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A retrospective review with prospective follow up of renal function, blood pressure and proteinuria post living donor nephrectomy at Groote Schuur Hospital, Cape Town South Africa.

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Abstract

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Introduction

Renal transplantation is the treatment of choice for patients with end stage renal disease [ESRD]. An increased risk of ESRD has been demonstrated when comparing donors to age matched healthy non-donors. There are no outcome data in Africa on long term donor renal function or mortality. Therefore, this study aimed to assess long term health complications in the living donor population and evaluate risk factors associated with poor health outcomes of the donors.

Methods

This was a retrospective review with prospective follow up of persons undergoing living related donor nephrectomy for renal transplantation, at Groote Schuur Hospital (GSH) from January 2005 to November 2017. We retrospectively analysed baseline demographics, clinical information including blood pressure and renal function (creatinine, eGFR and proteinuria) and compared them with follow up blood pressure and renal function.

Results

The majority of the donors were of mixed ancestry 94/154(61%) and 1st degree relatives 111/154 (72%) of which 63/111 (56.8%) donors were siblings. Hypertension developed in 16/31 (51.6%) donors at follow-up. Those developing hypertension had a higher mean baseline blood pressure (systolic blood pressure 139±11.3 mmHg and diastolic blood pressure 85.5±7.3 mmHg). 21/49(42.9%) developed chronic kidney disease [CKD], of which, 16 donors had an eGFR < 60 ml/min/1.73m^2. In those that developed CKD there was a higher percentage of males (p=0.018) and they were older (p=0.048) at baseline. Baseline systolic and diastolic blood pressures was not statistically different in those that developed CKD. 3/31(9.6%) donors developed diabetes.

Conclusions

In South Africa, CKD is on the rise and the need for kidney donors for patients with ESRD is therefore also increasing.

This study demonstrates that our living donors are at increased risk of CKD and hypertension and therefore need to be followed up more rigorously.

Chapter 1: Literature review

History

Jean Hamburger, a French surgeon, performed the first temporary renal transplant in Paris, France in 1953.(1) The kidney failed after 3 weeks due to graft rejection. This procedure was later perfected in 1954 by Joseph Murray and colleagues who performed the first long term kidney transplant. Transplantation was performed between monozygotic twins to prevent the risk of graft rejection. The life span of the transplanted kidney was 8 years. The introduction of immunosuppression agents made transplantation between genetically unrelated patients possible in 1962.(1)

In the 1960's tissue typing was improved, and new immunosuppressive drugs were developed to address graft rejection. The first kidney transplant in South Africa was done in 1966 in Johannesburg.

Adverse risks to living kidney donors

It was initially thought that living kidney donors were at minimal risk of long-term adverse outcomes. This was shown in numerous studies between 1997 and 2010. (2 - 4). In contrast, multiple studies have shown a decrease in glomerular filtration rate (GFR) (ml/min/1.73m^2) post donor nephrectomy. As far back as the early 70's, Boner *el al.* showed a 35% reduction in GFR in 19 donors followed up 2 to 3 years post donation.(3) Similarly, in 1976 the Mayo Clinic published a study where they followed up 121 donors between 2 weeks and 6-years post nephrectomy and demonstrated a 30 - 40% reduction in GFR.(4) In 2001 Goldfarb *el al.* showed a 28 % reduction in GFR in a group of 70 donors followed up after approximately 25 years post donation.(5) Furthermore two recent studies have also demonstrated an increased risk. (6, 7)

Risk of renal impairment/ESRD post kidney donation

The burden of chronic kidney disease (CKD) is high. In sub- Saharan Africa about 14% of the adult population suffers from chronic kidney disease.(8) The major risk factors are hypertension, diabetes mellitus, HIV infection and glomerulonephritis.(9)

Earlier studies of living donors post nephrectomy showed no increased risk of end stage renal disease (ESRD). Fehrman-Ekholm- *et al (2)*showed an ESRD rate of 0.5% in their donor sample of 1112 donors, which demonstrated no change in the risk of ESRD in post donor nephrectomy patients to that of the general population. A Japanese study which had a cohort of 601 showed ESRD in 3 donors over a 35 year period.(10)

Two recent studies show the contrary, one in Norway(6) and another in America.(7) These studies both demonstrate that a calculated relative risk of ESRD was higher in the kidney donors than in the matched comparison group. There was however a lower absolute incidence of ESRD in kidney donors.

The Norwegian study consisted of 1901 living kidney donors from a single centre, [median follow up 15.1 years, range 1.5 to 43.9 years]. The exclusion criteria for this study consisted of the following: a body mass index[BMI] of less than 17 kg/m^2, and over 30 kg/m^2; any patient with a systolic blood pressure [SBP] above 130mmhg and diastolic blood pressure [DBP] more than 90mmHg and finally patients above the age of 70 years or less than 17 years. They showed that ESRD developed in 0.47% of their living kidney donors and in 0.07 % of health non-donors in the control group, which consisted of 32621 participants. The baseline characteristic of donors and control group were similar.(6)

The second large study confirming increased donor risk was a retrospective review by *Muzaale et al* (2014).(7) It consisted of 96 217 living kidney donors (median follow up of 7.6 years, [IQR 3.9-11.5 years] maximum follow up was for 15years. Healthy non-donors were matched based on education, sex, race, BMI, age, blood pressure and smoking history. ESRD developed in 0.1% of kidney donors and 0.04% of matched healthy non-donors. The risk factors for ESRD development included age (over 60 years) and African American race.

The estimated risk of ESRD in African American living donors was 74.7 per 10000 compared with an estimated risk of 22.7 per 10000 in white living donors. In this study 84% of the donors that developed ESRD were blood relatives of the recipient.

