Long-term *Non-ESRD* Kidney Donor Risks

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Conflict of Interest Disclosure

I have no relevant financial relationships to disclose

No off label use will be discussed

Minnesota data – Hassan Ibrahim: (*94% Caucasian*)

Donor Nephrectomy Outcomes Research Network

– Amit Garg et al, Canadian Group

Krista Lentine Dorry Segev

(data not provided [*high % Caucasian*])

Renal and Lung Living Donors Evaluation Study (RELIVE)

NIH funded: 3 kidney tx centers (U Alabama, Mayo, U Mn) (*93% Caucasian*)

What do we worry about post-donation?

Reduced GFR will impact (medical) health

a) direct impact e.g., In the general population, mild reduction in GFR is associated increase in mortality

Pregnancy in the setting of reduced GFR is associated with adverse outcomes for both the mother and fetus

b) indirect - Starting with a reduced GFR will accelerate the impact of other post-donation events; diabetes; Htn

Psychosocial Problems related to the donation

e.g., regret, financial, depression

"Risk" is used in 2 ways

1) Attributable Risk?

Most studies simply describe LD outcomes

? Are any adverse outcomes (medical or psychosocial) related to donation?

Steiner, R, NEJM 374: 479, 2016

In the general population, 90% ESRD cases occur after 44 yrs of age; 50% after 60 yrs of age

Many diseases that begin later in not present at evaluation when young

"Risk" is used in 2 ways

2) Identifying at evaluation a donor candidate at increased risk for a particular outcome.

e.g., there are risk calculators used in the general population to identify individuals at increased risk for type 2 diabetes.

Identifying donors at increased risk for other life-related events is helpful in both donor counseling and selection.

Are There (Non-ESRD) Risks Attributable to Donation?

Prospective Controlled study of LDs

Donors and controls enrolled before donation

At 3 years: 182 of LDs and 173 controls participating

***No difference* in BP or in urinary protein-creatinine ratios**

From 6 to 36 mos post-donation, donors had *higher* serum parathyroid hormone, uric acid, homocysteine, and potassium levels

Donors had *lower* hemoglobin

Linear slope of the GFR filtration rate (iohexal) ↓ 0.36±7.55 ml/min per yr in controls but increased in donors by 1.47±5.02 in donors (p=.005)

Kasiske et al, AJKD,66:114,2015

Longer-term studies (vs controls) have also not shown *increasing* BP or proteinuria

20 year follow-up of donors (n=57) and *sibling controls* (61). (Najarian, Lancet, 1992)

20 year follow-up of donors and Matched 1:1 with *NHANES controls* on: Age, sex, race and BMI (Ibrahim, NEJM, 2009)

	Donors	NHANES controls
Urinary ACR	2.2	2.2
Antihypertensives	40%	38%

Meta-analysis - Donation results in small increases in proteinuria and drop in GFR *without accelerated losses over a subsequent 15 years* (Garg, Kidney International 2006)

Increased CVD Disease and Mortality?

Compared to general population, no difference

Donors Compared to *Healthy Population Controls*

Country	Setting	n	median f/u
USA	National registry	80, 347	6.3 *yrs
	Segev et al, JAMA 2010		
Canada	Province (Ontario)	2,028	6.0 **yrs
	Garg et al, Transplantation 2008		
USA	>55	3,368	7.8**yrs
	Reese et al, AJT, 2014		

