End-stage Renal Disease Among Living-Kidney Donors: Single-center Experience

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Abstract

Objectives: **Renal transplant from living donors is widely accepted as a highly effective treatment for end-stage renal disease. Donors undergo a major operation with considerable perioperative risks of morbidity and mortality. Living with a single kidney also confers long-term risks. This study sought the incidence and causes of end-stage renal disease among living kidney donors.**

Materials and Methods: **This study included all donors who had reached end-stage renal disease among 2000 consecutive living-kidney donors. All operations and follow-up were performed in a single center. We studied the onset of renal disease, cause of end-stage renal disease, date of replacement therapy, and outcome. We also revised the donor's medical records related to their corresponding recipients.**

Results: **Of 2000 living donors, 8 developed end-stage renal disease; 6 were men (mean age, 30.87 ± 5.84 years. Renal failure occurred 5 to 27 years after donation. Renal transplant was done in 1 donor. Medical complications were proteinuria (6 patients), hypertension (7 patients), diabetes (3 patients), gout (3 patients), ischemic heart disease (5 patients), and hepatitis viral infection (4 patients). The causes of end-stage renal disease were diabetic nephropathy in 3 patients. Other possible causes included toxic nephropathy, chronic pyelonephritis, and preeclampsia.**

Conclusions: **Living kidney donation is safe, and development of renal failure after donation is caused by the same causes as in the general population.**

Key words: *Living donors, Kidney, Uremia*

The rapid increase in live-kidney donation has rekindled concerns about the risks involved in unilateral nephrectomy and its long-term consequences.[1] Enthusiasm for living donation waned somewhat in the early 1980s with experimental reports of hyperfiltration after uninephrectomy and fear that living-kidney donation would worsen proteinuria, hypertension, and eventually glomerulosclerosis. However, these data were not born out in human studies, and living-kidney donation has steadily increased in the past several years and surpassed deceased-donor donation.[2]

The fundamental principle of "first do no harm" to the donors must be the primary consideration when contemplating living donation. Donors undergoing such a major operation with potential risks of perioperative morbidity and mortality should follow strict exclusion and inclusion criteria. The Amsterdam Forum set forth a comprehensive list of medical criteria that is currently used in our center as well as internationally for evaluating potential kidney donors. Standard tests were performed to assure donor safety that addresses the risk of immediate and long-term negative health consequences for live donors.[3]

In spite of all effort done for donor protection, several reports denoting donor morbidity and even end-stage kidney disease among donor population are emerging.[4-6] During the follow-up, proteinuria, hypertension, reduced glomerular filtration rate, and long-term cardiovascular risk were on the top of the list.[1, 7] In most studies, incidence of end-stage kidney

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disease was reported to be 0.2% to 0.5% with varying follow-ups.[4, 8]

In 2004,[9] Steiner and Danovich showed that the baseline lifetime risk of end-stage kidney disease in unselected individuals who do not donate is 2% to 3%, showing a relatively lower incidence of end-stage kidney disease among donors than age-matched controls. This study sought to clarify the causes of end-stage renal disease among living-kidney donors and correlate these data with their predonation assessment and the original kidney disease among corresponding recipients.

Materials and Methods

Between March 1976 and September 2008, 2000 kidney transplants were performed in our center. All kidney donors were living and most of them were related.

The criteria for donor selection were normotension (systolic blood pressure < 140 and diastolic blood pressure < 90 mm Hg), age (between 21-60 years), and proteinuria (≤ 150 mg/24 hours, and measured creatinine clearance ≥ 100 mL/min for men and ≥ 90 mL/min for women). The criteria for donor exclusion were age > 60 years or < 21 years, diabetes mellitus, proteinuria, microscopic hematuria, *Mycobacterium tuberculosis* infection, impaired renal function, hypertension, coronary artery disease, and positive serology for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus.

All donors were recruited for follow-up in a specialized outpatient clinic. Donors were included until March 2009. Clinical, laboratory, and psychological work-ups were carried out. Donors who have approached end-stage kidney disease at variable times after donation were reported in this work.

Revision of their records was done regarding age at donation, sex, relation to the recipient, kidney function, blood pressure, and other comorbidities after donation. The time to renal failure, the condition at last follow-up, and the possible causes of end-stage kidney disease were analyzed. The corresponding recipients were studied regarding the original kidney disease, condition at last follow-up, and cause and time to graft failure (if end-stage kidney disease was reached).

