Long-Term Risks to Live Kidney Donors

Simin Goral MD
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania
Outline

• Background
• Survival
• Kidney disease; ESRD, CKD, proteinuria
• Cardiovascular disease: hypertension, ischemia and heart failure
• Risks to pregnancy
• Subgroups of concern: “complex donors”
Kidney Transplantation

- The **best** treatment option for majority of patients with ESRD regardless of sex, race, age or cause of ESRD
  - Increase in life expectancy
  - Better quality of life
  - Decrease in healthcare costs
- The demand for kidney transplantation exceeds the supply of transplantable organs
- Waiting times are quite long
Living Donors

- The survival of a kidney transplanted from a live donor is much better.
- Success of live donor transplantation no longer necessitates the consideration of an HLA match unless there is possibility of a transplant from HLA identical sibling.
- The survival rate of a kidney transplant from a genetically unrelated donor is excellent.
Living Donors

- In 1954: Requiring an identical twin for success
- During the 1980’s: Selection of an HLA-matched family member
- Current: any person (irrespective of the HLA match) can be a donor if they are medically and psychosocially suitable
- It is illegal to buy or sell kidneys or coerce a donor
Potential Living Donor

- Appropriate for donation from nephrologic standpoint – what is his//her renal risk?
- Healthy enough for surgery?
- Competent, willing to donate; free of coercion
- Medically and psychosocially suitable
- Fully informed of the risks and benefits of donation
- Fully informed of risks, benefits, and alternative treatment available to the recipient
Potential Advantages of Live Donation

- Better short-term and long-term results
- More consistent early function and ease of management
- Avoidance of long wait for cadaveric transplant
- Less delayed graft function
- Less aggressive immunosuppressive regimens
- Surgery can be planned ahead (medical and personal convenience)
- Emotional gain to donor
- Helps relieve stress on national cadaver donor supply
Potential Disadvantages of Live Donation

- Psychological stress to donor and family
- Inconvenience and risk of evaluation process (i.e. IV contrast)
- Operative mortality (0.03% or 1 in 3,500 patients)
- Major perioperative complications (4.4%, range: 0.0 to 13.0%)
- Minor postoperative complications (up to 50%)
- Long-term morbidity
- Risk of traumatic injury to remaining kidney
- Risk for unrecognized chronic kidney disease
Medical Follow-up of Living Kidney Donors by 1 Year After Nephrectomy

• In 2003, our program developed a policy recommending that donors receive medical follow-up by 1-year postnephrectomy.

• A retrospective cohort study of 137 live kidney donors at UPenn.

• Medically complex donors: hypertension, body mass index ≥30, nephrolithiasis, age 65 years or older, creatinine clearance<80 mL/min/1.73 m2, or had a first-degree relative with diabetes mellitus.

• Adequate follow-up: one visit with a nephrologist at our center, or blood pressure, serum creatinine, and urinalysis checked elsewhere.

Medical Follow-up of Living Kidney Donors by 1 Year After Nephrectomy

- Eighty-three donors (61%) had adequate follow-up, 42 did not, and 12 could not be contacted.
- At multivariate logistic regression, donors with adequate follow-up were more likely to be medically complex and older than donors with inadequate follow-up.
- A substantial minority of donors do not receive recommended care by 1 year after nephrectomy.

Mortality

• Peri-operative death rate: 1 in 3,500; did not change during the last 15 years

• Long-term mortality
  • Caucasian donors
    • No higher than demographically-matched individuals in the general population; even better survival in donors
      • Ibrahim H, et al. NEJM 2009
  
• All US donors (median follow-up 6 years)
  • No higher than demographically- and comorbidity-matched individuals in NHANES
    • Segev et al. JAMA 2010
Figure 1. Survival of Kidney Donors and Controls from the General Population.
I bars at 5-year intervals indicate 95% confidence intervals for the probability of survival among kidney donors.

Ibrahim H, et al. NEJM 2009
• Kaplan-Meier curves comparing cumulative mortality of live kidney donors and matched controls for the entire cohort of live donors
• Long-term mortality was similar or lower for live kidney donors than for the matched NHANES III cohort throughout the 12-year period of follow-up

Segev et al. JAMA 2010
Mortality: Issues

- Short follow-up in most of the studies
- Mostly Caucasians studied
- Medically complex donors/subgroups; donors with hypertension, black donors, obese donors-more information needed
End-Stage Renal Disease

- Low relative and absolute risk of ESRD among Caucasian donors
  - Minnesota: 1 in 180 million persons per year versus 1 in 268 persons per year among US Caucasians (<1%)
    - Ibrahim H, et al. NEJM 2009
  - Sweden: 6 of 1,112 donors (0.5%) at median 20 years follow-up
End-Stage Renal Disease

- OPTN and Center for Medicare and Medicaid Services (CMS) databases: the number of living kidney donors who donated between October 1, 1987 and March 31, 2003 and subsequently developed ESRD
- 126 cases of ESRD among 56,458 living kidney donors (0.22%)

• The living kidney donor ESRD rate was nearly five times higher for Blacks than for Whites and two times higher for males than females.