* No difference in mortality ** no difference in CVD or mortality

Mjoen, G et al, Kidney Int 2013: Median f/u=15.1 yrs

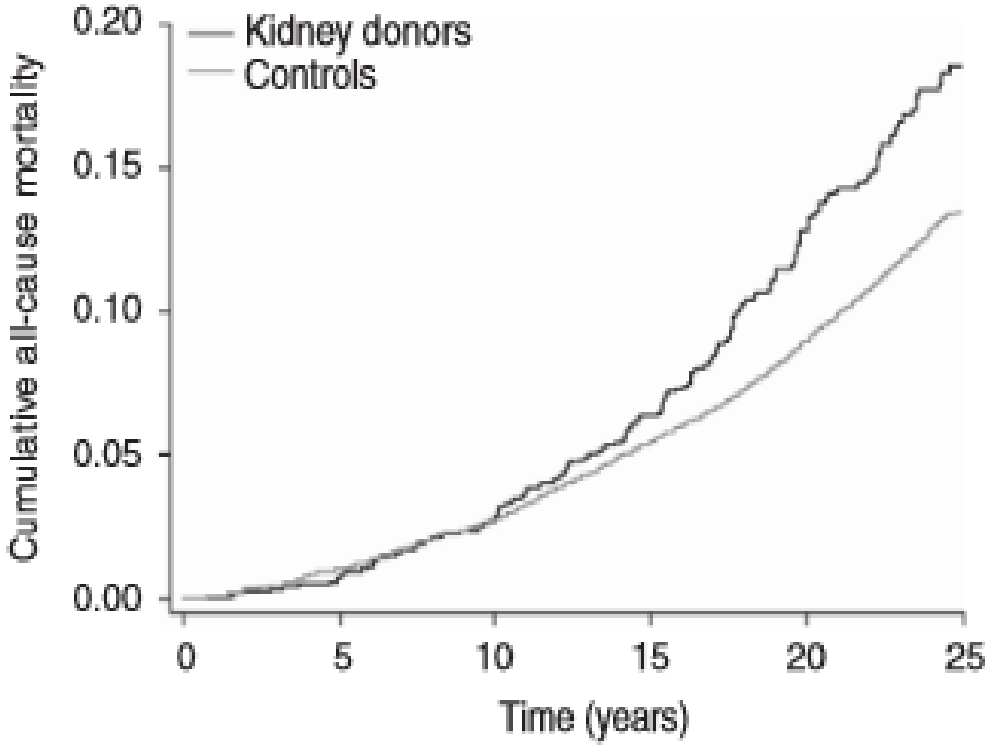


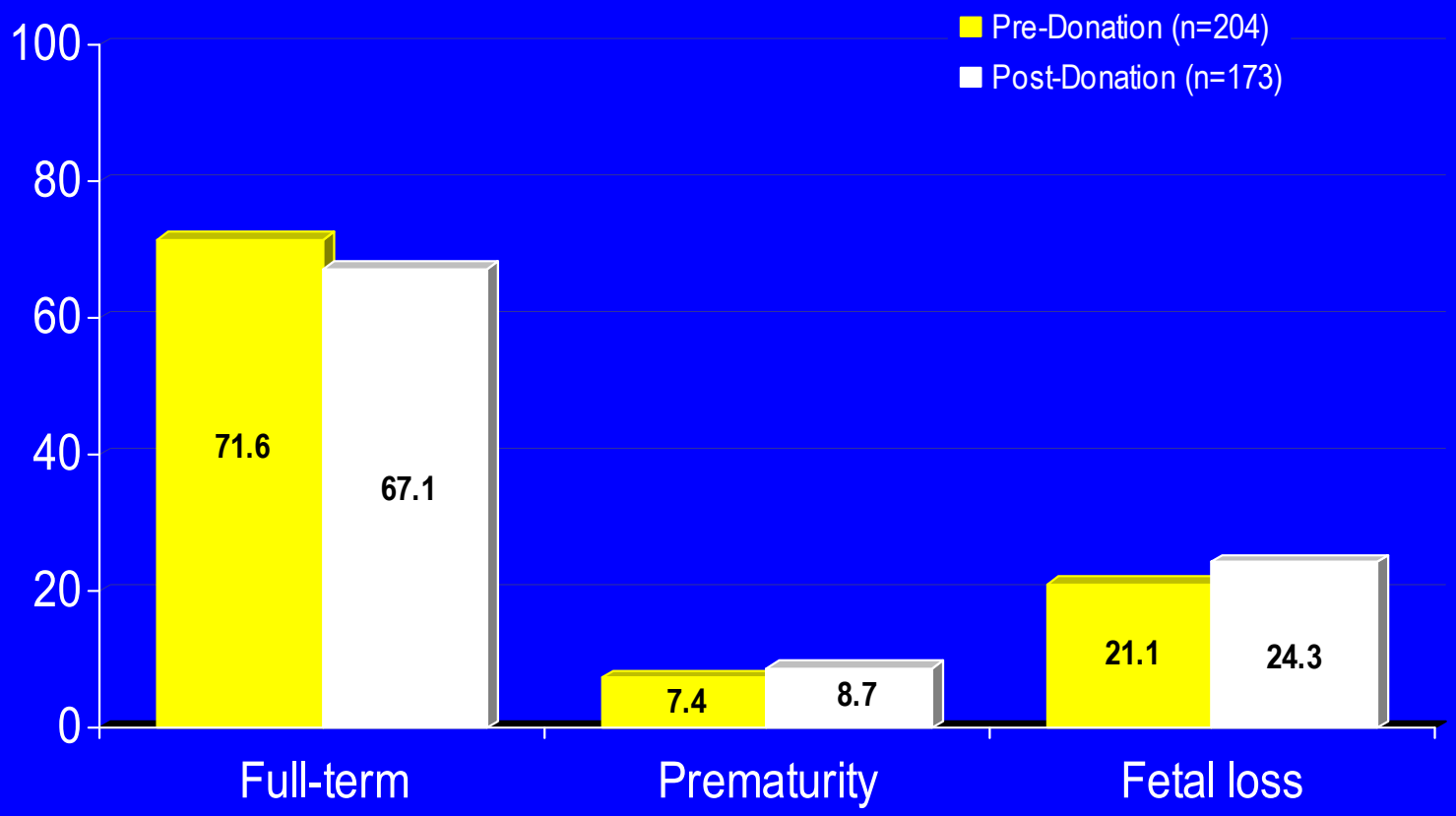
Figure 2 | Cumulative mortality risk in kidney donors and controls, adjusted for year of donation. Controls are matched to donors for age, sex, systolic blood pressure, body mass index, and smoking status.

