Obesity increases the risk of end-stage renal disease among living kidney donors

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Jayme E. Locke[1], Rhiannon D. Reed[1], Allan Massie[2], Paul A. MacLennan[1], Deirdre Sawinski[3], Vineeta Kumar[1], Shikha Mehta[1], Roslyn B. Mannon[1], Robert Gaston[1], Cora E. Lewis[1] and Dorry L. Segev[2]

[1]University of Alabama at Birmingham School of Medicine, Comprehensive Transplant Institute, Birmingham, Alabama, USA; [2]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; and [3]University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Determining candidacy for live kidney donation among obese individuals remains challenging. Among healthy non-donors, body mass index (BMI) above 30 is associated with a 16% increase in risk of end-stage renal disease (ESRD). However, the impact on the ESRD risk attributable to donation and living with only one kidney remains unknown. Here we studied the risk of ESRD associated with obesity at the time of donation among 119 769 live kidney donors in the United States. Maximum follow-up was 20 years. Obese (BMI above 30) live kidney donors were more likely male, African American, and had higher blood pressure. Estimated risk of ESRD 20 years after donation was 93.9 per 10 000 for obese; significantly greater than the 39.7 per 10 000 for non-obese live kidney donors. Adjusted for age, sex, ethnicity, blood pressure, baseline estimated glomerular filtration rate, and relationship to recipient, obese live kidney donors had a significant 86% increased risk of ESRD compared to their non-obese counterparts (adjusted hazard ratio 1.86; 95% confidence interval 1.05–3.30). For each unit increase in BMI above 27 kg/m^2 there was an associated significant 7% increase in ESRD risk (1.07, 1.02–1.12). The impact of obesity on ESRD risk was similar for male and female donors, African American and Caucasian donors, and across the baseline estimated glomerular filtration rate spectrum. These findings may help to inform selection criteria and discussions with persons considering living kidney donation.

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Correspondence: *Jayme E. Locke, MD, MPH, FACS, 701 19th Street South, LHRB 748, Birmingham, AL 35294, USA. E-mail: jlocke@uabmc.edu*

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The demand for transplantable kidneys remains high, and living kidney donors (LKDs) continue to be a critical source of organs, facilitating both timely transplantation and excellent outcomes.[1] Historically, LKDs were free of isolated medical abnormalities (IMAs) at the time of donation. However, in response to the organ shortage and changes in the general population, transplantation centers now commonly approve donors with IMAs such as obesity.[2–7] Currently, >25% of all LKDs are considered obese at the time of donation compared with <8% in the 1970s.[6] Relaxation of selection criteria to include obese LKDs has occurred despite a paucity of supporting safety data.

The National Institutes of Health defines obesity as a body mass index (BMI) of >30 kg/m^2.[8] According to data from the National Health and Nutrition Examination Survey, the prevalence of obesity has increased in the United States from 27.5% in 1999 to 36.5% in 2011 to 2014,[9] and in parallel with these general trends, the mean BMI of LKDs in the United States has increased over time, from 24.3 kg/m^2 in the 1970s to 27.3 kg/m^2 in the 2000s.[6] Obesity is strongly correlated with increased risk for cardiovascular disease, diabetes mellitus, and chronic kidney disease (CKD).[10–14] Data from a population-based, case−control study conducted in Sweden and 2 US studies (The Framingham Offspring cohort and the Hypertension Detection and Follow-up Program) have shown that higher weight for height is associated with an increased risk of new-onset CKD.[15–17]

Beyond CKD, obesity has been linked with increased risk for end-stage renal disease (ESRD). In the general population, Hsu *et al.* found that compared with persons considered normal weight (BMI: 18.5−24.9 kg/m^2), obese individuals (BMI ≥30 kg/m^2) were at 3.57-fold higher risk of developing ESRD (adjusted risk ratio [RR]: 3.57; 95% confidence interval [CI]: 3.05−4.18).[18] However, donors are not drawn from the general population, but are very carefully screened, and the impact of obesity might be different in these healthier individuals. In a multi-cohort study of individuals healthy enough to be potential donors (healthy nondonors), the adjusted risk of ESRD associated with obesity was only 1.16 (95% CI: 1.04−1.29).[19] The true risk among living donors likely falls somewhere in between these estimates; living donors are healthy at baseline, but then they lose half of their nephron mass, and the impact of obesity in this context remains unclear.

