Long-term Safety of Living Kidney Donation in an Emerging Economy

S. Adibul Hasan Rizvi, FRCS,[1] Mirza Naqi Zafar, PhD,[2] Fatema Jawad, FRCP,[3] Tahir Aziz, MD,[4] Zafar Hussain, MS,[1] Altaf Hashmi, MS,[1] Manzoor Hussain, MS,[1] Fazal Akhtar, FRCP,[4] Ejaz Ahmed, FRCP,[4] Rubina Naqvi, MD,[4] and S A Anwar Naqvi, MBBS, MHPE[1]

Background. Long-term follow-up and management of donors was undertaken in a specialist kidney transplant unit in Pakistan to identify risk and prevent adverse outcomes in living related kidney donors. **Methods.** In an observation cohort study between 1985 and 2012, 3748 donors were offered free medical follow-up and treatment 6 to 12 months after donation and annually thereafter. Each visit included history, physical examination, blood tests for renal, lipid, glucose profiles, and 24-hour urine for proteinuria and creatinine clearance. Preventive intervention was undertaken for new onset clinical conditions. Donor outcomes were compared with 90 nondonor healthy siblings matched for age, sex, and body mass index. **Results.** Of the 3748 donors, 2696 (72%) were in regular yearly follow-up for up to 27 years (median, 5.6; interquartile range, 7.9). Eleven (0.4%) died 4 to 22 years after donation with all-cause mortality of 4.0/10 000 person years. Six (0.2%) developed end-stage renal disease 5 to 17 years after donation, (2.7/10 000 person years). Proteinuria greater than 1000 mg/24 hours developed in 28 patients (1%), hypertension in 371 patients (13.7%), and diabetes in 95 patients (3.6%). Therapeutic intervention-controlled protein was less than 1000 mg/24 hours, blood pressure was below 140/90 mm Hg, and glycemic control in 85% up to 15 years after onset. Creatinine clearance fell from 109.8 ± 22.3 mL/min per 1.73 m^2 predonation to 78 ± 17 at 1 year, 84 ± 19 at 5 years, and 70 ± 20 at 25 years. Comparison of 90 nondonor sibling and donor pairs showed significantly higher fasting glucose and hypertension in nondonors. **Conclusions.** Long-term follow-up of donors has demonstrated end-stage renal disease in 0.6% at 25 years. Regular follow-up identified new onset of disease and allowed interventions that may have prevented adverse outcomes.

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Living donors provide the majority of kidneys available for transplantation in emerging economies.[1] Long-term consequences for the living donor must be understood to optimize selection criteria, maximize donor safety, and prevent adverse consequences of donation.[2] Studies over the last few decades, mostly from developed countries, suggest that health and life expectancy of kidney donors are similar to or better than the general population.[3-6] Recently, however, studies from Norway and the United States have shown increased relative risk of end-stage renal disease (ESRD) in donors compared with healthy nondonor populations.[7,8]

In emerging economies, the long-term outcome of kidney donors remains largely unknown with few reports on short-term outcomes.[3,9] Furthermore, reports on donor safety from developed countries may not be applicable to donors in emerging economies because paucity of healthcare facilities and economic constraints prevent follow-up care. In emerging economies, where per capita income is less than US $5000, expenditure on health less than 6% of GDP, 25% of the population live below poverty line, and greater than 50% rural dwellers health care is not a priority.[10] In fact, in Pakistan, where expenditure on health is 1.3% of GDP, renal

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[1] Department of Urology and Transplantation, Sindh Institute of Urology and Transplantation, Civil Hospital, Karachi, Pakistan.

[2] Department of Pathology, Sindh Institute of Urology and Transplantation, Civil Hospital, Karachi, Pakistan.

[3] Department of Diabetology, Sindh Institute of Urology and Transplantation, Civil Hospital, Karachi, Pakistan.

[4] Department of Nephrology, Sindh Institute of Urology and Transplantation, Civil Hospital, Karachi, Pakistan.

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S.A.H.R. participated in design, acquisition, interpretation, drafting, critical review, final approval, and agreed to be accountable for the work. M.N.Z. participated in design, acquisition, interpretation, analysis, drafting, critical review, final approval, and agreed to be accountable for the work. F.J. participated in design, acquisition, interpretation, analysis, drafting, critical review, final approval and agreed to be accountable for the work. T.A. participated in design, acquisition, interpretation, analysis, drafting, critical review, final approval and agreed to be accountable for the work. Z.H. participated in acquisition, interpretation, drafting, critical review, final approval and agree to be accountable for the work. A.H. participated in acquisition, interpretation, drafting, critical review, final approval and agreed to be accountable for the work. M.H. participated in acquisition, interpretation, drafting, critical review, final approval and agreed to be accountable for the work. F.A. participated in design, acquisition, interpretation, drafting, critical review, final approval and agreed to be accountable for the work. E.A. participated in design, acquisition, interpretation, analysis, drafting, critical review, final approval and agreed to be accountable for the work. R.N. participated in acquisition, interpretation, drafting, critical review, final approval and agreed to be accountable for the work. S.A.A.N. participated in design, acquisition, interpretation, drafting, critical review, final approval and agreed to be accountable for the work.

Correspondence: S Adibul Hasan Rizvi, FRCS, Sindh Institute of Urology and Transplantation Civil Hospital, Karachi 74200, Pakistan. (info@siut.org; arizvi@siut.org).