Impact of Donation on Pregnancy

Pregnancy after kidney donation is associated with:

A. no increased risks
B. Increased risk for the mother
C. Increased risk for the child
D. Increased risks to both mother and child

Fetal outcomes in donors with both pre- and post-donation pregnancies

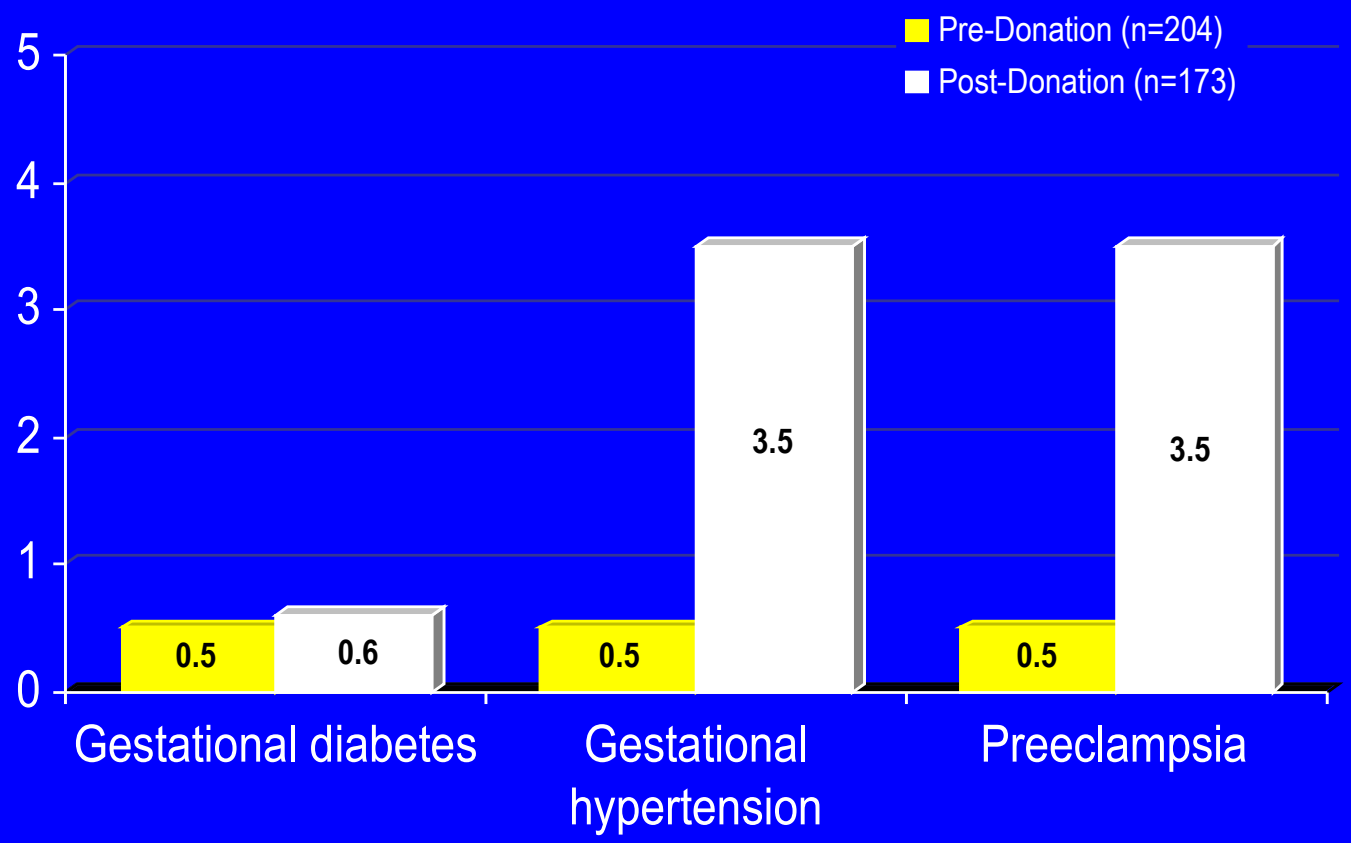


Ibrahim et al, AJT 9:825, 2009

Ibrahim et al. Am J Transplant 2009

Maternal outcomes in donors with BOTH pre- and post-donation pregnancies

Odds Ratio 5.21 (1.28-21.2)



Ibrahim et al. Am J Transplant 2009

Ibrahim et al, AJT, 9:825, 2009

Rates of all other complications lower than that seen in the general population

Reisaeter et al, AJT 9: 820, 2009

Matched donors with population controls

Preeclampsia increased in donors

Garg et al, NEJM, 372;124. 2015

Matched 85 donors with 510 healthy controls

Gestational hypertension or preeclampsia more common in the donors (11%) vs controls (5%).

- Implications --- pregnancies after donation should be considered "high risk" with frequent BP checks

Re-hospitalization

Schold et al, cJASN 9:355, 2014

9% rehospitalization (excluding pregnancy) within 3 years

- less than seen with appendectomy or cholecystectomy
- risk factors: older age Afr American
  depression hypothyroidism
  longer initial stay

? What % is attributable risk?

An eGFR <60 in a kidney donor:

A. should be treated as CKD
B. is associated with the same risks as low eGFR in the general population
C. both of the above
D. neither of the above

Inappropriate Diagnosis of CKD