All protocols involving human subjects were approved by the ethics committee of the institution before the study began, and that the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from the patients.

Results

The characteristics of 2000 living-kidney donors for nephrectomies are summarized in Table 1. Figure 1 shows the annual rate of kidney transplant and the donors who reached end-stage kidney disease. The demographic data of living donors who reached end-stage kidney disease are shown in Table 2A. They were composed of 8 donors; 6 were men, and 2 were women. The mean age at the time of donation was 30.87 ± 5.84 years. Renal failure occurred 5 to 27 years

Table 1. Characteristics of living kidney donors (1976-2008).

	Frequency	%
1. Donor age (years)		
< 30	782	39.1
30-40	546	27.3
41-50	419	21.0
> 50	253	12.7
2. Donor sex		
Males	953	47.7
Females	1047	52.4
3. Consanguinity		
Parents	577	28.9
Siblings	936	46.8
Offsprings	30	1.5
Other relative (cousins and nephews)	105	5.3
Emotionally related (husbands and wives)	122	6.1
	230	11.5
4. ABO compatibility		
Identical	1607	80.4
Compatible	393	19.7
5. HLA mismatch		
0	155	7.8
1	235	11.8
2	1061	53.1
3	311	15.6
4	164	8.2
6. DR mismatch		
0	200	10.0
1	1734	86,7
2	2	0.1
7. HLA-A, B, DR (class I and II) mismatch		
0	138	6.9
1	55	2.8
2	229	11.5
3	1038	51.9
4	265	13.3
5	139	7.0
6	-	-
8. Genetic considerations		
HLA-identical siblings	164	8.2
One haplotype MM (related)	1140	57.0
Two haplotype MM (related and unrelated)	577	28.9

Abbreviations: A, locus A; ABO, ABO blood group; B, locus B; DR, locus DR; HLA, human leucocyte antigen; MM, mismatch

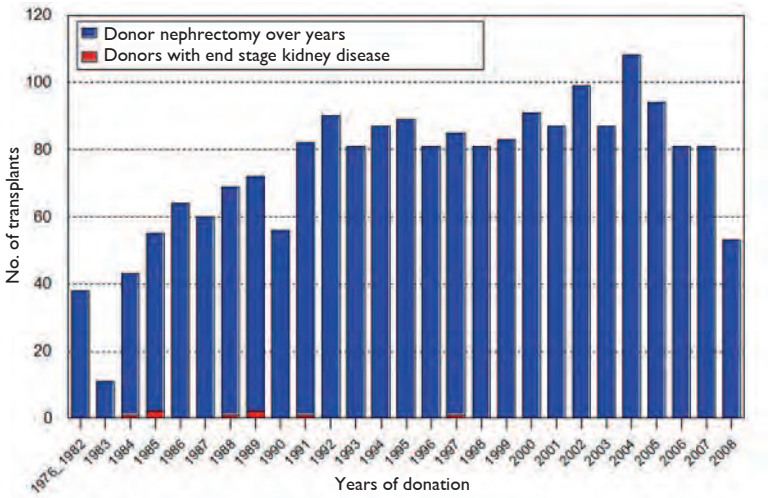

Figure 1. Annual number of living donors nephrectomy in Mansoura UNC (1976-2008).

Table 2A. Demographic data of donors with end-stage renal disease.

Donors	1	2	3	4	5	6	7	8
Age at donation	23	27	29	39	38	30	35	26
Sex	M	M	F	M	M	M	F	M
Consanguinity	Brother	Brother	Sister	Brother	Brother	Brother	Sister	Brother
Family history:								
HTN	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
DM	No	No	No	No	No	No	No	No
Kidney function:								
S Cr	0.8	0.7	0.7	0.9	1.1	1	0.7	0.9
Cr Cl	112	122	118	120	119	106	148	114
Date of donation	1991	1997	1985	1988	1989	1989	1984	1985

Abbreviations: Cr Cl, creatinine clearance; DM, diabetes mellitus; HTN, hypertension; S Cr, serum creatinine

Table 2B. Demographic data of donors with end-stage renal disease.