• However, these ethnic and gender-related differences were similar to those previously reported for ESRD in the general population.

Chronic Kidney Disease

- Conventional definition should not be applied
  - eGFR < 60 ml/min/m² is common among prior kidney donors, but no systemic diseases
  - Direct measurements among white donors suggest GFR in 60 – 70 ml/min range is common at 10 years


- Ten years after nephrectomy, donors had a GFR that was 10 ml/min lower compared to controls; 12% of donors developed a GFR less than 60 ml/min during follow-up

• For 30-year old donors, the median eGFR typically increases during the first 17 years, then remains constant for ~8 years and slowly declines thereafter. For 50-year-old donors, the median eGFR is expected to increase during the first 15 years or so and then to enter a phase of slight progressive decline.

Proteinuria

• Between 1973 and 2001, 152 living donor nephrectomies from Germany; all Caucasian
• Seven of 152 donors had died from nonrenal diseases
• Of the remaining 145, data collection on 135 (93%) donors
• The mean time from nephrectomy to the current evaluation: 11 ± 7 (range 1–28) years

Proteinuria

- A decrease in creatinine-clearance or GFR by 20–25%, but no correlation between residual renal function and blood pressure or the amount of proteinuria in this cohort
- An increase in urinary protein excretion, but pathological albuminuria was rare

Long-Term Consequences of Kidney Donation-A Meta-Analysis

- 48 studies from 27 countries: a total of 5048 donors
  - Follow-up: average of 7 years after donation (range 1–25 years); the average 24 h urine protein: 154 mg/day; the average GFR: 86 ml/min.
  - In controlled studies urinary protein was higher in donors - became more pronounced with time (3 studies in 59 controls/129 donors; controls 83 mg/day vs donors 147 mg/day)
  - An initial decrease in GFR after donation was not accompanied by accelerated losses over that anticipated with normal aging (6 studies in 189 controls/239 donors; controls 96 ml/min vs donors 84 ml/min)

• The average 24 h urine protein: 154 mg/day; the average GFR: 86 ml/min

• Kidney donation resulted in small increases in urinary albumin, which increased with time after donation

Proteinuria and Reduced Kidney Function in Living Kidney Donors- A Meta-Analysis

• Ten years after nephrectomy, donors had a GFR that was 10 ml/min lower compared to controls
• 12% of donors developed a GFR less than 60 ml/min during follow-up
• The pooled incidence of proteinuria: 12%

Hypertension

• Higher risk of HTN
  • Mean time since donation was 15 years, ranging from 2 to 43 years
  • 23% (126/546) of donors were on antihypertensive medication
  • An additional 22% (117/543) of the donors were found to have undiagnosed hypertension (BP >140/90 mm Hg) and were not on antihypertensive medication at the time of the medical follow-up
• Systolic BP increased with both time since donation (P = 0.002) and age (P < 0.001)

Cardiovascular Disease and Hypertension Risk

- A retrospective cohort from Ontario, Canada between the years 1993 and 2005
- 1278 living donors and 6359 healthy adults as controls
- Follow-up: a mean of 6.2 years (range 1-13 years) after donation
- There was no significant difference in death or cardiovascular events between donors and controls (1.3% vs 1.7%)
- Donors (mean age 41 years) were more frequently diagnosed with hypertension than controls (16.3% vs 12%) but were also seen more often by their primary care physicians

Cardiovascular Disease

- A population based matched cohort study in Ontario, Canada
- 2028 living kidney donors and 20,280 matched non-donors; The median follow-up: 6.5 years
- A total of 609 donors and 5744 non-donors were followed for a period of 10 years or more
- The risk of major cardiovascular events in donors is no higher in the first decade after kidney donation compared with a similarly healthy segment of the general population

Garg AX, et al for the DONOR Network BMJ 2012
Garg AX, et al for the DONOR Network BMJ 2012
Long-Term Consequences of Kidney Donation-Hypertension

- 3698 kidney donors who donated kidneys during the period from 1963 through 2007
- From 2003 through 2007: glomerular filtration rate (GFR) and urinary albumin excretion were measured; the prevalence of hypertension, general health status, and quality of life were assessed in 255 donors

Ibrahim H, et al. NEJM 2009
Long-Term Consequences of Kidney Donation-Hypertension

- The survival of kidney donors: similar to that of controls-matched for age, sex, and race or ethnic group
- At a mean of 12±9 years after donation, 85.5% of the subgroup of 255 donors had a GFR of ≥60 ml/min, 32.1% had hypertension, and 12.7% had albuminuria
- Older age and higher BMI, but not a longer time since donation, were associated with both lower GFR (<60 ml/min) and hypertension