The combined risk factor for ESRD in the above two mentioned studies included: age (60 years or old at time of donation), Africa descent and hereditary cause of renal failure in biologically related donors.(6, 7)

Risk of developing hypertension post kidney donation

Gomez-Olive *et al.* looked at the prevalence of hypertension in 3 sites in South Africa (Agincourt, Dikgale and Soweto).(11) Gender and age variations of the hypertensives at these sites were also reviewed. Hypertension was defined as a SBP of ≥ 140 mmHg or a DBP ≥ 90mmHg, or if a patient was on anti-hypertensives. In these 3 large South Africa cohorts the prevalence of hypertension was between 41.6% and 54.1%.(11)

Risk of hypertension post donor nephrectomy was reviewed by Boudville *et al.* who conducted a meta-analysis which consisted of 5145 kidney donors from 28 countries. Their average age at the time of nephrectomy was 41 years, the average SBP was 121 mmHg and average DBP was 77 mmHg. At 5 years the average blood pressure was 5 mmHg higher than the control group. A limitation of this study was the fact that one third of the donors were lost to follow up and there was a short duration of follow up time. (12)

The findings of increased incidence of hypertension post nephrectomy was shown in the following studies. In a study from Japan 31.1% of donors (Okamoto *et al.*) developed hypertension after 7 - 406 months post kidney donation.(10) FehrmanEkholm *et al. (*1997) (Swedish group) had similar findings.(2) Ibrahim *et al*. (2009) followed up 255 kidney donors 3-45 years post donation. This study showed a prevalence of hypertension of 32.1% in donors post nephrectomy. When the control group was matched to age, gender, ethnicity and BMI of the donor group the prevalence of hypertension was not increased.(13)

A recent study in America with 3700 kidney donors showed that 1126/3700(26%) developed hypertension over a mean of 16.6 ±11.9 years, of which, 4% developed hypertension at 5 years, 10% at 10years and 51% at 40years.(14)

Risk of proteinuria post kidney donation

Garg *et al.* (2006) conducted a systematic review, meta-analysis and meta-regression on 48 studies consisting of a total of 5048 donors. The average donor age was 41 years and creatinine 81 µmol /l. Forty two of the 48 studies quantified the incidence of clinically significant proteinuria. Proteinuria is important as it is considered a sign of early glomerular disease. The total number of donors followed in these studies were 4793 over an average of 7 years. The average incidence of proteinuria in these studies was 12 %. Men were more likely to have proteinuria. (15)

Two studies looked at the risks of microalbuminuria post donor nephrectomy. In 1988, Watnick TJ et al. reported on 29 donors reviewed after 9 -18 years post living donor nephrectomy. They were compared to a control group, of 31, matched to gender, ethnicity and age. Elevated albumin excretion occurred in a third of the donors.(16) The other study consisted of 45 donors followed up 1- 10 years post living donor nephrectomy. The control group consisted of 20, matched to age and gender only. This study showed that 11% of the donors excreted a higher amount of albumin compared to the control group. They showed a pooled risk of microalbuminuria of 3.9% post donor nephrectomy which was statistically significant. Age and blood pressure at time of nephrectomy were not risk factors for the development of proteinuria post donation.(17)

Risk of diabetes post kidney donation

The study by Ibrahim *et al.* consisted of 2919 kidney donors followed up for a mean of 16.8 years post nephrectomy. There were 154/2919(5%) donors who developed diabetes mellitus type 2. The characteristics of those who developed diabetes at follow up were Caucasian ethnicity (95%), male (50.4%) and mean age of 57.5 years. The time from donor nephrectomy to developing type 2 diabetes mellitus was estimated to be 17. 7 ± 9.0 years. 25.3% had a baseline BMI more than 30kg/m^2, 54.6% smoked and the average age at donation was 39.8 ± 11years.(18)

Kidney donors with BMI >30 kg/m^2, male, family history of type 2 diabetes mellitus, age over 45 years and hypertension were associated with an increased risk of diabetes mellitus. The serum creatinine at nephrectomy and smoking history were not found to be risk factors.(18)

Okamata *et al*. prospectively observed 444 living kidney donors, of which, 71 kidney donors were noted with pre-existing impaired glucose tolerance tests. He found no statistically significant difference in the survival rate or perioperative complications in donors with an impaired glucose tolerance test when compared to those with normal glucose tolerance test.(10) KDIGO recommends that potential donors with type 1 diabetes mellitus should not donate a kidney. In patients where an impaired glucose tolerance test or type 2 diabetes mellitus is identified, the decision for donation should be individualised. These potential donors should be counselled on the added risks.

Risk of perioperative morbidity

International literature reports on risk factors for perioperative complications. Patel et al found that obesity, smoking, donor age > 50 years increased the risk of complications as well as centres that performed less than 50 donor nephrectomies per year.(19) Okamoto *et al.* [2009] of 481 kidney donors from a single Japanese centre between 1970 and 2006 showed a rate of major complications of 0.5%. The actual number was 3, a femoral nerve compression, pulmonary embolism and an acute renal failure.(10) Fehrman Ekholm *et al*. [1997] observed a major complication rate of 2% which consisted of pulmonary embolisms and severe bleeding that required a re-look.(2)

African studies including Naicker *et al.* showed that out of 135 living donors, 22 developed post-operative infection (which included chest infections, mild wound sepsis and lower urinary tract infections) and 15 developed surgical complications such as ileus, pneumothorax and prolonged pain.(20)