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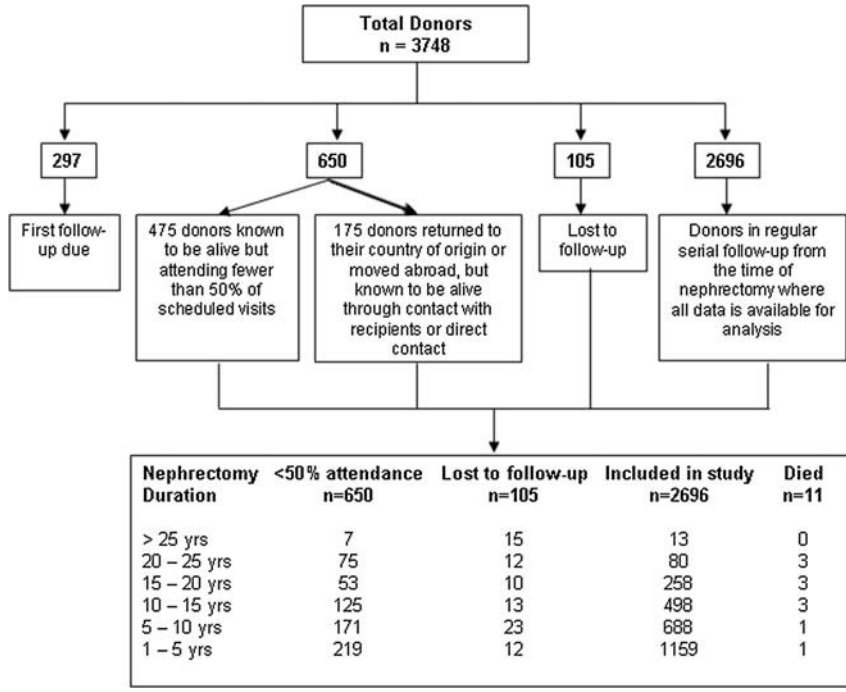

Nephrectomy Duration	<50% attendance n=650	Lost to follow-up n=105	Included in study n=2696	Died n=11
> 25 yrs	7	15	13	0
20 – 25 yrs	75	12	80	3
15 – 20 yrs	53	10	258	3
10 – 15 yrs	125	13	498	3
5 – 10 yrs	171	23	688	1
1 – 5 yrs	219	12	1159	1

FIGURE 1. Follow-up status of donors.

replacement therapy is not a priority for government due to unmet needs of primary health care. This renders greater than 90% of the population with ESRD disfranchised from renal replacement therapy where the estimated incidence is greater than 100 pmp/yr.[11] The Sindh Institute of Urology and Transplantation has thus developed a model of community-government partnership where dialysis, transplantation, lifelong medical follow-up, and medications have been integrated and provided "free of cost" to all patients presenting with ESRD.[11]

To provide for the safety of donors, the program also provides free lifelong follow-up and therapeutic intervention after living kidney donation with a high follow-up rate driven by "free care" in the backdrop of poor health facilities.[3] This study reports our observations of long-term follow-up outcomes of living kidney donors from an emerging economy and the impact of preventive and therapeutic interventions undertaken for new onset medical conditions in a dedicated donor clinic.

MATERIALS AND METHODS

Study Population

Between November 1985 and September 2012, 3748 donor nephrectomies were performed at Sindh Institute of Urology and Transplantation, 2696 (72%) individuals received annual physical examination and laboratory investigations and 105 (2.8%) were lost to follow-up (Figure 1).

Donor Selection Criteria

Donors were genetically related or spouses of their recipient, normotensive; aged between 18 and 60 years; with urine protein excretion less than 150 mg/24 hours; creatinine clearance (CrCl) greater than 80 mL/min per 1.73 m^2 for men and greater than 70 mL/min per 1.73 m^2 for women; and absence of renal or systemic disease. In the first decade of program, donors with 1 haplotype match or more, age younger than 60 years, and single vessels were preferentially selected. Later, with developing expertise and better immunosuppression facilities less than one haplotype donors and those with multiple vessels or older than 60 years were also selected. Family donors older than 60 years and those with CrCl less than 80 mL/min were accepted in 163 cases when they were the only available donor.

Follow-Up Protocol

The initial visit was between 6 and 12 months after nephrectomy and thereafter annually or when intercurrent medical problems occurred. Each visit included a complete medical history, psychological assessment, physical examination (including height, weight, and blood pressure), and laboratory investigations complete blood picture, renal function, urea, electrolytes, creatinine, liver functions, serum proteins, lipid profile, diabetes screening by fasting blood glucose, bone profile, uric acid and 24-hour urine collection for protein excretion, and estimation of glomerular filtration rate (GFR) by CrCl. Donors with fasting blood glucose greater than 120 mg/dL were subjected to glucose challenge test to exclude diabetes.

The CrCl was established as a standard method to determine GFR in donors for the selection and follow-up. The adequacy of collection was checked by urine creatinine[12] and urine volume. The GFR by dynamic renal scintigraphy using Tc99M was used in problem cases. In case of inadequate collection, test was repeated in many instances more than once. Renal anatomy angiography and intravenous pyelography were the standard procedures in the first decade which were later replaced by computed tomography angio and computed tomography pyelogram.

Therapeutic Interventions

Diagnosed hypertension, diabetes mellitus, proteinuria, liver disease, hyperlipidemia, or any other medical condition were treated. Hypertension was defined as systolic blood

pressure greater than 140 mm Hg or diastolic BP greater than 90 mm Hg on more than 1 occasion. Proteinuria was greater than 150 mg protein excretion over 24 hours, diabetes was diagnosed according to the World Health Organization criteria,[13] obesity was defined by body mass index (BMI),[14] hyperlipidemia was defined by fasting cholesterol greater than 200 mg/dL or fasting triglycerides greater than 150 mg/dL. Interventions were provided for:

(a) Hypertension—lifestyle changes followed by angiotensin-converting enzyme (ACE) inhibitor, calcium channel blockers, and β blockers.
(b) Proteinuria—lifestyle changes and ACE inhibitor.
(c) Hyperlipidemia—lifestyle changes, plus statin for hypercholesterolemia, and fibrates for hypertriglyceridemia.
(d) Diabetes—lifestyle changes, sulphanylurea, biguanide, dipeptidyl peptidase 4 inhibition, or insulin.

Follow-up investigations included renal function, lipid profile, cholesterol, triglycerides, and fasting glucose. Glycosylated hemoglobin (HbA1c) test in follow-up was included in the last 15 years of the study.

Matched Cohort of Nondonating Siblings

Pretransplant work-up records of recipients identified 198 siblings who were assessed and deemed medically suitable for kidney donation but did not donate because another donor was selected. Of these, 137 responded to attend a follow-up evaluation. From the 137, 90 nondonors could be matched for age, sex, and BMI with evaluated donors.