eGFR <60 leads to diagnosis of CKD

- automated printout on lab tests
- U of Mn: 35% eGFR <60; 14% mGFR <60

In the general population low eGFR is a consequence of kidney or systemic disease *whereas* in donors it may be a consequence of nephrectomy

Inappropriate Diagnosis of CKD can lead to numerous problems - e.g., multiple ongoing lab tests, psychological concerns

Other potential attributable risks

Amit Garg: Donor Nephrectomy Outcomes Research Network

Fractures: Am J Kidney Dis, 59: 770, 2012

G.I. bleeding: Clin Transplant, 28:530, 2014

Acute kidney injury: Nephrol Dial Transplant, 27: 3291, 2012

Gout: more likely to be given a diagnosis of gout (3.4% vs 2.0: HR, 1.6; P<0.001).

more likely to receive a prescription for allopurinol or colchicine (3.8% vs 1.3%; OR, 3.2; P=0.002)

AJKD 65: 925, 2015

Impact of Post-Donation Events

Time Dependent Analysis of Subsequent Donor Diabetes Contribution to Major Events

Outcome	Events	Adjusted Hazards Ratio (95% CI)	P-Value
Death	7%	1.03 (0.67-1.6)	0.89
Hypertension	26.8%	2.53 (1.91-3.35)	<0.0001
Proteinuria	6.6%	3.18 (2.18-4.65)	<0.0001
eGFR < 60	38.5%	1.26 (0.99-1.61)	0.06
eGFR < 30	2.8%	2.42 (0.82-7.11)	0.06
ESRD	0.6%	2.52 (0.86-7.36)	0.11

Adjusted for age, sex, BMI, glucose, year of donation

Ibrahim, ATC

Post-Donation Development of Diabetes and Hypertension

Postdonation diabetes more than doubled the risk of eGFR<30 ml/min per 1.73 m^2 or ESRD

Postdonation hypertension produced a similar magnitude of increased risk of eGFR<30 or ESRD (HR, 2.79; 95% CI, 1.55 to 5.03; *P*<0.002)