In a study by Muturi *et al.* (Kenyatte National Hospital, Kenya), which consisted of 84 living donors there were significant post-operative complication after nephrectomy. These included: bleeding 2.4%, ileus 32.1 %, wound infection 6%, urinary tract infection2.4%, pneumonia 2.4 %, atelectasis 21.4 %, persistent pain 67.9%, breach of the peritoneum 1%, breach of the pleural space 3.6% and paraesthesia 15.5%. This unit has the highest rate of renal transplants in East Africa.(21)

Perioperative mortality risk post nephrectomy

Segev *et al*. reported perioperative mortality rate of 3.1 per 10000 donor nephrectomies. Mortality was higher in men, black donors and donors with hypertension. (22).Patel *et al*. reported no perioperative deaths in 3074 donors post nephrectomy. (19) Two Africa studies also reported the same findings. (20)(21)

Long-term mortality risk post Nephrectomy

Long term mortality has also been reported in international studies. Fehram-Ekholm *et al.* observed 430 living kidney donors between 1964 and 1994.There were 41 deaths among the donor group, up to 31years post nephrectomy. The major causes of death were cardiovascular disease and cancer; and the minor causes were pulmonary disease, infections and accidents.(2)

Okamoto *et al*. found in 601 Japanese donors with survival rate of 98% at 5 years, 94.7% at 10 years, 86.4 % at 20 years. Similar rates were reported by Fehram-Ekholm *et al* [1997] at 20 years) The mean interval between nephrectomy and death was 183± 102 months and mean age to death 70 ± 11 years. Survival rate was better when matched to a group in the general population in terms of age and gender.(10) The reason for the difference in survival rate is most likely due to the fact that living kidney donors are normally healthier than the general population and have fewer comorbidities.

In an attempt to align the donors with a control group Segev *et al.* analysed 80347 living kidney donors from the national USA database (NHANES). He used a control group that was matched to age and comorbidities of the living kidney donor group thus his control group was better matched to the donors than previous studies.(22) This study showed no difference in long-term survival rates between the two groups.

On the African continent Muturi *et al*. showed no kidney donor deaths at Kenyatta National hospital Kenya between 2010 and 2014. (21) In a study of living donors conducted in South Africa in 1998, of 135 donors followed up over ten years there was no donor mortality.(20)

Recipient donor relationship

Most studies show that predominantly siblings donate kidneys to recipients. A South African study in 1998 showed sibling donors 57%.(20) In Kenya between 2010 and 2014, 61/84(72.6%) were sibling donors.(21) In a large registry from the United States of America (USA), non-related living donors exceeded sibling donors for the first time in 2010. It reported a decrease from 33.1% to 24.1% for sibling donation. The reason for this change is reported is multifactorial. Decreased cadaver donor waiting times and older population groups requiring kidneys are less likely to have eligible sibling donors as they too are likely to have chronic disorders themselves.(23)

Standard of care post donation

In 2017, Kidney Disease Improving Global outcomes (KDIGO) clinical practice guidelines and care of living kidney donors recommended an individualized follow up care plan post donation with, at least, annual follow up.(24) Routine biochemical and clinical features which should be assessed on follow up are blood pressure, BMI, albuminuria serum creatinine and eGFR. Healthy lifestyles also need to be continuously advocated for as well as support for psychosocial health and well-being. An individualized follow up plan should be created for each donor, including the health care professional who will attend to him/her and the time intervals of follow up.

Conclusion

It was previously thought that kidney donation was safe and low risk. New studies have shed new light and demonstrate that the calculated relative risk of ESRD is higher in kidney donors than in matched comparison groups. However there is a well-documented lower absolute risk of ESRD in kidney donors due to the overall better health profile in this group. The 2017 Kidney Disease Improving Global outcomes (KDIGO) clinical practice guidelines and care of living kidney donors recommended a minimum annual follow up post kidney donation but it is essential that a follow up care plan should be individualized for each donor.(24)

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Chapter 2: Publication ready manuscript

INTRODUCTION

Renal transplantation is the renal replacement of choice for patients with chronic kidney disease. It is more cost effective, with improved survival benefits long-term compared to patients on the waiting list.(1, 2) The lifespan of a kidney graft has significantly improved since the first transplant in 1952. The advances can be accounted for by better immunosuppression, improved tissue typing techniques and improved advances in technical approaches.(1)

Initial studies confirmed that living kidney donor's mortality and risk for long-term adverse health outcomes were low.(3-6) However, the control groups used in these studies for comparison were that of the general population. Due to the stringent selection criteria, the donor subgroup is healthier than the general population hence conclusions from these early studies are questionable.

In contrast to these early studies new information was emerging that demonstrated an increased risk of estimated glomerular filtration rate (eGFR) reduction post donor nephrectomy. As early as the 1970's, two groups demonstrated a 30 - 40% decline in eGFR in donors post donor nephrectomy (7, 8). In 2001, Goldfarb *et al*. also demonstrated a 28% reduction in eGFR in a group of 70 donors followed up 25-years post donation.(9)

Two recent large landmark studies have compared donors to age-matched healthy non-donors. Mjøen G *et al.* demonstrated a 3 to 4 times increased risk of developing end stage renal disease [ESRD] with median time to development of ESRD as 18.7 (10.3 - 24.3) years.(10) Muzaale AD *et al* confirmed this by stating an increased lifetime risk of ESRD (90 per 10000) post donation.(11) The donor risk factors for progression to ESRD from these 2 studies included age of 60 years or greater, African descent and hereditary cause of renal failure in biological relatives.(10, 11)

There are no reported outcome data in Africa on donor renal function or mortality post donor nephrectomy. This is essential considering that a third of our transplant programme currently consists of living related donors with Africans constituting 45% of the living donors.(12) Therefore, this study aimed to assess long term health complications in the living donor population i.e. renal dysfunction, proteinuria and

hypertension. Secondary objectives included evaluation of risk factors associated with poor health outcomes of the donors.