Statistical Analysis

In donor follow-up clinic, all data pertaining to predonation, first follow-up after donation and yearly follow-up, were entered into the donor database. The data were transferred and analyzed using SPSS version 10.0. The missing values at yearly follow-up were incorporated by taking the values at ±3 months of the missing year or by taking the average of preceding and following year of the missed value

The baseline characteristics of the donors are expressed as mean ± SD or median where applicable for quantitative variables, whereas categorical data were summarized as frequencies and percentages. The comparison of mean values for 2 independent groups was performed by Student *t*-test and Mann-Whitney *U* test and more than 2 groups were analyzed by analysis of variance and Kruskal-Wallis where applicable. For comparison of means between donor and nonsibling donors matched for age, sex, and BMI we used paired *t* test and Wilcoxon signed rank test where appropriate. Fisher exact test or χ^2 test was used for categorical variables. A *P* value less than 0.05 was considered as significant.

Risk Factor Analysis

We used logistic regression for risk factor analysis for CrCl less than 60 mL/min, persistent proteinuria greater than 300 mg/24 hours and hypertension. The predonation factors that were included in the analysis were: age at donation, sex, baseline systolic and diastolic blood pressure, BMI, CrCl, and urinary proteins, whereas postdonation factors were time since donation, hypertension, diabetes, CrCl, urinary protein and smoking. Univariate analysis was performed to identify the factors to include in the logistic regression model at a *P* value less than 0.05. The continuous variables were categorized according to known risk values, such as CrCl, less than 80; protein, greater than 150; age, older than 40 years; systolic BP, greater than 130; diastolic BP, greater than 80; BMI greater than 25; time since donation, longer than 5 or 10 years.

Cumulative Incidence and Lifetime Risk

Kaplan-Meier method was used to estimate the cumulative incidence of ESRD, hypertension, diabetes, and other diseases. Donors were censored at death or at the end of the study. Survival rates and lifetime risk to develop ESRD were also calculated by using Kaplan-Meier technique. The overall incidence of ESRD was calculated by using the persons-year method.

RESULTS

Baseline Donor Characteristics

There was no 90-day mortality from the 3748 donor nephrectomies. The mean age at donation of the 2696 donors in regular follow-up was 34.3 ± 9.8 years with a median follow-up time of 5.6 years (interquartile range [IQR], 7.79) and person follow-up times of 20 939 years. The baseline characteristics of the 3748 donors, 2696 donors under study, 947 with irregular follow-up, and 105 lost to follow-up are shown in Table 1. Of 2696, 1159 were followed up for 5 years, 688 for longer than 5 to 10 years, 498 for longer than 10 to 15 years, 258 for longer than 15 to 20 years, and 93 > 20 to 27 years. The baseline characteristics of the donors followed up and those lost to follow-up were essentially similar.

Long-Term Outcomes of Donors

Eleven donors (0.4%) have died with all cause estimated mortality rate by Kaplan-Meier of 1.1% at 25 years and crude incidence of 4.0/10 000 person years. In the follow-up period, 371 (13.7%) became hypertensive and 95 (3.5%) developed diabetes (Table 2A). The incidence per 10 000 of hypertension was 202; diabetes, 47.2; ischemic heart disease, 10.5; chronic liver disease, 17.4; malignancy, 5.2; and stone disease, 5.2. Six (0.22%) have developed ESRD with rates of 0.1% at 10, 0.3% at 15, and 0.6% at 25 years with overall crude incidence of 2.7 per 10 000 person years. These 6 donors presented late for follow-up at a mean of 6.5 years after donation with hypertension and proteinuria greater than 300 mg/24 hours. Two have died, 2 have transplants and 2 are on dialysis (Table 2B). The 2 renal deaths were due to sepsis on dialysis in women aged 56 and 57 years. The 9 nonrenal deaths were as follows: 3 cardiovascular deaths in men aged 48 and 63 years and 1 woman aged 69 years; liver failure in 2 men aged 48 and 64 years; ovarian and breast cancer in women aged 48 and 54 years, respectively; lymphoma in a 69-year-old man and road traffic accident in a 24-year-old man.

Renal Function

Donors yearly GFR by CrCl is shown in Figure 2A in age groups, 18-39, 40-49, and older than 50 years at donation. The overall mean predonation CrCl mL/min per 1.73 m^2 was 109 · 8 ± 22.3 (range, 68-166). Nephrectomy lead to a reduction to 32 mL/min per 1.73 m^2 or 72% of the predonation CrCl. A 9% rise of CrCl occurred between 1 and 5 years to a CrCl of 83.7 ± 19 mL/min per 1.73 m^2. A gradual fall was observed from 5 to 25 years to a mean of

TABLE 1.

Baseline characteristics of donors (3748)

	Regular follow-up	<50% or first follow-up due	Lost to follow-up	
	n = 2696	n = 947	n = 105	*P*
Mean age at donation, y	34.3 ± 9.8 (18-68)	35.1 ± 10.9 (18-70)	34.8 ± 10.8 (18-60)	0.10
Male/female ratio	1.2:1	1.3:1	1.4:1	
Male (%)	1465 (54.3%)	544 (57.4%)	64 (60.9%)	0.12
Mean age of male donors, y	32.4 ± 9.9 (18-68)	33.5 ± 11.1 (18-75)	32.5 ± 10.5 (18-60)	0.02
Mean age of female donors, y	36.6 ± 9.1 (18-67)	37.4 ± 10.4 (18-65)	37.9 ± 10.8 (19-57)	0.04
Age groups, y				
18-39	1782 (66%)	576 (60.8%)	64 (60.9%)	
40-49	671 (25%)	226 (23.9%)	23 (21.9%)	0.001
>50	243 (9%)	145 (15.2%)	18 (17.1%)	
Predonation serum creatinine, mg/dL	0.80 ± 0.20 (0.50-1.80)	0.84 ± 0.20 (0.50-1.89)	0.86 ± 0.22 (0.49-1.59)	0.001
Urinary volume, 24 hr/d	2214 ± 1423 (760-8900)	2137 ± 1481 (680-9000)	1974 ± 1255 (780-6000)	0.10
CrCl at donation, mL/min per 1.73 m^2	109.8 ± 22.3 (68-166)	107.1 ± 26.8 (69-171)	106.7 ± 27.9 (70-163)	0.006
Cr Cl > 110 mL/min per 1.73 m^2	1294 (48%)	410 (43.3%)	46 (43.8%)	
Cr Cl 80-109 mL/min per 1.73 m^2	1186 (44%)	433 (45.7%)	49 (46.7%)	0.02
Cr Cl < 80 mL/min per 1.73 m^2	216 (8%)	104 (11%)	10 (9.5%)	
Protein excretion (median), mg/24 hours	76 (18-375)	81 (18-390)	81 (12-320)	0.22
Mean BMI at donation	23.7 ± 5.9 (19.6-41.1)	23.6 ± 4.7 (17.8-46.2)	23.7 ± 4.7 (16.5-36.5)	0.89
BMI < 25.0	1711 (63.4)	631 (66.6%)	67 (63.8%)	
BMI 25.1-30.0	722 (26.8%)	218 (23%)	26 (24.8%)	0.24
BMI > 30.0	263 (9.8%)	98 (10.4%)	12 (11.4%)	
Mean cholesterol at donation, mg/dL	159 ± 30 (95-220)	166 ± 39 (6-260)	164 ± 37 (79-231)	0.001
Mean triglyceride at donation, mg/dL	111 ± 44 (43-223)	115 ± 56 (19-238)	117 ± 74 (33-265)	0.05
Mean systolic BP at donation, mm Hg	123 ± 11 (97-150)	121 ± 13 (90-149)	123 ± 14 (86-158)	0.001
Mean diastolic BP at donation, mm Hg	78 ± 7 (64-92)	77 ± 9 (60-92)	78 ± 9 (58-94)	0.002

