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Long-Term (20–37 Years) Follow-Up of Living Kidney Donors

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Numerous studies with < 20 years of follow-up have shown no significant long-term consequences of living kidney donation. However, hypertension and proteinuria have both been described; it is unknown whether either complication presages future kidney dysfunction. Between June 1, 1963, and December 31, 1979, we did 773 living donor kidney transplants for 715 recipients. We attempted to contact all donors to determine long-term outcome regarding their remaining kidney. We obtained information on 464 (60%) of the donors. Of these, 84 had died and 380 were alive; of the 380, 256 returned a questionnaire and 125 sent in current laboratory results and/or records of a recent history and physical examination. Of the 84 donors who had died, three were known to have had kidney failure. Of the 380 still alive, three had abnormal kidney function and two had undergone transplantation. The remaining donors had normal kidney function. The rate of proteinuria and hypertension was similar to the age-matched general population. We conclude that most kidney donors have normal renal function 20–37 years post donation. However, some do develop renal dysfunction; some, renal failure. Our data underscore the need to develop prospective trials for long-term follow-up of kidney donors.

Key words: Donors, kidney, living, outcome

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Introduction

Patients with end-stage renal disease (ESRD) have two options for treatment: dialysis or a transplant. Those opting for a transplant must then decide whether to have a living donor transplant (if there is a suitable donor) or to go on the waiting list for a cadaver kidney.

A living donor transplant offers many advantages. First, both short- and long-term graft survival rates are better for recipients with a living (vs. cadaver) donor. Second, the long wait on dialysis is avoided. Favorable patient and graft survival rates are inversely related to prolongation of the wait on dialysis (1,2). Third, with a living donor, a preemptive transplant is possible; patient and graft survival rates for those having a preemptive transplant are better than for those having pretransplant dialysis (1–3).

However, a living donor transplant does have one serious disadvantage: the donor needs to have a major operative procedure that is associated with morbidity, mortality, and the potentially negative long-term consequences of living with a single kidney. Perioperative mortality after living kidney donation has been estimated to be 0.03% (4,5); morbidity, including minor complications, < 10% (6). Thus far, numerous studies (follow-up < 20 years) of living donors have noted no evidence of long-term deterioration of the remaining kidney's function [reviewed in (7)].

We previously reported on our cohort of living kidney donors after 20–30 years of follow-up (5). In that report, we compared 57 donors with 65 siblings who had not donated; we found no significant differences in serum creatinine level, proteinuria, or need for antihypertension medications. Here, we report on a larger series of donors after over 20 years of follow-up, including, for the first time, a cohort after 30 years or more of follow-up.

Materials and Methods

Between June 1, 1963, and December 31, 1979, we did 773 living donor transplants for 715 recipients. We attempted to contact all 773 donors (or donor families). We used the last known donor address in our records. If the donor could not be found and the recipient was still alive, we called the recipient to get current donor information and a contact number. If the donor could not be found and the recipient had died, we contacted the family.

Donors were first contacted by phone and then sent a questionnaire regarding current health and medications, post-donation urogenital problems or pregnancies, and any family history of diabetes. In addition, they were asked to undergo a complete history and physical examination and to have serum creatinine levels measured and urinalysis done. Finally, they were asked to fill out the MOS 36-item Short Form Health Survey (SF-36), a nationally standardized health questionnaire about health-related quality of life (8).

Families of donors who had died were asked to provide details about the health of the donor before death and about the cause of death.