METHODS

This was a retrospective review with prospective follow up of persons undergoing living related donor nephrectomy for renal transplantation, at Groote Schuur Hospital (GSH) from January 2005 to November 2017. The study received approval from the Human Research Ethics Committee of the University of Cape Town (HREC 756/2016). All living kidney donors during the above time period were included for the baseline analysis. All donors were above the age of 18 years. There were no exclusion criteria.

Retrospective data were collected from donor medical folders and from electronic records, including NHLS laboratory reports. The following demographic data were collected at the time of donation: donor age, gender, ethnicity and relation to recipient. The following clinical and biochemical parameters were measured including blood pressure (mmHg), serum creatinine (µmol/l), estimated glomerular filtration rate (eGFR) (ml/min/1.73m^2) and urine albumin creatinine ratio (ACR) (mg/mmol).

After retrospective data were collected consenting patients were followed up prospectively within the renal unit at GSH. Donors were reviewed clinically by the research doctor and transplant co-ordinator.

At follow up, donors were evaluated for evidence of hypertension, diabetes and chronic kidney disease. The patients were followed up for one-year post nephrectomy. The information collected was compiled from patient records and tabulated. Diabetes was not specifically tested for; it was determined by self-reporting by the patient for the development of diabetes since donor nephrectomy. We defined chronic kidney disease as an eGFR less than or equal to 60 ml/min/1.73m^2 for more than 3 months. Significant proteinuria was defined as an albumin creatinine ratio more than 3 mg/mmol. Hypertension was defined as a raised systolic blood pressure (SBP) more than 140 mmHg and diastolic blood pressure (DBP) more than 90 mmHg..

Each donor underwent a clinical examination. The following clinical parameters were measured: blood pressure (mmHg), height (meters), weight (kg), body mass index

(BMI) (kg/m^2) and urine dipsticks. In patients where an elevated BP was found, 3 repeat BP readings 20 minutes apart were taken.

The lowest value was then taken for evaluation. The following biochemical investigations were performed: urine albumin creatinine ratio [mg/mmol], serum creatinine (µmol/l) and eGFR (ml/min/1.73m^2). The eGFR was calculated using the CKD-EPI formula. Patients with abnormal laboratory results were called and referred for further investigation and management. Clinical and laboratory information was searched for from medical and electronic records in those patients who did not make their follow up appointment.

Data was collected of donors that participated in this study, of donors that missed their appointment for the study but had partial data from folders/laboratory systems and of uncontactable donors who had partial data from folders and laboratory system.

Statistics

Patient demographics are summarised using descriptive statistics. Categorical variables are presented as frequencies and proportions. Categorical variables were analysed using the Chi-Squared analysis and Fisher's exact test was used to compare the data. Continuous variables are reported as means and standard deviations. Students t test was used to compare continuous data.

When more than two groups were compared the Pearson's Chi-Squared test was used to compare categorical variables and for continuous variables one-way analysis of variance was used.

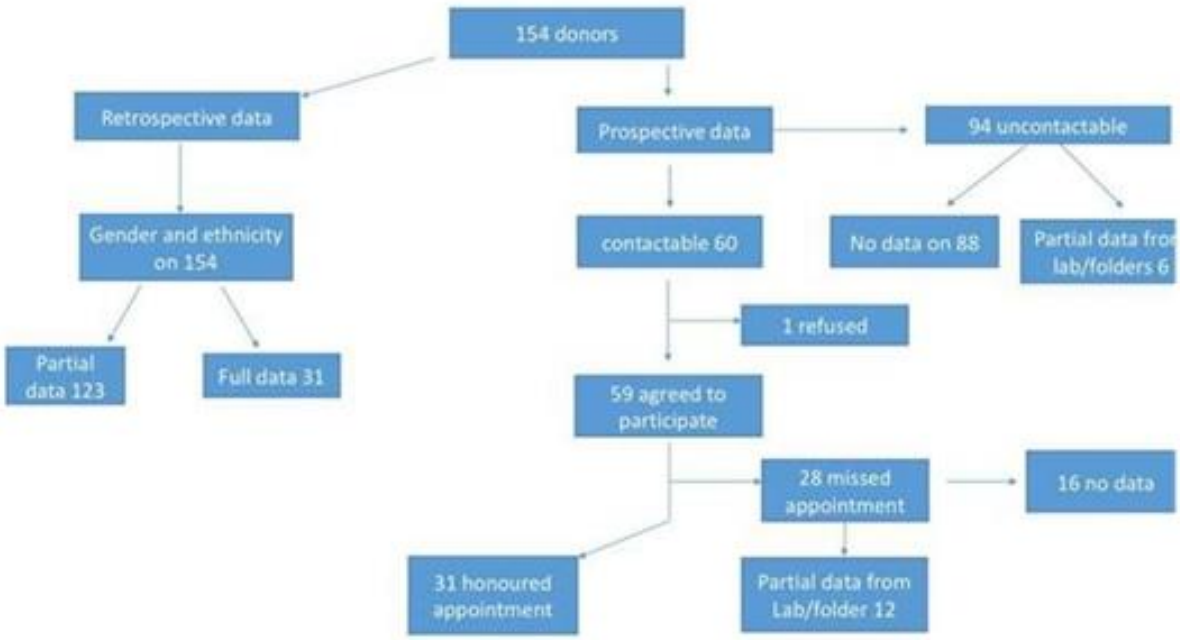
When there were paired data available for analysis continuous variables were analysed using the Paired samples t test. A p value of <0.05 was considered statistically significant.