Unfortunately, the 4 recent major studies of LKDs that establish the existing evidence of living donor risk for ESRD were done in the context of standard selection criteria, healthy and IMA-free, and did not address the impact of obesity, highlighting a remaining gap in our knowledge of living donor outcomes.[20–23] To better understand ESRD risk in obese LKDs, and to better inform selection criteria for potential obese kidney donors, we performed a national study of the association between BMI and postdonation risk of ESRD among LKDs, adjusting for potential confounders and exploring the potential effect modifiers of this association.

RESULTS

The mean BMI among obese donors was 32.7 kg/m^2 compared with 24.8 kg/m^2 among nonobese donors. At the time of donation, obese and nonobese living donors were similar with regard to age, baseline estimated glomerular filtration rate (eGFR), smoking history, insurance status, and relationship to the recipient. However, compared with their nonobese counterparts, obese living donors were more commonly men (43.1% vs. 39.2%), African American (16.4% vs. 11.1%), and had higher mean systolic (124.1 mm Hg vs. 119.9 mm Hg) and diastolic (75.6 mm Hg vs. 72.9 mm Hg) blood pressures (Table 1).

The cumulative incidence of ESRD per 10,000 living donors was 3-fold greater among LKDs who were obese at the time of donation compared with their nonobese counterparts. At 20-years postdonation, obese LKDs had a cumulative incidence of ESRD of 93.9 per 10,000 compared with 39.7 per 10,000 among their nonobese living donor counterparts (Table 2 and Figure 1; Supplementary Table S1 for absolute numbers).

After controlling for multiple risk factors, including age at donation, ethnicity, sex, baseline eGFR and blood pressure, and relationship to the recipient, the only potentially modifiable factor that remained independently associated with an increased risk for development of ESRD postdonation was obesity. Compared with nonobese LKDs, obese LKDs had a 1.9-fold increased risk of ESRD postdonation (adjusted hazard ratio [aHR]: 1.86; 95% CI: 1.05−3.30; $P = 0.04$) (Table 3). This finding was consistent with the results seen with analyses performed only among donors who had complete data available (Table 4). On stratified analyses, for each 1-U increase in BMI >27 kg/m^2, there was an associated 7% increase in the risk of ESRD (aHR: 1.07; 95% CI: 1.02−1.12; $P = 0.004$). This same effect was not observed for those with a BMI ≤27 kg/m^2. The potential for effect modification was explored using interaction term analyses. No significant interactions were observed between obesity and sex (aHR: 1.09, 95% CI: 0.51−2.34; $P = 0.82$), African American ethnicity (aHR: 0.89; 95% CI: 0.41−1.92; $P = 0.75$), relationship to the recipient (aHR: 1.15; 95% CI: 0.45−2.93; $P = 0.76$), or eGFR (aHR: 1.00; 95% CI: 0.98−1.02; $P = 0.99$).

DISCUSSION

In this national study of 119,769 LKDs linked to Centers for Medicare and Medicaid Services (CMS) data for ascertainment of ESRD, we estimated that approximately 40 nonobese and 94 obese living donors per 10,000 developed ESRD within 20 years of kidney donation. Although the absolute risk for postdonation ESRD was low, donor obesity was independently associated with an increased risk for ESRD 20 years after kidney donation. Compared with nonobese living donors, obese donors had a 1.9-fold increased risk for postdonation ESRD, and for each 1-U increase in predonation BMI >27 kg/m^2 there was an associated 7% increased risk of ESRD postdonation.

Studies from the general US population have demonstrated the relationship between excess weight or obesity and risk of ESRD. However, these cohorts included individuals with baseline comorbidities such as diabetes and hypertension, which are conditions known to be along the CKD and/or ESRD causal pathway.[18,24] Although our cohort of LKDs was free of diabetes and hypertension at the time of donation,

Table 1 | Demographics of living kidney donors by obesity status at time of donation*

Donor characteristic	Obese (BMI ≥30 kg/m^2) (n = 20,588)	Nonobese (BMI <30 kg/m^2) (n = 58,004)	Missing BMI (n = 41,177)
Age, yr, mean ± SD	40.7 ± 10.7	40.8 ± 11.4	38.5 ± 10.9
Sex, no. (%)			
Male	8,864 (43.1)	22,763 (39.2)	17,744 (43.1)
Female	11,724 (56.9)	35,241 (60.8)	23,433 (56.9)
Ethnicity			
African American	3,374 (16.4)	6,450 (11.1)	5,485 (13.3)
Non-African American	17,214 (83.6)	51,554 (88.9)	35,692 (86.7)
BMI,† kg/m^2, mean ± SD	32.7 ± 3.2	24.8 ± 2.9	-
Systolic BP,† mean ± SD	124.1 ± 13.1	119.9 ± 13.3	121.2 ± 14.0
Diastolic BP,† mean ± SD	75.6 ± 9.3	72.9 ± 9.4	74.1 ± 9.3
eGFR,† ml/min/1.73 m^2, mean ± SD	96.8 ± 18.9	97.2 ± 18.5	95.5 ± 20.0
Ever smoked cigarettes†	3,192 (15.5)	8,926 (15.4)	278 (0.7)
Insured†	8,981 (43.7)	25,996 (44.8)	1,360 (3.3)
Related to recipient†	12,953 (62.9)	35,482 (61.2)	34,124 (82.9)

