Living Kidney Donation: Does Unilateral Nephrectomy in Living Kidney Donors Impact Long-term Health Outcomes?

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A. Introduction

Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD). When compared with chronic dialysis, kidney transplantation is cost-effective, offers improved quality of life, and confers a progressive survival benefit.[i,ii] Unfortunately, the demand for donor kidneys vastly outpaces supply. At present, nearly 60,000 patients are listed for kidney transplant in the US, a number that has more than doubled over the past 10 years.[iii] Despite advances in organ preservation techniques, the supply of cadaveric kidneys remains limited. A total of 8,661 deceased-donor kidneys were recovered in 2003, a number that is just 13% higher than a decade ago.

While the ESRD population will continue to grow, the supply of cadaveric kidneys for transplantation is unlikely to increase significantly. Even in European nations where consent for organ donation is presumed upon death (Belgium), or where extensive use of 'marginal' donors is pursued, a large gap exists between the demand for donor kidneys and the cadaveric supply.[iv,v] Fortunately, living kidney donation has proven an attractive alternative to cadaveric transplant. With the advent of laparoscopic donor nephrectomy and constantly improving recipient outcomes, the number of living kidney donations in this country has grown by 115% over the past decade.[iii] 6,462 live kidney donors, accounting for 43% of all kidney transplants, were reported for last year, a number that will likely continue to rise.

From a recipient standpoint, living-donor transplant is regarded as superior to cadaveric transplant in every respect. Living-donor transplant allows for a full donor evaluation prior to transplant, elective scheduling of surgery at a time of optimized recipient health, and a minimum of graft ischemic time during the transplant operation.[vi] In many cases, recipients of living-donor allografts are able to undergo "preemptive transplantation" before the initiation of chronic dialysis, an intervention that improves patient and graft survival, reduces long-term costs, and improves recipient quality of life when compared to transplantation after the initiation of dialysis.[vii]

Across a range of measures, recipients of living-donor renal allografts have improved outcomes when compared to recipients of cadaveric organs. Their incidence of delayed graft function is reduced, they experience fewer episodes of acute and chronic rejection, and they require less maintenance immunosuppression.[vii] Living-donor recipients have shorter hospital stays, and they are able to return to work more quickly than those receiving cadaveric grafts.[vii] Renal allografts from living donors have been conclusively shown to offer better graft and patient survival in both the short and long term, with superior graft function.[vi] The overall survival of allografts from unrelated, 0/6 HLA-matched living donors equals or exceeds that of allografts from 6/6 HLA-matched cadaveric donors, a situation so highly prized that it triggers automatic national sharing of cadaveric donor kidney(s).[vii]

The major downside of living-donor renal transplantation is that it subjects a healthy patient to unnecessary surgery, with its attendant risks, as well as life after surgery with reduced renal mass. Fortunately, donor nephrectomy is a relatively safe procedure. The risk of donor death is most commonly cited as 0.03%, the risk of major complications 0.23-2.1%, and the risk of minor complications 8.0-14.7%.[vii,xiv] While any risk to an otherwise healthy patient must be closely scrutinized, the risks of living donor nephrectomy are generally considered to be acceptable.

Data regarding long-term health outcomes for kidney donors, while reassuring, is almost entirely retrospective in nature. A large NIH-funded study reported from Minnesota found no evidence for increased hypertension, proteinuria, or renal dysfunction in kidney donors as compared to sibling controls. On the other hand, creatinine clearance was significantly lower in donors when compared to

their siblings, the populations were not compared at baseline, and 40% of the donors were dead or lost to follow-up.[Error! Bookmark not defined.] Retrospective studies in Norway[vii] and Sweden[viii] have concluded that kidney donors have a decreased risk of death when compared to the population at large, although they make no attempt to correct for the fact that kidney donors are a highly screened and selected group. As many as two-thirds of potential living kidney donors evaluated in those centers were deemed unfit for donation, and the degree of bias this exclusion has on donor outcome data has not been adequately quantified.[Error! Bookmark not defined.]

In animal models, the reduction of renal mass has been associated with hypertension, proteinuria, glomerulosclerosis, and progressive renal insufficiency; data in humans is conflicting.[ix] A meta-analysis examining patients with reduced renal mass found evidence for lower glomerular filtration rate, increased incidence of proteinuria, and higher systolic and diastolic blood pressure in such patients, although these factors were not progressive in kidney donors.[xii] Other data suggests that the incidence of ESRD in living kidney donors ranges to as much as 1% with long follow-up (compared to an incidence of 0.03% in the general population), despite the extensive screening of donors for ESRD risk factors before nephrectomy.[Error! Bookmark not defined.]