Patients who had developed hypertension, diabetes mellitus, albuminuria or chronic kidney disease at the time of follow up were reviewed. Their baseline and follow up data were compared with those that did not develop each specified disease. Categorical variables were compared with a t test and the Chi squared analysis was used to compare proportion.

Results

In total, 154 kidney donor nephrectomies were performed between January 2005 and November 2017. We were able to get gender and race for all 154 donors. Partial retrospective data were obtained for 123 donors and full data for 31 donors. There were 60 donors that were able to be contacted for prospective follow up. Fifty-nine consented to be part of the study. Only 31 donors kept their appointments for prospective follow up. Of the 28 that missed their appointment, there were 12 patients where information was able to be obtained from folders and/or the electronic records.

FIGURE 1. The study flow diagram



Baseline Characteristics Prior to Nephrectomy

Table 1 describes the baseline characteristics of the donors at the time of nephrectomy. There were 66/154 (42.9%) males with a mean age of 40.1 ± 9.8 years. There were 88/154 (57.1%) female donors with a mean age of 35.4 ± 9.2 years. The females were significantly younger (p=0.01). The racial breakdown of the

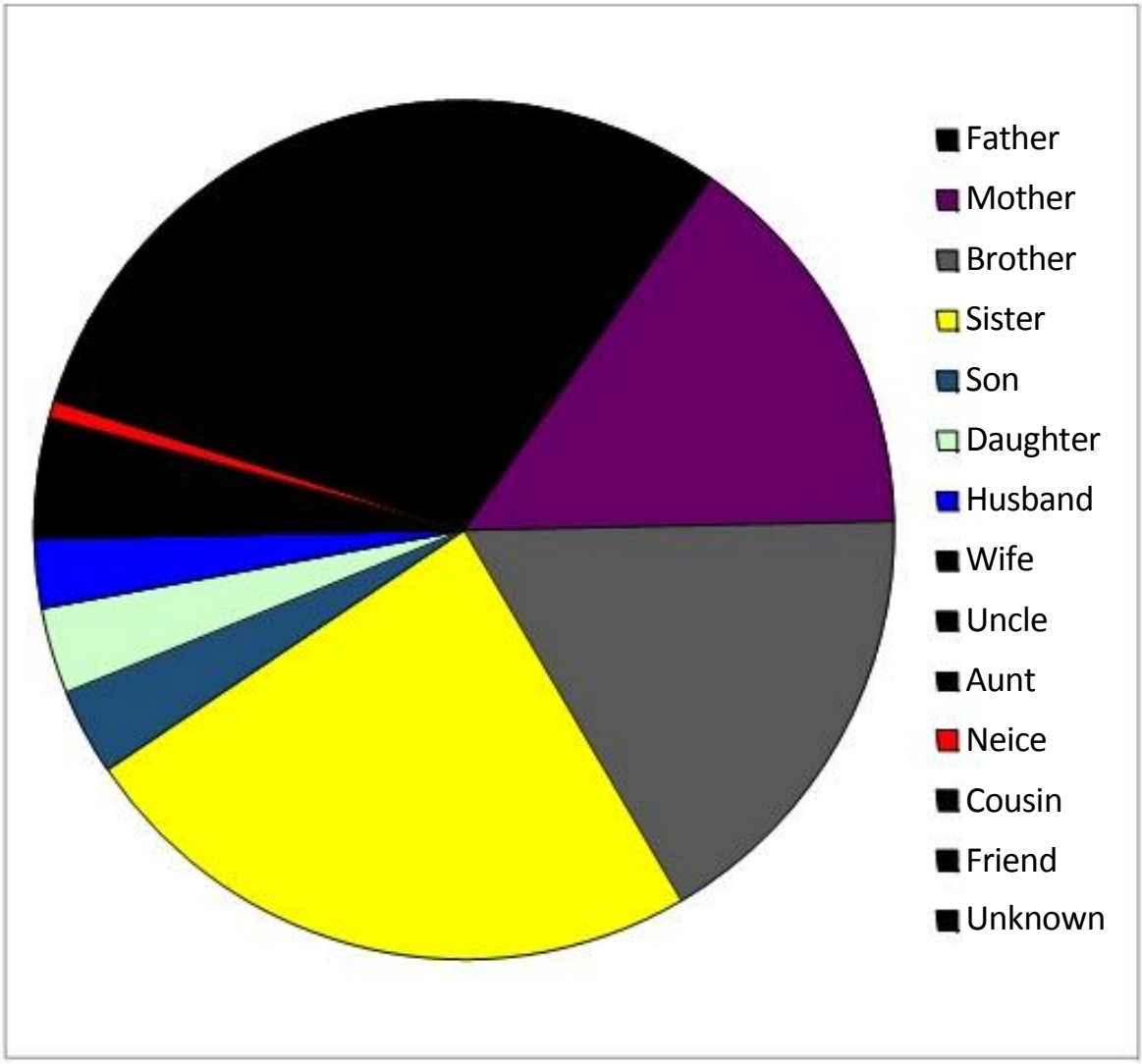
donors consisted of 94/154 (61%) mixed race, 36/154 (23.4%) blacks and 24/154 (15.6%) whites. There are limited retrospective data on BP, creatinine, eGFR and albumin creatinine ratio (ACR) for 123 donors and these data are presented in Table 1. Figure 2 demonstrates the relationship of the donor to recipient. The majority of the donors were 1st degree relatives 111/154 (72%), 63/111 (56.8%) being siblings.

Table 1: Baseline donors characteristics prior to nephrectomy.