Results

We were able (as of August 1, 2001) to obtain information on 464 (60%) of the 773 donors (Table 1). Of the 464 donors

Table 1: Donor status

Living donors (6/01/1963–12/31/1979)		773
Deceased at time of study		84
No kidney problems	24	
Kidney problems	3	
Unknown cause of death	57	
Living at time of study*		380
Returned questionnaire	256	
(Underwent lab tests at time of study)	(125)	
Well, but did not yet return questionnaire	109	
Well, but did not want to participate	13	
Alive and well, but address unknown	2	
Unknown (no contact at time of study)		309

* Some donors sent in lab results but no questionnaire.

we obtained information on, 84 had died. The cause of death was available for 27: 24 had no kidney disease, but three were on dialysis at the time of death. Of these three who died with kidney failure, one developed diabetes and diabetic nephropathy, and started dialysis 10 years after donating a kidney and partial pancreas; one developed kidney failure secondary to hemolytic uremic syndrome at age 76 (32 years post donation); and one had prerenal failure secondary to cardiac disease.

In all, 380 of our kidney donors are known to be alive >20 years after donation. Of these, 13 reported no kidney problems, but did not want to participate in our study. Another 111 stated that they were well and had no kidney problems, but did not return our questionnaire and did not undergo a history and physical examination (Table 1).

Of the 256 donors who returned our questionnaire, 125 also sent in records of a history and physical examination (done by their local physician), laboratory results, or both.

In all, 198 donors were studied 20–29 years post donation; of these, 74 had serum creatinine levels measured (Table 2). The average serum creatinine level was 1.2 ± 0.04 mg/dL (range, 0.7–2.5 mg/dL). Of these 198 donors, 92 underwent urinalysis for proteinuria: 82 (89%) had no proteinuria, seven (8%) had trace, one (1%) had 1+, one (1%) had 2+, and one (1%) had 3+ proteinuria. Of these 198 donors, 72 (36%) stated they have high blood pressure: 36 (50%) take one antihypertensive medication, 17 (24%) take two, and 8 (11%) take three (11 did not provide this information). Table 3 shows the average serum creatinine level (as below), and the incidence of proteinuria and hypertension by current donor age (all 20–29 years post donation). Similar to the general population, the incidence of hypertension increases with increasing donor age.

In addition, 58 donors were studied 30–37 years post donation; of these, 29 had serum creatinine levels measured. The average serum creatinine level was 1.3 ± 0.1 mg/dL (range, 0.7–2.3 mg/dL). Of these 58 donors, 21 underwent urinalysis for proteinuria: 20 (95%) had no proteinuria and one had trace proteinuria. Of these 58 donors, 22 (38%) stated they have high blood pressure: 11 (50%) take one antihypertensive medication, 6 (27%) take two, and 2 (9%) take three (3 did not provide this information). Table 4 shows the average serum creatinine level and the incidence of proteinuria and hypertension by current donor age (all ≥ 30 years post donation).

Of all 256 donors who returned our questionnaire, five had serum creatinine levels >1.7. The first, age 69 (at the time of the study), developed ESRD secondary to chronic glomerulonephritis and underwent a transplant 24 years post donation. The second, age 69, developed renal failure secondary to gout, renal stones, and repeated episodes of pyelonephritis, and underwent a transplant 32 years post donation. The third, age 87, has a serum creatinine level of 2.3 (30 years post donation); he has an extensive history of cardiovascular disease, and prerenal failure has been diagnosed. The fourth, age 47, has a creatinine level of 2.5

Table 2: Kidney function

	Interval post donation	
	20–29 years	≥30 years
n (returned questionnaire)	198	58
Age (years)		
Mean (±SE)	59.7 ± 0.8	66.7 ± 1.3
Range	38–89	51–89
Serum creatinine level (mg/dL)		
n (lab tests at time of study)	74	29
Mean (±SE)	1.2 ± 0.04	1.3 ± 0.1
Range	0.7–2.5	0.7–2.3
Proteinuria		
n studied (% with proteinuria)	92 (11%)	21 (5%)
Degree proteinuria	7 trace; 1, 1+; 1, 2+; 1, 3+	1, 1+
Hypertension, n (%)	72 (36%)	22 (38%)
n on 1 medication	36	11
n on 2 medications	17	6
n on 3 medications	8	2
Not stated	11	3