Ibrahim H, et al. NEJM 2009
Diabetes

- Retrospective study of 4650 living kidney donors from October 1987 through July 2007
- Black donors had a higher risk of diabetes, perhaps lower in magnitude than the association of race with diabetes in the general population

Lentine KL, et al. NEJM 2010
Long-Term Morbidity

- 73 patients who had unilateral nephrectomy
- Normal kidney function, no proteinuria at the time of surgery
- Reasons for nephrectomy: stones in 29, renal mass in 14, hydronephrosis in 11, and renal tuberculosis in 5 patients
- Mean follow-up: 13.6± 8.6 years (18 months-35 years)
- 20 in 73 patients (27%) developed proteinuria/renal insufficiency

In 14 obese patients (BMI>30 at the time of nephrectomy), 13 (92%) developed proteinuria/renal insufficiency.

Rate of Hypertensive-Diseases of Pregnancy and Birth Complications

- Hypertensive disorders of pregnancy (preexisting HTN, gestational HTN, preeclampsia, eclampsia and preeclampsia superimposed on preexisting HTN): about 10% in general population cohorts
- Average incidence of gestational hypertension: 7.9%; preeclampsia: 3.3%; and eclampsia: 0.06%
- Premature birth and low birth weight: overall incidence of 2% to 13%
- In the United States, fetal death (still birth and neonatal death) is less than 1% and maternal death is less than 0.1%

Pregnancy After Kidney Donation

- Retrospective cohort study from Norway: 106 occurred after donation in 69 of the donors
- Mean time from donation to delivery was 5.0 years
- Comparison of female kidney donors to:
  - Pre-donation pregnancies
  - Randomly selected controls from the general population
- Gestational hypertension: in 3/106 (2.8%) pregnancies after donation and in 11/620 (1.8%) pregnancies before donation

• Small, but statistically significant increase in the risk of preeclampsia (5.7%) after kidney donation (vs 3.3% in general population)
• The rate of preeclampsia in the control group was 3.1%

Donors-Pregnancy
Minnesota Experience

- Donors from 1963 – 2007
- 2102 women “not taking anti-hypertensive medications” and “normal urinary protein excretion” and non-obese
- 490 pregnancies in 239 donors
- Attempts to contact donors by phone, mailing and through recipient
  - Data through questionnaires and telephoning
  - Not validated through medical records

Donors-Pregnancy
Minnesota Experience

• Gestational HTN: 5.7%, preeclampsia 5.5%: similar to Norwegian experience, gestational diabetes: 2.7%, full-term birth: 73.7%, prematurity: 7.1% and fetal loss 19.2%

• 239 donors with pregnancies after donation had their renal function assessed about 20 years after donation (13 years after last pregnancy)

• Mean serum creatinine: 1.0 mg/dL (88 μmol/L), 26% were hypertensive and 9% had proteinuria

Pregnancy and Donors

- Women should be asked about prior gestational complications.
- Prior preeclampsia or gestational diabetes should probably be a contraindication to donation, especially if there is a family history of kidney disease.
- If feasible, donors should complete child-bearing before donation.
- Young female donors should be counseled about increased risk to future pregnancies.
  - Post-donation: about 6% will develop pre-eclampsia during pregnancy.
Subgroups of Concern

- Obese donors
- Hypertensive donors
- Strong family history of diabetes or hypertension
- Donors over 60 years
Amsterdam Forum Guidelines

- A **GFR**<80 ml/min or 2 SD below normal (based on age, gender, and BSA corrected to 1.73 per m2) generally preclude donation
- Patients with a **BP**>140/90 mmHg by ABPM are generally not acceptable as donors
- Patients with a **BMI**>35 kg/m2 should be discouraged from donating
- **Dyslipidemia** alone does not exclude kidney donation (keep an eye on “Metabolic Syndrome”)

*Transplantation March 27, 2005*
Amsterdam Forum Guidelines

• A 24 h urine protein of >300 mg is a contraindication to donation

• Individuals with a history of diabetes or fasting blood glucose \( \geq 126 \text{ mg/dl} \) (7.0 mmol/l) on at least two occasions (or 2 h glucose with OGTT \( \geq 200 \text{ mg/dl} \) (11.1 mmol/l) should not donate
Amsterdam Forum Guidelines

- Asymptomatic potential donor+history of a **single stone** may be suitable if:
  - No hypercalcuria, hyperuricemia, or metabolic acidosis
  - No cystinuria or hyperoxaluria
  - No urinary tract infection
  - No evidence of multiple stones or nephrocalcinosis on CT scan
Amsterdam Forum Guidelines

- **Stone** formers who should not donate are:
  - Nephrocalcinosis on X ray or bilateral stone disease
  - Stone types with high recurrence rates, and are difficult to prevent
Living Donation

- Among Caucasian donors without risks for future kidney disease
  - Long life and low risk of ESRD
  - No increased risk of cardiovascular disease
- Much less information about medically complex donors – e.g. obese and hypertensive donors