A report based on records from the Organ Procurement and Transplantation Network (OPTN) reveals that as of 2002, even limited data allowed the identification of 56 living kidney donors who had subsequently been listed for kidney transplant themselves due to ESRD.[x] Of those, 20 had donated since the establishment of the OPTN database in 1987, a total of 0.04% of all living donors during that period. The predicament of these 20 patients is particularly worrisome, as they all underwent extensive, modern screening before donation, and they were all less than 15 years status-post donor nephrectomy at the time they were listed for transplant. Furthermore, counting only those listed for transplant significantly underestimates the true incidence of ESRD, suggesting that there may be more kidney donors with ESRD than were identified in that report. Prospective studies with long follow-up are needed to determine the true effect of elective donor nephrectomy on donor health outcomes.

B. Study Purpose and Rationale

Living donor registries have been established in Switzerland[viii] and Norway[xiv] to follow the health of living kidney donors, but no registries of kidney donors along with equally healthy control subjects have been reported. This study will establish a cohort of healthy living kidney donors and healthy control subjects in an effort to conclusively demonstrate what effect unilateral donor nephrectomy has on long-term health outcomes. Prospective data will be collected from subjects during initial transplant evaluation and at regular follow-up, and analyzed on an ongoing basis.

C. Study Design and Statistical Analysis

This is a prospective, non-randomized, controlled, partially-blinded study. Subjects will be potential kidney donors presenting for transplant evaluation. All subjects will undergo a full pre-transplantation donor workup irregardless of blood type, and will then be stratified by a transplant nephrologist blinded to patient identity into two groups: "suitable for donor nephrectomy" and "unsuitable for donor nephrectomy." Transplant recipient characteristics will not be considered during this stratification, and the choice of which potential donor actually does go on to donate a kidney (if any) will be left to the patient and the primary team.

Subjects deemed unsuitable for transplant will not be followed on a prospective basis. Those deemed eligible to donate will be further stratified into two groups ("donors" and "eligible non-donors") based on their decision to donate or to not donate a kidney. These two groups will be followed regularly for an indefinite period as outlined below. The location of follow-up visits will be at the CUMC Comprehensive Transplant Center or with outside providers chosen by the study participants in the course of their regular medical care.

The primary end point will be incidence of renal insufficiency defined as age-adjusted serum creatinine (Cr) >2SD above the mean. Secondary end points include incidence of microalbuminuria (urinary albumin to creatinine ration of 30 to 300 mg/g) or proteinuria (urinary albumin to creatinine ratio of ≥300mg/g), incidence of ESRD, incidence of hypertension according to NHLBI criteria, and incidence of death from any cause.

Statistical analysis will be using chi-square test with an alpha of 0.05 and power of 80%. Taking p=0.025 for control subjects having serum Cr >2SD above the age-adjusted mean, 127 subjects and 127 controls will be needed to detect a quintupling (to p=0.125) of the risk for serum Cr elevation greater than 2SD above the age-adjusted mean. This sample size would allow for detection of a 60% increased risk of hypertension among donors (assuming p=0.30 for controls over long-term follow-up), and an increase in the risk of ESRD from 0.03% to 7.5%. A sample size of 1000 subjects and 1000 controls would be needed to detect a risk for ESRD of 1% among kidney donors according to the above statistical parameters.

D. Study Procedures

Initial testing required includes at minimum:

- Full medical history
- Full physical examination including serial blood pressure measurements
- EKG
- Chest X-ray
- Urinalysis, urine microscopy, and urine culture
- 24-hour urine for protein, electrolytes, and creatinine
- Blood type, crossmatch, and HLA typing
- Complete Blood Count
- Comprehensive Metabolic Panel including serum BUN, Creatinine and LFTs
- Fasting glucose and/or Hemoglobin A1c
- HBV, HCV, HIV, EBV, CMV, and syphilis serologies
- Renal imaging by renal ultrasound with doppler, CT angiogram, or MR angiogram
- Psychosocial evaluation as per transplant protocol
- Administration of the SF-36v2 form for baseline measurement

Follow-up testing will be at 6 months after transplant (donors) or 6 months after the initial workup has been completed (controls), and then at 1 year, 2 years, 5 years, and every 3-5 years thereafter.

Follow-up testing includes any tests clinically indicated in addition to:

- Interval history
    - Full physical exam including serial blood pressure measurements
- Urinalysis
- If within normal limits: no further urine studies
    - -f positive for protein or albumin: 24-hour urine for protein, electrolytes, and creatinine
- Basic Metabolic Panel including serum BUN and creatinine
- Administration of the SF-36v2 form

All initial testing may be done at the CUMC Comprehensive Transplant Center or by an outside physician with the results forwarded to CUMC, as per existing transplant center protocol.