Table 3: Outcome after 20–29 years

	Age in years (at time of study)				
	40–49	50–59	60–69	70–79	80–89
n*	48	54	48	28	18
Serum creatinine level (mg/dL)					
n (lab tests at time of study)	11	18	21	19	5
Mean (±SE)	1.2 ± 0.1	1.1 ± 0.07	1.2 ± 0.06	1.1 ± 0.08	1.3 ± 0.1
Range	0.9–2.5	0.8–1.7	0.9–2.0	0.8–1.6	1.2–1.6
Proteinuria					
n studied (% with proteinuria)	20 (20%)	17 (12%)	22 (9%)	15 (27%)	3 (0%)
Degree	3, trace; 1, 1 +	1, trace; 1, 3 +	1, 1 + ; 1, 2 +	3, trace; 1, 1 +	5
Hypertension, n (%)	12 (24%)	17 (31%)	19 (40%)	17 (49%)	7 (64%)
1 medication	3	9	8	11	5
2 medications	3	4	7	3	–
3 medications	2	1	2	2	1
Not stated	4	3	2	1	–

* Two donor ages not available.

Table 4: Outcome 30 or more years post donation

	Age in years (at time of study)			
	50–59	60–69	70–79	80–89
n*	16	20	17	3
Serum creatinine level (mg/dL)				
n (lab tests at time of study)	7	12	9	1
Mean (±SE)	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	2.3
Range	0.7–1.4	0.7–1.5	1.0–1.7	2.3
Proteinuria				
n studied (% with proteinuria)	8 (0%)	9 (11%)	4 (0%)	0
Degree	–	1 trace	–	–
Hypertension, n (%)	2 (13%)	10 (50%)	9 (53%)	1 (33%)
1 medication	1	7	2	1
2 medications	1	2	3	–
3 medications	–	–	2	–
Not stated	–	1	2	–

* Two donor ages not available.

(25 years post donation). The fifth, age 66, has a serum creatinine level that vacillates from 1.7 to 2.2 (22 years post donation); creatinine clearance (24-h collection) is 52 mL/mm. A kidney biopsy reportedly showed nephromegaly with segmental and global glomerular sclerosis.

Specific issues

Donors were asked about their general health and specific diseases (e.g. cardiovascular, malignancy). Given the age of these donors, it is not surprising that we found sporadic reference to a variety of diseases. However, no data suggested a preponderance of any one disease. In addition, their SF-36 scores were similar to the age-matched general population.

We specifically asked about urogenital problems occurring post donation. Of our 256 donors, 11 (in addition to the five with elevated creatinine levels) reported problems. Of these 11, three had bladder infections and three had kidney infections. Another donor reported subsequent ureteral injury during a hysterectomy; temporary ureteral stenting was required. Another reported a traumatic laceration of the remaining kidney during a baseball game; the injury resolved. Another was treated for bladder cancer. And two donors (one had a serum creatinine level of 1.1; the other did not have it measured) reported having kidney stones.

A total of 33 donors reported 72 pregnancies post donation. Of these 33 donors, 25 had not had pregnancies before donation. Two donors reported having hypertension during their first pregnancy and a third had preeclampsia. Only one donor reported needing treatment for hypertension, during a second pregnancy.

Of interest, 250 donors responded to the question about family history of diabetes. Of these, 87 reported a family history (20 Type 1, 43 Type 2, 24 not specified). Post donation, 19 donors developed diabetes (Table 5); nine of them (47%) have no other family members with diabetes. Of the donors