Donors	1	2	3	4	5	6	7	8
Time to significant comorbidity (years after donation)	5	18	19	8	2	6	15	12
Time of ESRD (years after donation)	10	27	21	15	5	14	23	23
Possible causes of ESRD	HTN IHD HU	HTN DM IHD CPN HCV	HTN PET	HTN DM IHD HCV	CPN Brucellosis	HTN IHD HBV DM	HTN HU IHD	CPN HTN HCV
Last follow-up status	Living on HD	Living on HD	Living on HD	Living on HD	Transplanted and died with failing graft	Died	Living on HD	Living on HD

Abbreviations: CPN, chronic pyelonephritis; DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; HU, hyperuricemia; IHD, ischemic heart disease; PET, preeclamptic toxemia

after donation. Time to significant comorbidities, time to end-stage kidney disease, possible causes of renal failure, and the status of the last follow-up of the donors who reached end-stage kidney disease are shown in Table 2B. All donors who reached end-stage kidney disease were treated by regular hemodialysis, and only 1 patient received a renal allograft.

Postdonation comorbidities (Table 3) showed that hypertension, cardiovascular morbidities, diabetes mellitus, and hyperuricemia were the most-probable causes of renal failure among our donors.

Table 3. Postdonation comorbidities.

Comorbidity	Number of cases	%
Hypertension	7	87.5
Diabetes mellitus	3	37.5
Hyperuricemia and gout	3	37.5
Obesity (BMI > 30)	3	37.5
Proteinuria	6	75
Cardiovascular (IHD)	5	62.5
Toxemia of pregnancy	1	12.5
Infections:		
Viral:		
HBV	1	12.5
HCV	3	37.5
Depression	1	12.5

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; IHD, ischemic heart disease

Table 4. Original renal disease and outcome of the corresponding recipients.

The corresponding recipients	1	2	3	4	5	6	7	8
Original kidney disease	Not identified	CPN (Stone disease)	CGN	CGN (MPGN)	CPN	CPN	HTN GOUT	Nephrectomy after trauma of ectopic pelvic
-Graft survival (y)	3	15	24	5	21	20	15	1/12
- Last follow-up status	Died with functioning graft (cancer breast)	Died with perfect graft	Living with perfect graft	Died with a failed graft (recurrent MPGN)	Living with perfect graft	Living with perfect graft	Living with a failed graft	Died with a failed graft

Abbreviations: CGN, chronic glomerulonephritis; CPN, chronic pyelonephritis; HTN, hypertension; MPGN, membranoproliferative glomerulonephritis

The original kidney disease is summarized in Table 4, as is graft survival, outcome, and state at the last follow-up of their corresponding recipients. It is worth mentioning that the corresponding recipients of 5 of 8 donors who developed end-stage kidney disease enjoyed perfect graft function at the time of diagnosis of end-stage kidney disease among their donors.

Discussion

Kidney donation is a relatively safe procedure with little morbidity and no mortality in most series and registries.[10-16] Developing countries have and will continue to rely heavily on living-kidney donation for some time. To date, there are limited data from these regions on general health status and the development of comorbid factors among kidney donors.[12]

We addressed this issue by starting a regular follow-up clinic. In a recent report from our center,[17] the authors have reported the long-term follow-up of live-kidney donors. In their report, renal function at 5 to > 30 years after donation was normal, even though there was insignificantly high serum creatinine level and a lower creatinine clearance. They also noted that overall, 22% of donors developed hypertension and were under treatment, proteinuria > 1 g/d in 3.3% (but none developed complete nephrotic syndrome), diabetes mellitus (type 2) in 7%, hyperlipidemia in 19%, and hyperuricemia in 6%. The authors found that the incidence of diabetes mellitus, hypertension, and cardiovascular morbidity among live-kidney donors were lower than those of age- and sex-matched Egyptian general population, and they confirmed the safety of live-kidney donation.

All the above comorbidities in few published reports have led to end-stage kidney disease at different time intervals after donation.[4, 5, 18-20] Screening for these factors and strict adherence to donor eligibility criteria are important means by which we can help to preserve the long-term health of kidney donors.[21] In our institution, all donors undergo a rigorous screening procedure to fulfill donor and recipient safety. The criteria for donor selection in our donor series were recently published.[22] However, in spite of all our efforts, several reports denoting donor morbidities are emerging.