70.5 ± 20.3 at 25 years, a decline of 0.66 mL/min per 1.73 m^2 per annum. The CrCl at most recent follow-up was greater than 90 in 593 (22%), between 61 and 90 in 1736 (64%), and 40-60 in 341 (12.6%). A small group of donors, 26

TABLE 2.

New clinical diagnoses in donors during follow-up (n = 2696)

(A) Clinical diagnoses

Nonrenal		Renal	
Hypertension	371 (13.7%)	ESRD	6 (0.22%)
Diabetes	95 (3.5%)	CKD	8 (0.29%)
Ischemic heart disease	20 (0.74%)	Glomerular disease	3 (0.11%)
Chronic liver disease	36 (1.33%)	Stone disease	11 (0.40%)
Malignancy	11 (0.40%)	Deaths	2 (0.07%)
Psychological disorders	6 (0.22%)		
Tuberculosis	9 (0.33%)		
Cerebrovascular accident	2 (0.07%)		
Deaths	9 (0.33%)		

(B) Characteristics of Donors Who Developed ESRD

		First Presentation After Donation			Time to ESRD, y	ESRD Causes	Outcome
Age/Sex	y	CrCl	Protein	BP			
35/M	6	49	4095	130/97	11	Secondary FSGS	Dialysis
22/F	13	36	1200	127/100	17	Secondary FSGS	Transplant
45/F	10	15	913	125/90[a]	11	Unknown	Died
47/F	4	65	689	130/95[a]	10	Hypertension	Died
31/M	2	55	825	140/100[a]	5	Hypertension	Transplant
30/M	4	90	360	130/100	13	Secondary FSGS	Dialysis

[a] Hypertensive on medication, nonadherent to therapy.
CKD, chronic kidney disease; M, male; F, female

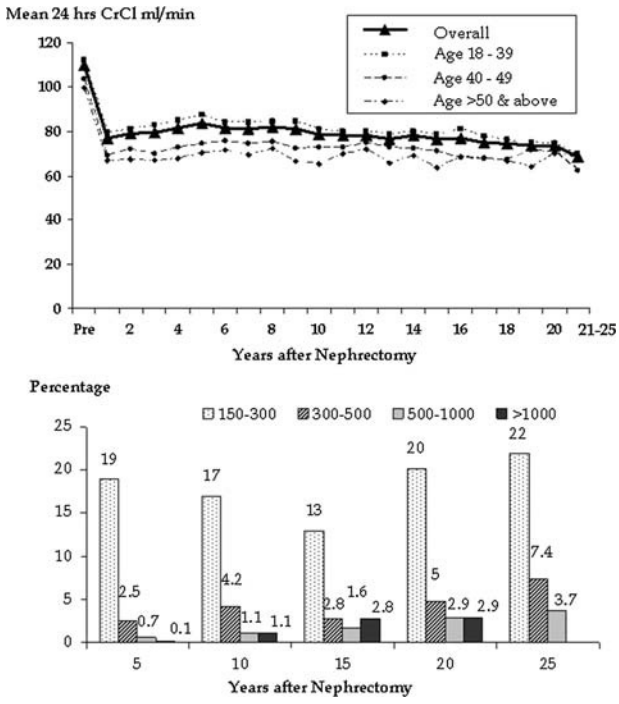

FIGURE 2. A, Serial GFR by creatinine clearance after nephrectomy (n = 2696). B, Range of proteinuria by years after nephrectomy (n = 2696).

(0.9%) had CrCl less than 45 mL/min per 1.73 m^2 at a mean follow-up of 8.9 ± 4.7 years at a mean age of 53.8 ± 9.5 years. Their age at donation was 41.6 ± 11.4 years and CrCl 102 ± 22 mL/min per 1.73 m^2. In this follow-up period of 8.9 years, 3 (11.5%) developed diabetes and 11 (42.3%) had hypertension with a median protein excretion of 60 mg/24 hours.

Predonation CrCl was assessed in different age groups. The CrCl was higher in donors aged 18 to 39 years, (mean, 112 ± 22) compared with donors aged 40 to 49 years (mean, 103.5 ± 20.7) ($P < 0.001$) and donors 50 years or older (mean, 99.5 ± 20) ($P < 0.001$). The average fall per year after the fifth year was highest in donors aged 18 to 39 years (0.67 mL/min per year) but less for donors aged 40 to 49 years (0.21 mL/min per year; $P = 0.04$) and donors 50 years or older (0.10 mL/min per year; $P = 0.02$). Donors older than 50 years, postcompensatory rise, had a CrCl of 68.14 at 5 and 66 mL/min per 1.73 m^2 at 20 years.