Table 5: Onset of diabetes post donation

Age at donation	Age (years) at time of study	Interval from donation to diabetes (years)	Duration of diabetes (years)	Treatment	Diabetes in family	Serum creatinine level (mg/dL)
	48	?	–	Diet	No	
24	49	23	2	Diet	Type 2	1.3
34	49	15	<1	Diet	No	
23	51	13	15	Oral*	Type 2	
26	55	27	2	Diet	No	
23	57	34	<1	Oral*	Type 2	
23	59	16	20	Insulin	No	
39	62	16	7	Oral*	No	
37	63	21	5	Diet	Type 1	
37	66	26	3	Diet	Type 2	
	66	?	–	Insulin	Unspecified	0.7
36	67	27	4	Oral*	No	1.2
40	67	23	4	Insulin	No	
50	72	19	3	Insulin	Type 2	
53	74	6	15	Oral*	No	1.2
	75	7	–	Insulin	Type 2	
43	76	16	17	?	Type 2	
52	81	17	12	Insulin	Unspecified	1.1
	89	?	–	Insulin	No	2.0

* Oral = oral medications for hypoglycemia.

with diabetes, six control it with diet alone, five take oral hypoglycemics, and seven take insulin. Six have had serum creatinine determinations (Table 5).

Discussion

The most important issue in kidney transplantation today is the tremendous shortage of donor organs. Each year, more patients go on the cadaver waiting list than are actually transplanted. Thus, the waiting list continues to grow and, as a result, the waiting time gets longer.

One solution to this problem is to increase the number of living donor kidney transplants. In fact, such an increase has recently occurred in the United States. At least three factors have contributed to this increase. First, outcome for recipients of living donor kidneys has improved steadily over the last 2 decades; thus, centers previously reluctant to recommend living donation are now doing so. Second, outcome for recipients of living unrelated donor (LURD) kidneys has been shown to be equivalent to outcome for recipients of non-HLA-identical living related donor (LRD) kidneys (9); the increased acceptance of LURD kidneys has expanded the potential donor pool. Third, laparoscopic donor nephrectomy is now an option; it is associated with less pain and a quicker recovery time than conventional open nephrectomy (10). Consequently, more potential living donors may be willing to donate.

The major risks of living donation are the perioperative morbidity and mortality and the long-term (potentially negative) consequences of living with one kidney. Open nephrectomy is associated with a 0.03% mortality rate and roughly a 10% morbidity rate (5,6); as more centers start to do laparoscopic nephrectomy, these numbers will need to be reevaluated.

Almost all donors report an excellent long-term quality of life (11). According to a prospective randomized study, laparoscopic donors needed less pain medication, were discharged from the hospital sooner, drove sooner, and felt fully recovered sooner, as compared with donors having an open nephrectomy (10).

A major long-term concern regarding the use of living donors is whether unilateral nephrectomy (open or laparoscopic) may be associated with the development of kidney disease and with premature death. In fact, recent data suggest that kidney donors live longer than the age-matched general population (12). Although this finding may be due to selection bias, it contradicts the concept that donor longevity may be limited.

In some experimental animal studies, significant reduction of kidney mass resulted in proteinuria, glomerulosclerosis, and progressive kidney failure (13). Yet, in most of these studies, the contralateral kidney had been damaged. Importantly, many other animal studies did not show progressive decline in kidney function after unilateral nephrectomy (14,15).

In humans, no large clinical series supports the fear that, in an individual with two normal kidneys, unilateral nephrectomy leads to an increased risk of progressive kidney failure. However, with unilateral kidney agenesis or with uninephrectomy for nontransplant reasons, there are individual case reports of patients developing kidney disease, proteinuria, and

kidney failure (16,17). Thus, long-term follow-up of kidney donors is crucial.