Anderson and associates[24] reported a small decrease in renal plasma flow in kidney donors at a mean of 10 years follow-up, which was similar to that seen in the normal population. In a review of 402 donors with a mean follow-up of 12 years, Fehrman-Ekholm and associates,[24] reported that the remaining renal function of kidney donors did not deteriorate any faster than would have been expected as a result of normal aging. However, they also reported that one-third to one-half of patients developed hypertension after donation. A recent metaanalysis of living-kidney donors predicted that kidney donors may have a 5 mm Hg increase in blood pressure within 5 to 10 years after donation over that anticipated with normal aging.[25]

The incidence of end-stage kidney disease after donation ranges from 0.2% to 0.5%[8, 26, 27] reported on 736 kidney donors who were followed in a dedicated postdonation clinic. In their cohort, there was 1 instance of end-stage kidney disease who developed donor nephrectomy 12 years after surgery. The mean donor follow-up was 3 years. The family history of the patient who developed end-stage kidney disease was not presented. Said and Soyannwo[28] reported a patient who developed end-stage kidney disease 11 years after donation to his brother who had end-stage kidney disease of an undetermined cause.

A significant milestone occurred in 2002 upon publication of the united network of organ sharing/organ procurement transplant network

study (UNOS/OPTN) noting that 56 out of 6371 donors developed end-stage kidney disease and were listed for deceased-donor renal transplant.[29] They also reported that hypertensive nephrosclerosis (43%), focal segmental glomeruloscleroses (16%) and chronic glomerulonephritis (13%) were the causes. A more-recent UNOS report of 102 donors was published.[6] All were waiting for kidney transplant. Hypertension, diabetes mellitus, glomerulosclerosis, and other glomerulopathies were the main causes (28%, 9%, 13%, and 16% respectively).

This report focused primarily on donors who reached end-stage renal disease and were maintained on renal replacement therapy. End-stage kidney disease was encountered in 8 donors (0.4%) of our series of live-kidney donation in spite of careful donor selection. The incidence of end-stage kidney disease in our series was different from several reports that ranged between 0.2% and 0.5%,[26, 27] yet a thorough analysis of records predonation and postdonation and on long-term follow-up of donors found causes that led to end-stage kidney disease in our donor group were not related to the process of donation or to the causes of end-stage kidney disease in their corresponding recipients. Newly developed hypertension, progressive proteinuria, cardiovascular disease, intercurrent bacterial or viral infections, obesity, diabetes mellitus, hyperuricemia, and eclamptic toxemia were the possible contributing factors for developing end-stage kidney disease in the donors in our series that occurred at different times after donation. However, the incidence of the present comorbidities was lower than that in the age-matched Egyptian general population, 26.9% for hypertension, 9.3% for diabetes mellitus, and 6.2% for cardiovascular morbidities.[17, 30, 31]

Interestingly, donor follow-up was done regularly, all donors were generally available for follow-up and hence, underestimation for development of end-stage kidney disease among donors was ruled out in our study. Although donors' comorbidities were diagnosed, the most-probable causes of end-stage kidney disease were evident and were totally unrelated to the donation process or to family history of renal disease. Yet donor biopsy should be encouraged for proper and clear definition of the cause of decline of renal function or end-stage kidney disease among live-kidney donors.

In this report, over a 33-year period of donor follow-up, 0.4% of our kidney donors developed end-stage kidney disease, 1 had undergone kidney transplant, and the others were on hemodialysis. When strict eligibility criteria are met, progression to end-stage kidney disease after kidney donation is rare. Although most live donors were related, yet no added risks for end-stage kidney disease were observed over that in the general population. However, the family history of renal disease as well as the original kidney disease of his corresponding recipient should be carefully evaluated.

In our series of living donors, it is worth mentioning that the corresponding recipients of 5 of the 8 donors who developed end-stage kidney disease were enjoying perfect graft function at the time of diagnosis of end-stage kidney disease among their donors, ruling out the probability of improper donor selection.

Our results coincide with the work recently published by Ibrahim and associates.[32] The authors concluded that kidney donors have a normal life span, similar to the general population, as well as having no excessive risk of developing end-stage renal disease, and are enjoying an excellent quality of life.

Finally, we conclude that live-kidney donation is a safe procedure, with a minimal complication rate in long-term follow-up. Strict eligibility criteria, close follow-up, and use of kidney biopsy for donors with declining renal function after nephrectomy are mandatory for better understanding of the natural history of their illnesses. Furthermore, consideration also should be given to establish a national, as well as an international, database for living-kidney donors for better evaluation for the policy of living donation.

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