Proteinuria

The median overall predonation 24-hour protein excretion was 76 mg/24 hours. Median predonation protein excretion was similar in donors aged 18 to 39 years (75), 40 to 49 years (77), and older than 50 years (80 mg/24 hours) ($P = 0.75$). Overall, protein excretion increased after nephrectomy from a median of 76 mg/24 hours to 90 at 1 year, a rise of 14 mg/24 hours or 18% ($P < 0.001$). Median protein excretion at 5, 10, 15, and 25 years were 81, 75, 92, and 142 mg/24 hours, respectively. The rise of excretion at 25 years was 46%. Of the 2696 donors, 2165 (76%) had normal protein excretion (<150) in the entire follow-up period. Protein excretion was up to 300 mg/24 hours in 485 (18%) and greater than 300 mg/24 hours in the rest of 146 (5.4%) donors. The degree of proteinuria after nephrectomy is shown in Figure 2B. Twenty-eight donors (1%) had protein greater than 1000 mg/24 hours. The median predonation protein excretion of these 28 donors was 110 mg/24 hours and the onset of their significant proteinuria was at a mean of 9.37 ± 4.7 years postnephrectomy. The median protein excretion at last follow-up was 1145 mg/24 hours.

Outcome of Donors Who Survived 15 Years

A total of 523 donations occurred before 1999, of which 351 (67%) have had regular follow-up (180 men and 171 women) and 172 have not (74 had undertaken <50% of scheduled visits, 61 are known to be alive in another country, and 37 are lost to follow-up). The estimated incidence of ESRD in the first 15 years was 3.4 per 10 000 person years and mortality rate of 0.6%. Their age at donation was 35.8 ± 10.9 years (range, 18-67 years), 50.9 ± 10.1 years at 15, 55.2 ± 10.3 years at 20 and 58.1 ± 7 years at 25 years of follow-up (Table 3). Predonation CrCl was 95.6 ± 17.5 mL/min per 1.73 m^2 and median protein excretion 110 mg/24 hour. Hypertension had developed in 109 by 15 years with 12 becoming hypertensive beyond 15 years, whereas 41 (11.7%) had developed diabetes by 15 years, no individuals developed diabetes between 15 and 27 years.

The mean CrCl of 93 donors followed up for more than 20 years at their last follow-up was 69.9 ± 16.7 at a mean age of 53.7 ± 8.7 years. Of the 351 donors in follow-up where nephrectomy occurred before 1999, 1 went into ESRD and 3 died.

Comparison of Donor and Nondonor Siblings

Potential donors who had been evaluated and accepted as donors, but who did not proceed to donate for nonmedical reasons were selected to provide a control group for the donors. Ninety nondonors' siblings could be paired with actual donors for age, sex, and BMI. The mean follow-up period

TABLE 3.

Characteristics of donors with follow-up of 15 y or longer

	15 y	20 y	25 y
Characteristics	**n = 351**	**n = 93**	**n = 13**
Mean age, yr	50.9 ± 10.1	55.2 ± 10.3	58.1 ± 7.0
Range	32-82	38-81	46-72
Up to 45 yr	133 (37.9%)	17 (18.3%)	—
46-65 yr	192 (54.7%)	59 (63.4%)	12 (92.3%)
>65 yr	26 (7.4%)	17 (18.3%)	1 (7.7%)
Male (%)	180 (51.3%)	41 (44.1%)	6 (46.1%)
CrCl, mL/min per 1.73 m^2	77.2 ± 20.8	73.4 ± 12.3	70.5 ± 20.3
<60	64 (18.2%)	21 (22.6%)	3 (23.1%)
61-90	214 (61.0%)	50 (53.8%)	7 (53.8%)
>90	73 (20.8%)	22 (23.6%)	3 (23.1%)
Protein (median), mg/24 hr	92	103	142
<150	291 (82.9%)	62 (66.7%)	7 (53.8%)
151-300	56 (15.9%)	21 (22.6%)	5 (38.5%)
301-500	4 (1.1%)	6 (6.4%)	1 (7.7%)
>500	—	4 (4.3%)	—
Mean BMI	25.96 ± 5.15	26.6 ± 5.2	28.6 ± 5.2
Up to 25.0	156 (44.4%)	36 (38.7%)	3 (23.1%)
25.0-29.99	128 (36.5%)	37 (39.8%)	6 (46.1%)
≥30.0	67 (19.1%)	20 (21.8%)	4 (30.8%)
New hypertension	—	8	4
New diabetes	—	—	—

TABLE 4.

Comparison of outcome of donors and nondonor siblings

	Donors	Nondonors	*P*
	n = 90	n = 90	<
Age, y	37.7 ± 11	37.7 ± 11	1.0
Male (%)	63 (70%)	63 (70%)	1.0
BMI	25.3 ± 4.6	25.3 ± 4.8	1.0
Follow-up period, y	5.8 ± 4.4	5.2 ± 5.1	0.4
Blood glucose, mg/dL	86 ± 15	96 ± 15	0.001
Cholesterol, mg/dL	174 ± 42	179 ± 33	0.4
Cholesterol > 200 mg/dL	18 (20%)	24 (27%)	0.4
Triglyceride, mg/dL	129 ± 69	137 ± 75	0.5
Triglyceride >150 mg/dL	25 (28%)	30 (33%)	0.6
Serum creatinine, mg/dL	1.12 ± 0.25	0.99 ± 0.27	0.005
Predonation CrCl, mL/min per 1.73 m^2	109.8 ± 22	109.5 ± 20	0.92
CrCl, mL/min per 1.73 m^2	84 ± 24	96 ± 26	0.02
24 h urine volume	2117 ± 1008	2092 ± 900	0.85
CrCl < 60 mL/min per 1.73 m^2	10 (11.1%)	7 (7.8%)	0.5
Protein excretion (median), mg/24 hr	75	71	0.66
Protein >300 mg/24 hr	4 (4.4%)	5 (5.5%)	0.8
Hypertension	13 (14%)	26 (29%)	0.05
Systolic BP, mm Hg	122 ± 11	123 ± 17	0.88
Diastolic BP	81 ± 9	84 ± 11	0.08
Diabetes mellitus	2 (2.2%)	3 (3.3%)	0.7
Ischemia heart disease	1 (1.1%)	1 (1.1%)	1.0

after first evaluation of nondonor siblings was 5.2 ± 5.1 years and 5.8 ± 4.4 years for donors (Table 4). Fasting glucose, percent with raised cholesterol greater than 200 mg/dL, percent with triglycerides greater than 150 mg/dl, and hypertension were higher in nondonor siblings and both had similar proteinuria. Serum creatinine was obviously higher and CrCl was lower in donors. Of the 198 nondonor siblings, 1 developed ESRD 10 years after initial evaluation, and 1 died due to hepatitis.