Ibrahim, JASN 2016

Determining Increased Risk at Donor Evaluation

Minnesota dataset (3956 Caucasians; 93% returning surveys); Mean age at donation = 39 yrs

Utilizing this dataset and baseline and laboratory values available at donor evaluation, we developed a model that predicts the risk of many of these outcomes (at 5 yr intervals)

Ibrahim et al, JASN 2016 (epub, February 17)

(live version in Supplemental material)

Limitations:

a) Caucasian population

b) needs to to be validated in other cohorts

Ibrahim et al, JASN 2016

Of those with information:

	Median age post-donation	Median yrs
6% developed proteinuria	55.8	18 yrs
35% eGFR <60	56.6	9 yrs
3% eGFR <30	68.4	24 yrs
6% diabetes	56.6	19 yrs
28% hypertension	55.1	18 yrs

(in a subset with measured GFR, 14% mGFR<60

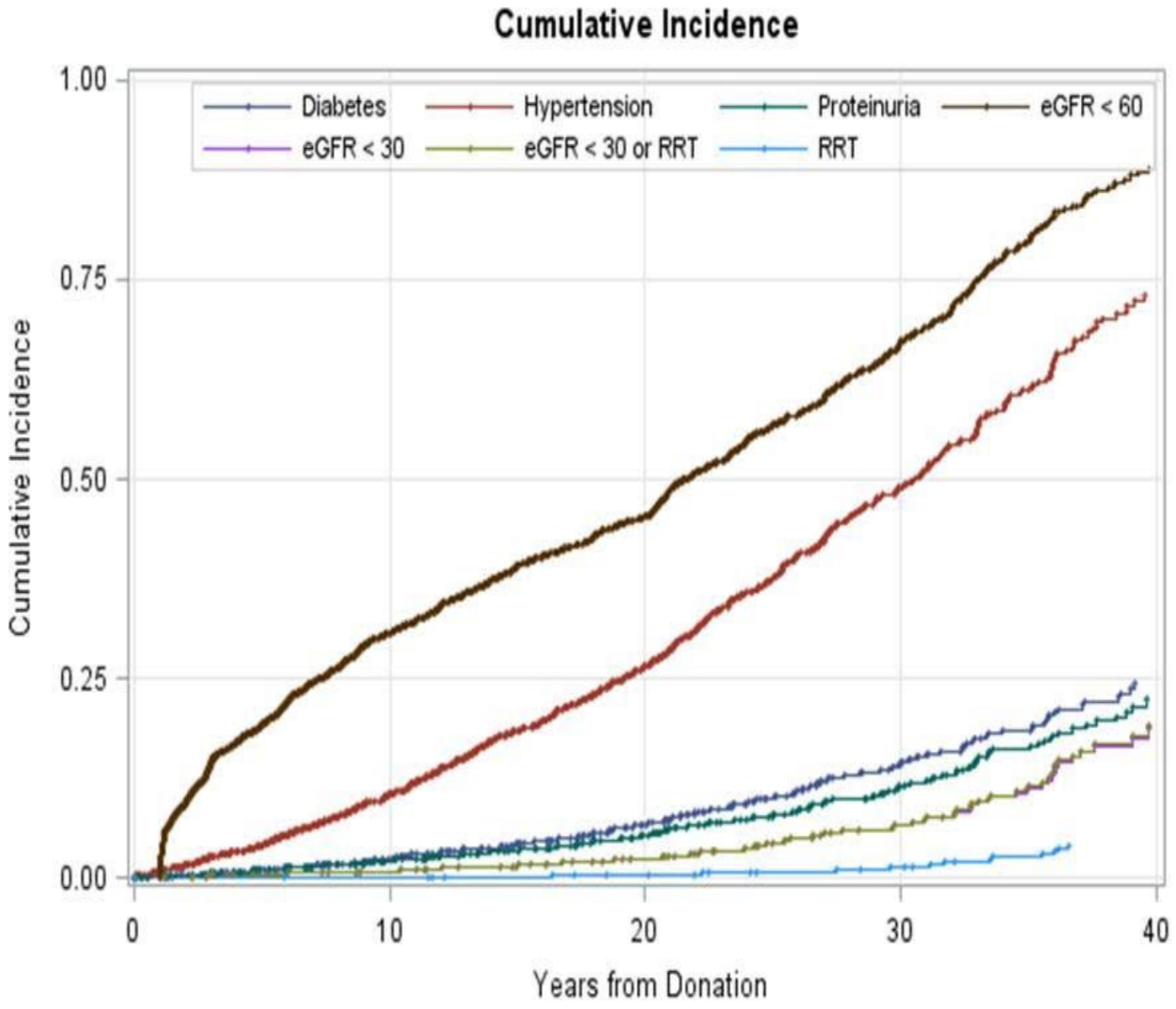
Ibrahim et al, JASN 2016

Predictors of (post-donation) Hypertension

Variable	HR (95% CI)	P-value
Age (per year)	1.04 (1.03-1.05)	<0.0001
BMI (per kg/m2)	1.06 (1.05-1.08)	<0.0001
Glucose (per mg/dL)	1.01 (1.01-1.01)	<0.0001
SBP (per mm Hg)	1.03 (1.02-1.04)	<0.0001
Year of donation (per year)	1.04 (1.03-1.05)	<0.0001
eGFR (per mL/min/1.73 m2)	1.01 (1.00-1.01)	0.0371

Predictors of Post-donation Diabetes

Variable	HR (95% CI)	*P-value*
BMI (per kg/m2)	1.12 (1.09-1.15)	<0.0001
Glucose (per mg/dL)	1.01 (1.01-1.02)	<0.0001
Smoking	1.44 (1.11-1.87)	0.01


Cumulative Incidence
Diabetes
Hypertension
Proteinuria
eGFR < 60
eGFR < 30
eGFR < 30 or RRT
RRT
1.00
0.75
0.50
0.25
0.00
Cumulative Incidence
0
10
20
30
40
Years from Donation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Racial Variation in Medical Outcomes among Living Kidney Donors

Krista L. Lentine, M.D., Mark A. Schnitzler, Ph.D., Huiling Xiao, M.S., Georges Saab, M.D., Paolo R. Salvalaggio, M.D., Ph.D., David Axelrod, M.D., Connie L. Davis, M.D., Kevin C. Abbott, M.D., M.P.H., and Daniel C. Brennan, M.D.

NEJM 363:724, 2010

Race, Relationship and Renal Diagnoses After Living Kidney Donation

Krista L. Lentine, MD, PhD,[1,2] Mark A. Schnitzler, PhD,[2] Amit X. Garg, MD, PhD,[3] Huiling Xiao, MD,[1] David Axelrod, MD, MBA,[4] Janet E. Tuttle-Newhall, MD,[2] Daniel C. Brennan, MD,[5] and Dorry L. Segev, MD, PhD[6]