Variables	N	Mean± SD	Range
Age (years)	108	37.5±9.8	22.0-64.0
SBP (mmHg)	41	127.2±13.2	90.0-153.0
DBP(mmHg)	41	77.2±8	59.0-98.0
eGFR (ml/min/1.73m^2)	70	105.6±20	59.4-175.4
Creatinine (µmol/l)	76	73.5±15.3	43.0-106.0
ACR (mg/mmol)	28	0.64±0.65	0.0-2.2

*eGFR-estimated glomerular filtration rate, ACR- albumin creatinine ratio, SBP-systolic blood pressure, DBP-diastolic blood pressure

Figure 2: Relationship to recipient



Prospective follow up:

Within the donor cohort, hypertension developed in 16/31(51.6%) donors, diabetes mellitus in 3/31 (9.6%) and chronic kidney disease in 21/49 (42.9%). The 49 donors assessed for impaired renal function comprised of the 31 donors that participated in this study plus 12 donors that missed their appointment for the study but had partial data from folders/ laboratory system plus 6 donors of the uncontactable donors who had partial data from folders/laboratory system. There was clinically significant Proteinuria in 9/47 (19.1%) of donors at follow up. The 47 donors prospectively assessed for proteinuria comprised of the 31 donors that participated in this study plus 10 donors that missed their appointment for the study but had partial data from folders/laboratory system plus 6 donors of the uncontactable donors who had partial data from folders/laboratory system.

Hypertension

There were 31 patients who prospectively presented for study follow-up. Table 2 compares the biochemical and demographic parameters of those donors at nephrectomy and at follow up post nephrectomy who develop hypertension with those who did not. The statistically significant findings in those developing hypertension include: a higher mean baseline SBP and DBP: 139/86 mmHg in the group that developed HPT versus 128/76mmHg in the normotensive group (SBP p value = 0.018 and DBP p value = 0.012). The donors who developed hypertension had a longer follow up duration post nephrectomy, 101 vs. 69 months (p value = 0.007). Age was not statistically different at baseline but by follow-up those who developed hypertension were significantly older. At baseline, the non-hypertensive donor's mean age was 35.6 ±11.2 years vs the mean age of donor's that developed hypertension was (43.6 ± 8.5 years p = 0.92) and at follow up the non-hypertensive donor's mean age was (43.1±11.9 years vs the hypertensive donors mean age 52 ± 8.7 years (p = 0.024).

Renal function, albuminuria and BMI were not different at baseline or at follow up.

Table 2: Comparison of donor that developed hypertension vs normotensive donors at follow up.

	Donors that were normotensive at follow up		**Donors that developed Hypertension**		
	N (%)	Mean ± SD	N (%)	Mean ± SD	P value
Baseline data:					
Age(years)	24	35.6±11.2	16	43.6±8.5	0.092
Male	12 (44.4)		8(50)		
Female	15 (55.6)		8(50)		
Black	4 (14.8)		3(18.8)		P=0.868 for race
Mixed	19 (70.4)		10(62.5)		
White	4 (14.8)		3(18.8)		
SBP (mmHg)	25	127.6±9.8	6	139±11.3	0.018
DBP (mmHg)	25	76.2±7.7	6	85.5±7.3	0.012
eGFR (ml/min/1.7	23	107.4 ±23.9	10	102.3±20	0.563

3m^2)					
Creatinine (µmol/l)	23	74.5±149	10	73.1±15.6	0.808
ACR (mg/mmol)	9	0.3±0.34	6	0.8±0.64	0.083
BMI (kg/m^2)	15	25.6±5.6	16	28.3±4.4	0.150
Follow up data:					
SBP (mmHg)	15	127.9±8.5	16	165.2±24.1	0.000
DBP (mmHg)	15	76±7.0	16	96.5±13.4	0.000
Creatinine (µmol/l)	26	97.3±20.7	15	109.9± 34.7	0.237
eGFR (ml/min/1.73m^2)	26	76.7±22	15	63.8±18.9	0.064
ACR (mg/mmol/0	24	2.5±8.7	16	3.1±5.2	0.811
Time (months)	15	69.3±32.6	16	101.9±30.3	0.007
Age (years)	15	43.1±11.9	16	52±8.7	0.024
Complications that arose in donors N%					
	N	%	N	%	
CKD	8	32	9	60	0.139
DM	1	6.7	2	12.5	1.000

Cr-creatinine, SBP- systolic blood pressure, DBP-diastolic blood pressure, eGFR- estimated glomerular filtration rate, ACR-albumin creatinine ratio, HPT - hypertension, DM- diabetes mellitus, CKD –chronic kidney disease

Diabetes Mellitus (DM)

There were 31 donors questioned prospectively for diabetes mellitus (DM). Three donors developed diabetes (9.6%). All were male, 2 with hypertension and all of mixed ancestry. Although not statistically significant the 3 donors were older (mean 41.3±6.7 years vs 38.5±11.1 years) than those who did not develop diabetes (p=0.675). The baseline BPs in the donors that developed DM were: 152/90mmHg, 118/70mmHg and 130/80mmHg. At follow up their mean BP was 176 ± 43.3/ 104.7±21.5 mmHg compared with 144.1 ± 22.7/ 84.6±13.1mmHg for the non-DM donors (p= 0.042 and 0.024) Baseline BMIs were: 21.5, 22 and 23.1 kg/m^2 respectively. The mean follow-up BMI was 28.3±4.4 kg/m^2, which was higher than donors that did not develop DM (25.9 kg/m^2), however this was not statistically significant (p= 0.445). The mean follow-up time post nephrectomy of non-diabetic donors was 70.1±40.7 months compared to 118±10.6 months for the diabetic donors. Two out of the 3 donors that developed DM also had CKD.

