminuria and susceptibility to hypertension-induced microalbuminuria in this group of patients (Thiel *et al.* 2016). Microalbuminuria is an early marker of glomerular injury (National Kidney Foundation Kidney Disease Outcomes Quality Initiative 2002), and most studies with long-term follow-up of living kidney donors have reported the presence of microalbuminuria in these patients (Gossmann *et al.* 2005; Von Zur-Muhlen *et al*. 2014).

A reduced GFR in the kidney donors in this study was also observed. The MDRD formulae showed greater effectiveness in detecting individuals with a GFR lower than 60 ml/min/1.73 m^2 than the CG formulae, a finding that aligns with previous studies (Louvar *et al.* 2007; Ibrahim *et al.* 2009; Macias *et al.* 2013), which proposed that the MDRD formulae was one of the most viable alternatives when monitoring the renal function of these patients.

It is well known that the GFR tends to decline with age and that this process appears to be a physiologic process of senescence (Glassock & Winearls 2009; Garasto *et al.* 2014). The findings of our study were consistent with those of Ibrahim *et al.* (2009), who found that advanced age, but not donation time and, consequently, the adaptation mechanisms were associated with decreased renal function (Table 2).

The most recent studies reported that the renal function of the donor's remaining kidney does not deteriorate faster than expected based on age, resulting in no excess risk of terminal kidney disease (Fehrman-Ekholm *et al.* 2001; Garg *et al.* 2006; Louvar *et al.* 2007; Ibrahim *et al.* 2009; Oppenheimer Salinas 2010; Wafa *et al.* 2011; Von Zur-Muhlen *et al*. 2014; Lenihan *et al.* 2015).

Hypertension is one of the main modifiable risk factors. Control of such factors can prevent several problems such as coronary, cerebral, renal and circulatory diseases (James *et al.* 2014). High blood pressure is also one of the symptoms of individuals with CKD, and blood pressure levels also increase with age. The existence of this last correlation in our sample data, while the first one was not identified (i.e. reduced GFR was not associated with increased blood pressure) supports the idea that age should be the main factor that influences chronic disease development, including kidney disease, as these associations are compatible with the data in the literature (Hasegawa *et al.* 2012; Dutra *et al.* 2014).

Obesity was another condition that was observed in our sample. Since its incidence is increasing exponentially worldwide and it has been identified as a risk factor of several chronic diseases (Brauer *et al.* 2015), it is important to be aware of its negative impact on patient health. In this study, 36.36% of the individuals were obese (BMI $\geq$30 kg/m^2), and the reasons for this finding are multifactorial. At first, it was thought that elevated BMI would be a problem among donor candidates and that it could possibly lead to their exclusion from the programme. However, the literature showed that high BMI is not associated with significant increased complication rates at transplant centres and that donors with a high BMI can safely donate their kidneys (Uguz *et al.* 2015).

LIMITATIONS

Our study also had certain limitations. The main limitations were the sample size and the lack of a control group, which should have been composed of individuals who were registered as donors on the waiting list for kidney transplant. Such individuals represent a population that is more similar to the subjects in this study, which would allow for comparisons of risk between the donors and the general population. Another limitation was the prescription of antihypertensive drugs (beta blockers, angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors) in patients with hypertension, which could have influenced the results related to blood pressure and microalbuminuria levels.

IMPLICATIONS FOR PRACTICE

The positive finding of an early marker of glomerular injury (microalbuminuria) in some of our patients highlights the necessity for long-term follow-up of living kidney donors. Our study also shows that some living donors may presumably have reduced GFR years after nephrectomy. Although the reason for that finding is not totally understood yet, this information is crucial, and those patients

should be screened annually for the rest of their lives until the long-term implications of donating a kidney are fully comprehended.

Therefore, it is extremely important to make health professionals involved in renal care aware that all living kidney donors need monitoring of their renal function. It is also important to screen these individuals routinely for cardiovascular risk factors and other prevalent chronic diseases such as diabetes and hypertension, as these conditions can negatively affect their quality of life.

CONCLUSION

Kidney transplantation is the best therapeutic option for patients with end-stage renal disease. Kidney donation is unquestionably a safe procedure; however, a better understanding of the long-term consequences of live donor kidney transplant is still needed. This knowledge may have important implications for the follow-up of these patients. Our study showed a non-negligible presence of an early marker of glomerular injury and a decrease in the GFR of some patients, thereby reinforcing the proposal for long-term follow-up of living kidney donors. Transplant centres, physicians and all renal professionals need to be aware of their responsibilities and, thus, guarantee lifelong medical care for these patients. Further research in this field should be done to elucidate which interventions can be performed to avoid long-term risks in these patients.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

AUTHOR CONTRIBUTIONS

TSR: participated in the design and coordination, conducted the interviews and helped to draft the manuscript. ALA: assisted with the data analysis, helped to draft the manuscript and revised it critically for important intellectual content. FAO: assisted with the data analysis and helped to draft the manuscript. JAM: participated in the design, conducted the interviews and helped to draft the manuscript. IM: participated in the design and coordination and completed the interviews. FT: participated in the design and coordination. AFP: served as the principal project leader, conceptualised the study, participated in the design and coordination and analysed the data. The final manuscript was read and approved by all authors.

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