Transplantation 99:1723, 2015

After kidney donation, *black and Hispanic donors*, as compared with white donors, had an increased risk of hypertension, diabetes mellitus requiring drug therapy, proteinuria and chronic kidney disease.

- similar to disparities seen in the general population

N Engl J Med. 2013 Dec 5;369(23):2183-96. doi: 10.1056/NEJMoa1310345. Epub 2013 Nov 9.

APOL1 risk variants, race, and progression of chronic kidney disease.

Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, Feldman HI, Parekh RS, Kusek JW, Greene TH, Fink JC, Anderson AH, Choi MJ, Wright JT Jr, Lash JP, Freedman BI, Ojo A, Winkler CA, Raj DS, Kopp JB, He J, Jensvold NG, Tao K, Lipkowitz MS, Appel LJ; AASK Study Investigators; CRIC Study Investigators.

Ken Newell – AST blog re recent AST conference: there was broad agreement that the presence of APOL1 risk variants could not be used in isolation for determining managagement of either living kidney donors…….

Instead currently available information should be used to educate patients and considered as part of … decision process (Feb 18, 2016)

Psychosocial Outcomes

Some Clearly Attributable to Donation

Health-Related Quality of Life

Numerous studies (multiple countries) using Sf-36 or other measures show that, *on average*, former donors have the same or better QoL than age and gender matched gen population and healthy non donor controls

- *however, in each study there is a proportion of donors (4%-20%) that report decreased QoL*. Often related to poor recipient of graft survival or to donation-related complications

Depression

Lower rate of depression in donors than general population

However, some donors are depressed and relate their depression to the donation experience

(? attributable risk)

Lentine et al, Transplantation 94: 77, 2012

4650 donors integrating OPTN and claims data

⇧in *nonspousal, unrelated* donors with recip death or graft loss (trend in spousal donors)

Renal and Lung LD Evaluation Study (RELIVE)