Chronic Kidney Disease (CKD)

The study evaluated 49 donors for CKD. Twenty-one (42.9%) had evidence of CKD at follow up; 16 had an eGFR <60ml/min/1.73m^2 and 9 had an elevated ACR (5 had both). Baseline eGFR was significantly higher in the non-CKD group (mean 113.7±20.2ml/min/1.73m^2) vs CKD group (90±17.2ml/min/1.73m^2) (p = 0.01). Those who developed CKD were older both at baseline and at follow up. The mean age of the donors who didn't developed CKD and those who did was 34.8 years vs 42.1 respectively, at baseline (p = 0.018) and at follow up 39.1 years vs 48.8 years, respectively (p = 0.005). The CKD patients were reviewed after a longer period, 79.8±42.3 months compared to 57±37.6 months for the non-CKD patients. There were no significant differences in baseline and follow up BPs based on the development of CKD. Males had a statistically significant increased risk of developing CKD (p=0.048). In those developing CKD, 9/21(42.9%) also had HPT and 2/21(9.5%) developed DM.

Table 3: Comparison of donor that developed CKD vs normal creatinine on follow up.

	Donors with normal renal function at follow up		**Donors that developed CKD**		
	N (%)	Mean ± SD	N (%)	Mean± SD	P value
Baseline data:					
Age(years)	26	34.8±9.1	20	42.1±10.9	0.018
Male	9(32.1)		13(61.9)		0.048
Female	19(67.9)		8(38.1)		
Black	4(14.3)		2(12.2)		0.117 for race
Mixed	17(60.7)		18(85.7)		
White	7(25)		1(4.8)		
SBP (mmHg)	18	126±11.4	11	131.5±10.8	0.214
DBP (mmHg)	18	75.3±7.8	11	80.1±9.4	0.148
eGFR (ml/min/1.73 m^2)	22	113.7.7±20.2	14	90±17.2	0.010
Creatinine (µmol/l)	24	68±14.2	14	84.4±12.7	0.010
ACR (mg/mmol)	11	0.7±0.8	8	0.5±0.3	0.462
Follow up data:					
BMI (kg/m^2)	22	25.5±5.7	17	26.1±4.3	0.712
SBP (mmHg)	16	142.3±24.6	13	153.8±29.2	0.261
DBP (mmHg)	16	83.0±16.9	13	91.5±12.3	0.139
Creatinine (µmol/l)	28	88.6±17.7	21	124.2±30.9	0.000
eGFR (ml/min/1.73 m^2)	28	81.6±18.0	21	56.3±14.9	0.000
ACR (mg/mmol)	28	0.5±0.7	18	6.3±10.5	0.034
Time in	26	57.5±37.6	21	79.8±42.3	0.063

months					
Age (years)	28	39.1±10.9	21	48.8±12.3	0.005
Complications that arose in donors N%					
	N (%)			**N (%)**	
HPT	6 (26.1)		HPT	9 (52.9)	0.107
DM	1 (4.3)		DM	2 (11.8)	0.545

Cr-creatinine, SBP- systolic blood pressure, DBP-diastolic blood pressure, eGFR- estimated glomerular filtration rate, ACR-albumin creatinine ratio ,HPT-hypertension, DM-diabetes mellitus,CKD-chronic kidney disease

Table 4: Mean changes of variables over time

	N	Baseline	Follow Up	P value
SBP (mmHg)	20	130.3±12.6	141.2±125.8	0.056
DBP (mmHg)	20	77.5±9.3	83.4±14.5	0.036
eGFR (ml/min1.73m^2)	39	104.8±22	74.4±20.2	0.000
Creatinine (umol/l)	39	73.9±15.7	97.8±22.6	0.000
ACR (mg/mmol)	18	0.6±0.6	3.8±10.4	0.202

Systolic blood pressure – SBP, diastolic blood pressure – DBP, estimated glomerular filtration rate - eGFR , albumin creatinine ratio - ACR

The data from the individuals with repeated measures at baseline and follow up clearly demonstrate that renal function deteriorated over time and blood pressure rose in these donors. These changes were statistically significant for renal function. While the rise in blood pressure was not statistically significant, a blood pressure increase of 11/6mmHg is clinically significant.

Discussion

This study was a retrospective review with prospective follow up of renal function, blood pressure and proteinuria after living donor nephrectomy at Groote Schuur Hospital, Cape Town, South Africa. It adds to the very limited existing outcome data on donor well-being post nephrectomy in Africa.

The majority of donors were of mixed ancestry 94/154 (61%) and 1st degree relatives 111/154 (72%) of which 63/111 (56.8%) donors were siblings. When assessing the sibling distribution, 37/63(58.7%) were sisters and 26/63 (41.3%) were brothers. This is similar to what is reported in other African transplant settings. (13, 14) In a large registry from the United States of America (USA), non-related living donors exceeded sibling donors for the first time in 2010.(15) It reported a decrease from 33.1% to 24.1% of sibling donation. The reason for this change is reported as being multifactorial and includes decreased cadaver donor waiting times and older population groups requiring kidneys are less likely to have eligible sibling donors as they too are likely to have chronic disorders themselves.

The ethnic profile of the Western Cape compared to the donor population is outlined in Table 5. Donation is therefore aligned with the known ethnic distribution in the region. The low percentage of black donors in our study is in keeping with global statistics, which show a low frequency of black living related donors.