Risk Factor Analysis

Risk factors were analyzed for development of impaired renal function (CrCl <60 mL/min per 1.73 m^2), persistent proteinuria greater than 300 mg/24 hours, and hypertension (Table 5). Impaired renal function was associated with age at donation, low predonation CrCl, and duration of follow-up. Postdonation hypertension and proteinuria did not impact on the development of CrCl less than 60. Persistent proteinuria was associated with: higher predonation proteinuria, male sex, smoking, postdonation hypertension, and longer duration of follow-up. Hypertension during follow-up was related to: age, BMI of 25 or higher, raised predonation blood pressure, and duration of follow-up. The overall incidence of ESRD and new-onset disease is given in Figure 3. Risk for diabetes, proteinuria, CrCl less than 60 mL/min per 1.73 m^2, and ESRD plateaus after 15 years.

Therapeutic Intervention

Therapeutic intervention was undertaken for new-onset disease specially comorbids that impact renal function and risk of ESRD.

TABLE 5.

Multivariate risk factor analysis for postdonation impaired renal function, proteinuria and hypertension

Factors	Odds Ratio	*P*
(A) CrCl < 60 mL/min per 1.73 m^2		
Age at donation (>40 y ≤ 40 y)	2.8	<0.001
Predonation CrCl (≤80 vs >80 mL/min)	1.7	0.03
(B) Persistent proteinuria >300 mg/24 hr		
Pre donation protein (>150 vs ≤150)	2.1	0.006
Male sex	1.8	0.006
Smoking	2.3	0.001
Postdonation hypertension	2.3	0.001
Nephrectomy donation (>10 yr vs ≤10 yr)	3.5	<0.001
(C) Hypertension		
Age at donation (>40 vs ≤40)	1.5	0.002
Predonation BMI (≥25 vs <25)	1.7	<0.001
Predonation systolic BP (>130 vs ≤130)	1.8	<0.001
Predonation diastolic BP (>80 vs ≤80)	1.6	0.001
Nephrectomy period (>5 yr vs ≤5 yr)	4.8	<0.001

CrCl < 60 was adjusted for time since donation >5 years, persistent proteinuria was adjusted for systolic BP >130, diastolic BP >80 and CrCl < 80 at donation. Hypertension was adjusted for Cr Cl <80 at donation.

Hypertension

Of the 2696 donors 371 (14%) were diagnosed at a mean duration of 5.1 ± 4.6 years after nephrectomy (median, 4 years; IQR, 6.2). Of these, 161 (43%) only required lifestyle changes, 168 (45%) 1 drug, and 41 (12%) drug combinations for control (Figure 4A). The mean systolic and diastolic BP were 143 ± 15 and 92 ± 9 mm Hg at diagnosis of hypertension. After intervention, blood pressure was maintained below 140 and 90 mm Hg for 15 years from onset till last follow-up. The mean systolic and diastolic pressure were 132 ± 16 and 84 ± 10 at 5 years, 131 ± 18 and 84 ± 18 at 10 years and 133 ± 20 and 87 ± 10 mm Hg at 15 years, respectively.

Diabetes

Ninety-five donors (3.6%) developed diabetes mellitus 4.3 ± 3.6 years after nephrectomy, (median, 3.2 years; IQR,

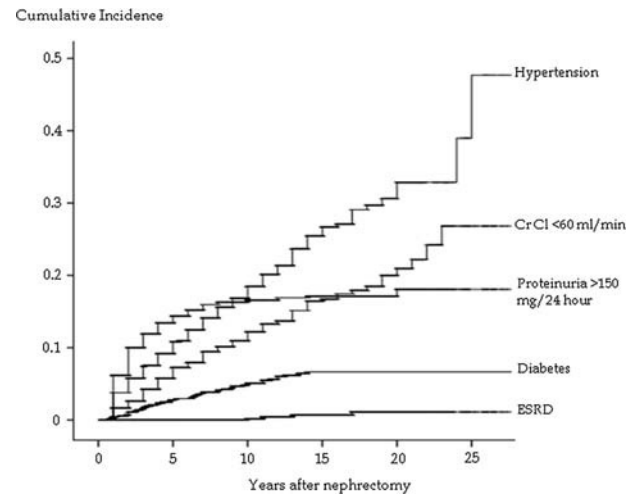

FIGURE 3. Cumulative incidence of comorbidity and ESRD after nephrectomy.

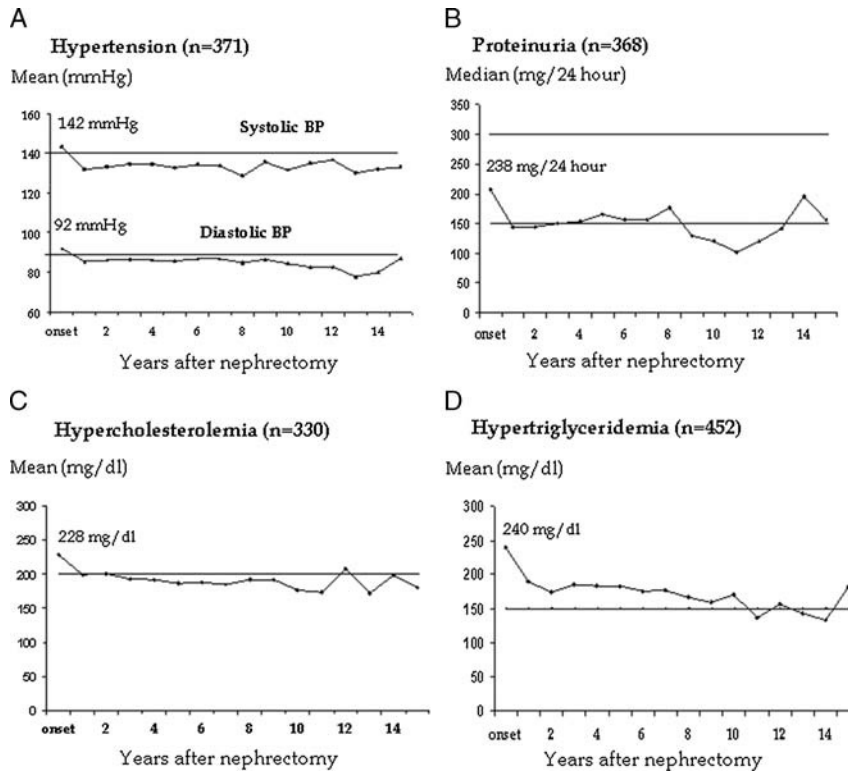

FIGURE 4. Impact of intervention on hypertension, proteinuria and hyperlipidaemia.