Psychosocial data on 2455 former (USA) donors

- avg 17 years postdonation; mean age =41

Health-related QoL - Gross et al, AJT 13: 2924, 2013

Depression - Jowsey et al, AJT 14: 2535, 2014

Satisfaction with Life

- Messersmith et al, Transplantation 98:1294, 2014

Overall Donor Experience

- Jacobs et al, CJASN, 2015 (ePub)

RELIVE – Identified Risk Factors

Decreased Health-related QoL

physical health: obesity, hx of psychiatric difficulties, and non-white race

mental health: hx of psychiatric difficulties

Depression: non-white race, longer recovery time, younger age at donation, greater financial burden, feeling morally obligated to donate

Decreased Satisfaction with Life: financial difficulties with donation, longer recovery time

Poor Overall Donor Experience: donor complications, psychological difficulties, recipient graft failure

Direct and Indirect Costs

Clarke et al, Nephrol dial transplant 21:1952, 2006

- reviewed 35 studies (donors 1964-2003) from 12 countries;

- all found donor costs

3 recent prospective studies

Klarenbach et al, AJT 14: 916, 2014 Canadian study (n=100) (universal health care)

Rodrigue et al, AJT, 15: 2387, 2015 (evaluation) USA (n=195) (high % caucasian and insured)

Rodrigue et al, AJT, 16: ePub, 2016 (donation)

> 90% had expenses (most common travel)

~ 50% had lost wages or used vacation time

THE CONSUMER

The Reward for Donating a Kidney: No Insurance

By RONI CARYN RABIN JUNE 11, 2012 3:11 PM 92 Comments

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When Erika Royer's lupus led to kidney failure four years ago, her father, Radburn, was able to give her an extraordinary gift: a kidney.

Ms. Royer, now 31, regained her kidney function, no longer needs dialysis and has been able to return to work. But because of his donation, her father, a physically active 53-year-old, has been unable to obtain private health insurance.

Like most other kidney donors, Mr. Royer, a retired teacher in Eveleth, Minn., was carefully screened and is in

HEALTHY Like most other kidney donors, Radburn Royer was carefully screened. Derek Montgomery for The New York Times

Boyarsky et al, AJT 14:2168, 2014 (Johns Hopkins)

7% difficulty in changing or initiating health insurance

25% difficulty in changing or initiating life insurance

Relive, Jacobs et al, cJASN, 2015

3% problems with health insurance

4% problems with life insurance

Donor Demographics are changing

Taler SJ et al, AJT 13:390-398 (2013) (RELIVE study)

8951 LDs at 3 institutions between 1963-2007

- ⇧% LDs >40 yrs old from 38% to 51%
- ⇧ % with obesity from 8% to 26%
- ⇧ % with glucose intolerance from 9% to 25%

Schold et al, CJASN 8: 1773, 2013

increased diagnoses of depression, hypothyroidism and hypertension (3x increase)

Cooper and Davis, CJASN, 5: 1873, 2010

increasing number of uninsured donors

Definitions have changed – elevated fasting glucose; hypertension

Summary

1) Increased risk for precursors of ESRD can be identified at time of evaluation
   - *improve donor counseling; ?Candidacy?*
2) Post-donation pregnancy assoc with increased htn and preeclampsia
   - *improve counseling; better OB care*
3) Increased psychosocial risk can be identified at time of evaluation
   - *improved counseling; ?candidacy?*
4) Transplant-related events can also lead to increased psychosocial problems
   - *increased recognition and care by tx centers*

Limitation to all of this data

Almost all the long-term data, to date, has been provided by a very small number of groups (single center or registry studies in Europe (Sweden, Netherlands, France), Japan and the USA; registry [big data] in Canada and the USA)

1) There is little long-term data on the non-Caucasian donor;

2) Donor acceptance criteria have expanded:

3) Other populations need to be studied

e.g., American Indian, uninsured, nondirected donors, paired exchange

Going Forward – What is Needed

A) Ongoing extended follow-up (tracking) (medical and psychosocial) of current populations (with appropriate controls) to clearly define risks *attributable to* donation;**

A) Long-term studies (medical and psychosocial) of additional populations (subgroups) to define risks;**

A) Development of a system to evaluate and care for donors having developed medical and/or psychosocial problems related to donation.

B) Development of a system so that donation is financially neutral

** See consensus conf recommendations AJT 11:2561-2568, 2011
AJT 15: 914-22, 2015