Follow-up testing may likewise be completed at the CUMC Comprehensive Transplant Center or by an outside physician, at the discretion of the study participants.

E. Study Drugs

No drugs will be used in this study other than IV contrast material for those undergoing CT or MR angiogram. Patients will not undergo CT or MR angiogram unless they provide informed consent for the procedure.

F. Medical Devices

No medical devices will be used in this study.

G. Study Questionnaires

Standard SF-36v2 Questionnaire

H. Study Subjects

Inclusion Criteria:

- Age >18
- Identified by patient requiring kidney transplant as a potential donor
- Independently expressed interest in undergoing donor evaluation
- Independently expressed desire to donate kidney
- Independently expressed interest in long-term participation in this study, regardless of outcome of donor work-up/selection process.
- Study approval and informed consent

Exclusion Criteria

- Age <18 years
- Known contraindication to kidney donation prior to evaluation (renal disease, cancer other than non-melanoma skin cancer, diabetes, hypertension, HBV infection, HCV infection, HIV infection)

I. Recruitment of Subjects

Subjects will be recruited from consecutive potential living kidney donors presenting for transplant evaluation at CUMC.

J. Confidentiality of Study Data

All subjects will be assigned a randomly-generated unique numerical identifier to be used throughout the study. All Protected Health Information will be kept in locked files by the Department of Surgery. Only the Principal Investigator and Study Coordinator will have access to Protected Health Information.

K. Potential Conflict of Interest

None.

L. Location of Study

CUMC Comprehensive Transplant Center (PH-12)

M. Potential Risks

The risks of this study to subjects are minimal. Standard venipuncture will be performed in all subjects. Imaging with IV contrast will be performed in subjects only after an individual discussion of the risks and benefits and if informed consent has been obtained.

N. Potential Benefits

In published data, donor evaluation has led to the discovery of previously unrecognized and treatable medical conditions in 10% or more of those evaluated.[xv]

O. Alternative Therapies

This study is not evaluating any specific therapy.

P. Compensation to Subjects

The cost of all study evaluations, tests, and procedures not otherwise covered will be provided for participants.

There will be no additional compensation; testing or evaluation triggered by this study but outside its confines will not be provided for.

Q. Costs to Subjects

No direct costs to subjects, other than time devoted to study procedures.

R. Minors as Research Subjects

No minors will be enrolled in this study.

S. Radiation

Standard chest x-ray will be provided for each study participant during the initial evaluation. Study participants may undergo standard CT angiogram after a discussion of risks and benefits on an individual basis; alternatives to CT angiogram are outlined in 'Study Procedures.'

T. References

i. Davis, CL. Evaluation of the Living Kidney Donor: Current Perspectives. *American Journal of Kidney Diseases* 2004 Vol 43(3):508-530.

ii. Gallon LG et al. Pretransplant Evaluation of Renal Transplant Candidates. *Seminars in Nephrology.* 2002 Vol 22(6):515-525

iii. Organ Procurement and Transplantation Network data at http://www.unos.org/data/about/viewDataReports.asp Accessed 7/19/04.

iv. Data from Eurotransplant at http://www.eurotransplant.nl/index.php?id=waitinglist Accessed 7/19/04.

v. Jakobsen, A et al. Ethics and Safety of Living Kidney Donation. *Transplantation Proceedings*. 2003 Vol 35:1177-1178

vi. 2,500 Living Donor Kidney Transplants: A Single-Center Experience. *Annals of Surgery.* 2001 Vol 243(2):149-164

vii. Liu EH et al. Ethical Issues in Living Renal Donation. *Transplantation Proceedings.* 2003 35:1174-1176.

viii. Thiel G. Living kidney donor transplantation- new dimensions. *Transplant International*. Vol 11[Suppl 1]:S50-S56

ix. Johnson, EM et al. Complications and Risks of Living Donor Nephrectomy. *Transplantation* 1997 Vol 64(8):1124-1128

x. Holdaas H et al. Mortality of kidney donors during 32 years of observation. *Journal of the American Society of Nephrology.* 1997 Vol 8:685A

xi. Fehrman-Ekholm, I et al. Kidney donors live longer. *Transplantation*. 1997 vol 64(7):976-978

xii. Kasiske, BL et al. Long-term effects of reduced renal mass in humans. *Kidney International* 1995 48(3):814-819

xiii. Ellison MD et al. Living kidney donors in need of kidney transplants: A report from the Organ Procurement and Transplantation Network. *Transplantation* 2002 Vol 74:1349-1351.

xiv. Hartmann A et al. The risk of living kidney donation. *Nephrol Dial Transplant* 2003 18:871-873

xv. Najarian JS et al. 20 years or more of follow-up of living kidney donors. *Lancet* 1992 Vol 340:807-810.