5.7 years). At diagnosis, diabetics had a higher BMI (26.4 ± 3.7 compared with 23.6 ± 3.7 for nondiabetics, $P < 0.001$) and 72% of the diabetics were women. Majority (92 [97%]) were maintained by lifestyle changes and oral hypoglycemic agents, whereas 3 (3%) were treated with insulin. To evaluate glycemic control, HbA1c was undertaken in diabetic donors since the last 15 years. The mean follow-up HbA1c in 72 donors was 6.04 ± 1.79 after treatment of 6.4 ± 4.7 years. In 58 (85%), HbA1c was below 6.5% and the rest was greater than 6.5%.

Proteinuria

The majority of the donors had proteinuria less than 150 mg/24 hours throughout the follow-up period. Persistent proteinuria greater than 150 mg/24 hours was managed by diet alone in 126 (34%) whereas 242 (66%) were treated with ACE inhibitors. Serial annual protein excretion is shown in Figure 4B. Median onset protein was 238 mg/24 hours and was maintained below 200 mg/24 hours in majority of the cases at different time points with median excretion at 1, 4, 8, 12, and 15 years of 165, 186, 160, 201, and 222 mg/24 hours, respectively. Of the 28 patients with proteinuria greater than 1000 mg/24 hours, 21 (75%) maintained proteinuria less than 1000 mg/24 hours for 1 to 12 years, 7 had proteinuria less than 3000 mg/24 hours, and 6 developed ESRD 5 to 17 years after donation.

Hyperlipidemia

Hypercholesterolemia occurred in 853 (32%) and hypertriglyceridemia in 1185 (44%). No donors exceeded cholesterol of 350 mg/dL or triglycerides of 1000 mg/dL. Hypercholesterolemia (>200 mg/dL) was treated with lifestyle changes in 523 (61%) whereas 330 (39%) received medication (Figure 4C). Mean onset cholesterol was 228 mg/dL, and it was maintained below 200 in the follow-up period. Mean cholesterol levels at 1, 4, 8, 12, and 15 years were 199, 192, 192, 208, and 181, respectively. Hypertriglyceridemia (>150 mg/dL) was treated in 452 (38%) with medication (Figure 4D). Mean onset triglyceride was 240 mg/dL and was maintained below 200 in the follow-up period. Mean levels at 1, 4, 8, 12, and 15 years were 190, 183, 166, 156, and 181, respectively.

Obesity

During the follow-up for a mean period of 8.1 ± 5.5 years, 1310 (77%) of those with a normal BMI maintained it, 351 (20%) became overweight, and 50 (3%) became obese (Table 6). Donors who became obese or overweight post-donation were predominantly women (58%), higher rates of hypertension (42%), diabetes (12%), and lower CrCl. Lifestyle changes and appropriate medications for clinical conditions were given in these cases. Weight reduction was achieved in one third of all donors who were overweight or obese before or after nephrectomy (Table 6).

DISCUSSION

Our study of 2696 donors followed up regularly for 1 to 27 years has shown that kidney donation is safe, with 6 (0.2%) developing ESRD between 5 and 17 years after donation with an incidence of 2.7 per 10 000 person years. Eleven donors died with all-cause mortality rate of 1.1% at 25 years with incidence of 4.0 per 10 000 persons. Two deaths were due to ESRD and 9 from other causes. In the follow-up period, 14% developed hypertension, 3.6% had diabetes, and

TABLE 6.

Characteristics of donors with increased postdonation BMI

	Normal	Overweight	Obese	
	n = 1310	n = 351	n = 50	*P*
Age at donation, yr	33.0 ± 10.1	33.8 ± 9.5	33.0 ± 9.6	0.4
Females, %	38.2	48.4	58.1	<0.001
Pre donation CrCl, mL/min per 1.73 m^2	110 ± 22	109 ± 22	106 ± 23	0.5
Pre donation protein (median)	72	74	81	0.9
Pre donation BMI	20.5 ± 2.4	22.7 ± 2.0	21.7 ± 2.5	<0.001
Time from donation, yr	4.3 ± 4.3	6.6 ± 5.4	9.80 ± 6.7	<0.001
BMI at last follow-up	21.1 ± 2.5	26.5 ± 1.2	32.6 ± 2.8	<0.001
Cr Cl < 60 mL/min per 1.73 m^2	8.4%	13.1%	12.1%	0.02
Protein at last follow-up (median)	80	86	86	0.45
Persistent proteinuria >300 mg/24 hr	2.9%	6.6%	12.0%	<0.001
Hypertensive	8.2%	19.1%	42.1%	<0.001
Diabetes	1.2%	2.8%	12%	<0.001
Cholesterol >200 mg/dL	24%	42%	62%	<0.001
Triglyceride >150 mg/dL	35%	53%	62%	<0.001

1% had proteinuria greater than 1 g/24 hours. Timely management and medical intervention allow modifications of comorbids preventing the risk of chronic kidney disease and ESRD.