Table 5: Ethnic general population vs donor population in Western Cape

Ethnic group	**General population**	**Donor population**
Mixed ethnicity	48.8%	61%
blacks	32.8%	23.4%
whites	15.7%	15.5.%

The reported prevalence of HPT in South Africa has been documented to be as high as 54%.(16) This compares to the degree of HPT established in this cohort, where 16/31 (51.6%) the donors developed hypertension. A recent study from the U.S.A showed the development of hypertension post kidney donation to be 26.8% after a mean follow up time of 16.6 ±11.9 years, of which, 4% developed hypertension at 5 years , 10% at 10 years and 51% at 40years.(17) In this study hypertension was diagnosed for the first time in 9/16 (56.3%) donors. Therefore if it wasn't for this study these donors with newly diagnosed hypertension would have gone undiagnosed and untreated. The follow-up time in this study was 69.3±32.6 months (5.75 years). Hypertension potentially leads to target organ damage, which can be prevented by early identification and treatment. This high rate of hypertension emphasises the need for regular standard follow-up protocols in our donors. There was no statistically significant difference between ethnic groups for those who developed hypertension.

Our results on the development of CKD in donor compared to other studies

This study identified 21/49 (42.8%) donors who developed CKD. There was a significant decline in renal function (baseline mean eGFR 105.9±20.3ml/min/1.73m^2 versus follow up eGFR 71.0±20.5ml/min/1.73m^2 with a p value of < 0.0001). The mean follow-up time for donors that developed CKD was 79.8±42.3 months. The CKD identified in this study is significantly higher than the 14% reported prevalence of CKD in sub-Saharan African(18). In a large American study on donor nephrectomy follow-up, Muzaale *et al.* reports that 0.1% of donors develop ESRD, in a mean of 8.6±3.6 years post donation, which was higher than the control group of matched healthy donors of 0.04%. This study did not evaluate break down in staging of CKD.(11) None of our donors developed ESRD however the numbers were much smaller (n =96217 vs n= 154) and the mean follow-up time shorter.

Mjoen *et al.,* reviewed 1901 living kidney donors from a single centre in Norway, (median follow up 15.1 years, range 1.5 to 43.9 years). They showed that ESRD

developed in in 0.47% of their living kidney donors and in 0.07 % of health non-donors in the control group, which consisted of 32621 participants.(10) This study also only looked at ESRD and not CKD stages as defined by KDOQI.

The donor risk factors for progression to ESRD from the donor nephrectomy studies by Mjoen *et al.* (10) and Muzaale *et al.* (11) included age of 60 years or greater, African descent and hereditary cause of renal failure in biological relatives. United states renal data system (USRDS) also shows an increased risk of ESRD in African Americans. Other identified risk factor for ESRD progression in the USRDS are hypertension, diabetes mellitus, cardiovascular disease and obesity.(19) In the Cape Town study, when reviewing baseline characteristics and the development of CKD only age (p=0.018) and male gender (0.048) were risk factors.

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Ethnicity **and CKD**

This study did not show an increase in CKD in African ethnicity. However, the majority of donors were of mixed ethnicity and not Black Africans. APOL 1 gene is a known risk factor for CKD in black South Africans. (20)

However the study of APOL 1, to the best of our knowledge, has not been performed in those with mixed ancestry. The number of black Africans in this cohort was too small to draw meaningful conclusions.

Diabetes Mellitus and CKD

In South Africa 7% of adults aged 21- 79 years have DM.(21)Three of 31 (9.6%) donors developed diabetes. Studies reviewing risk factors for developing DM post donation include male gender, hypertension, proteinuria and BMI >30kg/m^2.(22)All 3 donors that developed DM in this study were male, had proteinuria, and had an increased BMI (mean 28.8±4.4kg/m^2). Two patients had also developed hypertension.

Standard of care for follow up of donors:

In 2017, Kidney Disease Improving Global outcomes (KDIGO) clinical practice guidelines and care of living kidney donors recommended a personalized follow up care plan post donation with annual follow up.(23) The recommended follow-up should include routine biochemical and clinical features including blood pressure, BMI, albuminuria serum creatinine and eGFR. Also, healthy lifestyles need to be continuously advocated and as well as support for psychosocial health and well-being.

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During the study period of transplantation of this cohort (2005 - 2017) the protocol of follow up of post donor nephrectomies at our institute states: “blood pressure, BMI, albuminuria serum creatinine and eGFR to be measured every 3 months for the first year then annually”. This follow up would preferably be done at GSH or the donor referred to the nearest healthcare facility with a doctor who is capable of monitoring the donor. Currently there is poor adherence to the follow up protocol and more effort needs to be made to emphasise to donors the importance of follow up to prevent
complications and to detect them at an early stage.

Limitations to this study

The limitations to this study are as follows: Firstly, a retrospective folder review for baseline data was limited by a large amount of missing data. Secondly, there was a high loss to follow up rate within the cohort. Thirdly, there were small numbers of patients who were prospectively followed up. Lastly, no fasting glucose or glycosylated haemoglobin was performed to diagnose diabetes within the cohort.

The sample size was small, this made the interpretation of statistical significance challenging. Univariate and multivariate modelling for linear regression models was not performed therefore predictors for poor outcomes could not be stated

Conclusion

This study is important as it gives information regarding donor follow-up in a resource limited setting. It demonstrates that kidney donors in a single centre from Cape Town, South Africa do have an increased risk of developing CKD and hypertension although the degree of hypertension may be aligned with the current prevalence in South Africa.

This is a vulnerable group due to the high risk of post nephrectomy complications. The donor needs to be well informed about the risks of kidney donation and counselled extensively before donation as this can be a life altering event.

The loss to follow up rate in this study was high. Early identification of complications could potentially prevent long term sequelae. Therefore, a more intensive follow up plan needs to be implemented with the importance of follow-up strongly emphasized.

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