Long-term follow-up after unilateral nephrectomy has been reported in the nontransplant population. In the study with the longest follow-up, Baudoin assessed patients who had undergone uninephrectomy in childhood (18). At the time of that study, patients were 18–56 years old and had been followed for up to 52 years. In general, their kidney function had been maintained. However, those followed >25 (vs. <25) years had a higher incidence of kidney failure, higher blood pressure, and increased urinary protein excretion. In another study, Narkun-Burgess et al. assessed 56 World War II veterans who had lost a kidney because of trauma during the war (follow-up, 45 years) and compared them to other World War II veterans of the same age (19). Mortality was not increased in those who had lost a kidney. None of the 28 living veterans (average age, 64 ± 4 years; average interval after kidney loss, 45 ± 1 years) had serious kidney insufficiency. Similar studies with shorter follow-up have noted small increases in blood pressure and an increased incidence of mild proteinuria after uninephrectomy (7,20,21). None of these studies suggested that the proteinuria was a precursor of kidney insufficiency.

A key question is this: if donors develop any form of kidney disease, even years post donation, will they have an accelerated course to kidney failure? Of interest, the impact of uninephrectomy has been studied in non-donors: in patients with diabetes and in patients with polycystic kidney disease. Of nine diabetic patients with either unilateral renal agenesis or unilateral nephrectomy (22,23), none suffered accelerated kidney failure. Zeier et al. compared 47 patients with polycystic kidney disease who required uninephrectomy (24) with matched controls who did not undergo uninephrectomy. The uninephrectomy had been done for infection, stones, hemorrhage, or trauma. Both the mortality rate and the median time interval for serum creatinine levels to rise from 4 mg/dL to 8 mg/dL were similar in the 2 groups.

Numerous authors have reported on donor follow-up less than 20 years post donation [reviewed in (7)]. Proteinuria, hypertension, and elevated creatinine levels have been occasionally seen, but there is no evidence of any increased rate, beyond that expected in the age-matched population. And, in serial studies of donors with proteinuria, it does not seem to progress to kidney failure; these results are similar to the non-donor uninephrectomy studies.

We previously reported on our cohort of living kidney donors after 20–30 years of follow-up (5). In that report, we compared 57 donors (average age, 61 ± 1 years) with 65 siblings who had not donated (average age, 58 ± 1.3 years). We found no significant differences in mean serum creatinine levels, proteinuria, or hypertension.

In the current study, we report on a larger series of donors after 20–30 years of follow-up, and include, for the first time, a cohort after over 30 years of follow-up. Our findings provide reasons for both optimism and concern. In general, the donors are doing well. Average serum creatinine levels have not deteriorated, there is little proteinuria, and the incidence of hypertension is similar to the age-matched general population (25). But, we have had a few donors develop kidney insufficiency, which has progressed to ESRD in some.

Of interest, 19 donors developed diabetes 6–34 years post donation. Of these, nine had no family history of diabetes. All of our prospective donors with a family history of diabetes were given a glucose tolerance test (GTT). (Today, we use fasting blood sugar as a screening criterion.) Only those with a normal GTT were accepted as donors. Of the 19 donors who subsequently developed diabetes, six had current serum creatinine levels measured; all results were normal.

Our study has some limitations. First, we have information on only 60% of our donors. Therefore, we cannot determine the true incidence of kidney dysfunction. It may be that we know of all such cases, assuming such donors would have a tendency to contact our center. Or there may be numerous cases of kidney insufficiency or ESRD among those we were unable to reach. Encouragingly, Bia et al. surveyed transplant centers in the United States (75% response rate) and concluded that there is no increase in ESRD post donation (26).

A second limitation is that, even though most of the donors we contacted provided information on hypertension and diabetes, only 125 (50%) had laboratory tests done for our study (serum creatinine levels, urinalysis). These 125 donors represent only 16% of the 773 donors at our institution prior to 1980. Thus, it is possible our data underestimate the extent of renal dysfunction or other morbidity associated with donation.

In conclusion, our retrospective analysis demonstrates that, although most of our kidney donors did well, a few developed kidney dysfunction and ESRD. Until the true numerator and denominator are known, it is impossible to determine whether the incidence of ESRD is increased as compared with the age-matched general population. Clearly, transplant centers need to develop a registry or other system for long-term follow-up of kidney function after living donation.

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