Reliance on living kidney donation and poor practices of transplant tourism and kidney vending during the phase of global expansion of kidney transplantation has led to renewed focus on donor care and long-term outcomes.[2] Short-term results of living donor nephrectomy relate to assessment, surgical technique, and short-term follow-up care.[15,16] Long-term impacts have however proved to be difficult to assess. In emerging economies due to paucity of healthcare facilities kidney donors have limited access to follow-up care. Our institute therefore provided free care to donors in a dedicated donor clinic with lifelong care and management to ensure safety and health of donors. [3]

Reassuring reports on donor follow-up suggest kidney donation is not associated with excess long-term medical risks,[3-6] but these studies have limitations. First, kidney donors are tested and selected for being in the best state of health at donation and thus have better prognoses than the general population.[6,17] Second, these studies are largely retrospective, cross-sectional, and based on low rates of follow-up (30% to 70%).[18-20] Third, actual medical assessment of donors has only been undertaken in a cross-sectional design and with limited numbers.[6] Furthermore, recent studies from the United States and Norway where donors were compared with healthy nondonors have suggested a 10-fold increased ESRD risk in donors.[7,8] However, these 2 studies also have limitations. The US study had different enrollment periods for donors (1984-1994) and nondonors (1994-2011), whereas the Norwegian study had different accrual periods and difference in baseline characteristics of donors.[21] Finally, no studies have addressed long-term follow-up and management of medical problems arising in kidney donors in emerging economies with limited access to health care.

Our study thus has several unique features: it provides a prospective study of a cohort of 2696 donors followed up clinically for up to 27 years with a 72% response rate and only 105 lost to all contact either because of death of their recipient or residence abroad. Donors received preventive and therapeutic interventions based on complications as they were diagnosed. We were also able to compare donor outcome with that of nondonating siblings who were contemporaneously medically approved to donate.

In our study, the overall mortality rate of 4.0/10 000 population is below the crude death rate of 65.8/10 000 in Pakistani population.[22] Our all-cause mortality rate was 0.6% at 15 years as compared with the Norwegian study of 7%.[7] The overall ESRD incidence of 2.7/10 000 in our series is much lower than 30.9/10 000 in the US study[8] but similar to the Norwegian study of 3.02/10 000.[7]

Renal functional decline remains the second most important concern, thus we measured 24-hour CrCl which was standardized to provide comparable yearly serial estimations. Although the procedure was strictly standardized, there remains the possibility of inadequate collections underestimating function. Recent studies on donors have replaced this procedure by cystatin C and albumin/creatinine ratio.[23] The average fall of CrCl observed immediately after nephrectomy was 32 mL/min per 1.73 m^2 to 72% of the original level was comparable to other studies.[5,6] The subsequent 9% compensatory rise confirms other reports and was most pronounced in younger donors.[24,25] Risk factors for CrCl falling to less than 60 mL/min per 1.73 m^2 were age at donation, predonation CrCl, and time from nephrectomy as reported earlier,[6,26] but we did not observe female sex or BMI of 25 or greater to be risk factors.[6,27] A small proportion of donors (0.9%) dropped below 45 mL/min per 1.73 m^2 after an average of 9 years of follow-up and were older than 40 years at donation.

Previously reported risk factors for development of proteinuria greater than 300 mg/24 hours were duration of nephrectomy and female sex[6,28] to which we add predonation proteinuria greater than 150 mg/24 hours, male sex, smoking, and hypertension but not age.[6,29]

Hypertension occurred in 14% of the donors over the follow-up period of 27 years, lower than the reported range of 24% to 48%.[3,4,6,19,29] Risk factors were age, BMI, and nephrectomy duration as reported by others.[3,6] Interestingly,

the prevalence of hypertension in our general population is higher by 18% versus 14% in donors.[30]

Diabetes developed in 3.6% which was similar to the reported range of 2% to 5%.[3,6,31] These rates of 3.6% are much lower than the general population of 22% where risk factors were age, possible family history, and obesity.[32] New hyperlipidemia was a significant finding in our study. Donors are held in high esteem in the family in Pakistan, and this is reflected in their generously supplemented diet[3] with 20% of donors who had normal BMI less than 25 becoming overweight and 2% obese.

Our data provide some insights into what happens to donors in the longer term. We had 351 donors who were followed up beyond 15 years, 93 beyond 20 years with the longest being 27 years postnephrectomy. The rate of decline of renal function and incidence of newly diagnosed disease between 15 and 25 years was similar to or less than that in the preceding 15 years. Although donors older than 50 years were at risk of attaining a GFR less than 60 mL/min, postnephrectomy compensatory rise to 68 mL/min ensured that they maintained GFR greater than 45 mL/min. A recent study on longitudinal follow-up of kidney donors showed that adaptive hyperfiltration increases GFR and donors maintain their GFR in absence of added disease burden.[33]

An important aspect of our study was early diagnosis and management of new-onset disease. This is particularly important in emerging economies due to the lack of access to health care. Intervention at regular intervals for hypertension, diabetes, proteinuria, and increased BMI allowed us to modify the risk factors and thus reducing risk of chronic kidney disease or ESRD. This also perhaps is reflected by better health parameters in donors as compared with nondonors' siblings who did not have similar follow-up care.

There are a number of limitations in our study. First, 105 donors who were lost to follow-up. Although, there are a number of reasons for this, first, many of them donated in the early years when we did not have such organized regular follow-up; second, contact was difficult due to recipient death; and third, many moved abroad or came from abroad for donation. Nevertheless, we cannot be certain of their fate, and this loss to follow-up precludes us from accurately estimating the death rate. In case of renal failure or complications, it is highly likely that they would have returned to the institute for free care, dialysis, and transplantation as did the 6 donors with renal dysfunction. Second limitation is the number of nondonating siblings. Although they provide the ideal comparator for donors as they were selected as donors, their numbers were limited as in other studies on healthy nondonors.[7,8,23] Nevertheless, better health parameters in donors compared with nondonor siblings highlight the importance of regular follow-up and intervention.

Direct regular medical follow-up of 2696 donors for up to 27 years showed minimal risk of ESRD after uninephrectomy, perhaps related to the fact that new-onset medical conditions were actively diagnosed and managed. In an emerging economy, such as Pakistan, where public health facilities are poor, the donors are likely to face the same consequences as the general population where high rates prevail for hypertension, diabetes, and estimated ESRD.[11,30,32] Our study has shown that timely diagnosis and intervention can modify risk factors and prevent adverse outcome. Therefore, investment in the follow-up care of donors especially in emerging economies with poor health facilities will provide a reciprocity that may help community acceptance of safety of living kidney donation, since living donors still remain the mainstay of treatment for ESRD. Benefits of transplantation and good recipient and donor outcome may eventually promote and establish deceased organ donation.

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