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate.
*From October 1, 1987 to June 30, 2013.
†Not collected for the entire cohort.

Table 2 | Cumulative incidence of end-stage renal disease events per 10,000 living donors estimated from the multiple imputation analyses*

Obesity status	5 yrs	10 yrs	15 yrs	20 yrs
Obese (BMI ≥30 kg/m^2)	3.2	15.2	42.5	93.9
Nonobese (BMI <30 kg/m^2)	1.0	7.4	17.5	39.7

BMI, body mass index.
*From October 1, 1987 to June 30, 2013.

and beyond their baseline obesity were otherwise healthy, we also found that obesity was independently associated with an increased risk for ESRD. Moreover, we found this association began with living donor baseline BMIs >27 kg/m^2. In other words, although the greatest risk for postdonation ESRD might have been observed among obese LKDs, the increased risk for ESRD postdonation began among LKDs who would be labeled merely overweight at baseline. These findings have important implications for current living donor selection practices with regard to BMI cutoffs used as absolute contraindications for donation.

These data also suggest that it may be prudent to enroll potential obese LKDs in a predonation rehabilitation or weight loss program, because short-term weight loss has been associated with improvements in cardiovascular risk factors.[25–30] However, it is likely that long-term maintenance of weight loss would be required to mitigate the risk for ESRD associated with obesity. Studies have shown that even in the setting of an intense rehabilitation program with regular treatment contact, most participants regain 30% to 50% of their initial weight loss over a 2 to 3 year period,[31,32] and as such, predonation weight loss may do little to mitigate the long-term ESRD risk associated with obesity. Encouragingly, however, recent data from the Look Action for Health in Diabetes (Look AHEAD) trial, a randomized trial of intensive lifestyle interventions compared with a control condition in overweight/obese individuals with type 2 diabetes, found no negative associations of losing and regaining weight relative to not having lost weight; individuals with large initial weight loss but full regain of weight still had greater improvements in diabetes control than those with no initial weight loss.[33] These data lend some support for predonation weight loss for obese potential LKDs as an effort to modify short-term risk for postdonation ESRD; however, the impact of weight loss on long-term risk for ESRD remains uncertain. To date, no study has examined weight loss and/or gain among LKDs and its impact on risk for postdonation ESRD.

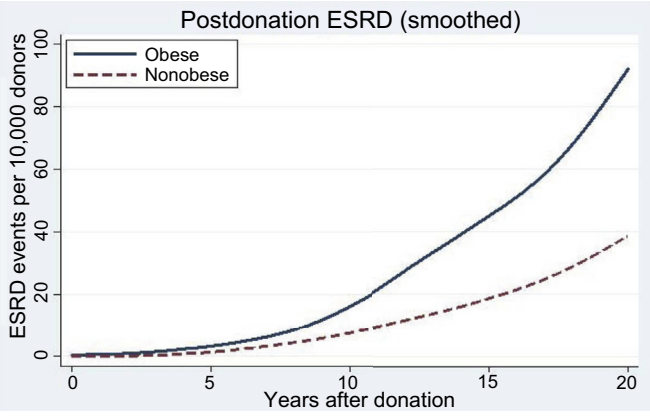

Figure 1 | Cumulative incidence of postdonation end-stage renal disease (ESRD) events among living kidney donors by obesity status at time of donation.

Table 3 | Adjusted risk of end-stage renal disease among living kidney donors estimated from multiple imputation analyses*

Characteristic	HR	95% CI	*P* value
Obese (ref, non-obese)	1.86	1.05–3.30	0.04
Age, per 1-yr increase	0.99	0.98–1.01	0.37
Female	0.51	0.39–0.66	<0.001
African American (ref, non-African American)	4.62	3.46–6.16	<0.001
Systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg	1.29	0.73–2.26	0.37
eGFR, per 1 ml/min/1.73 m^2 increase	0.97	0.95–0.98	<0.001
Related to recipient	1.51	1.00–2.28	0.05

BP, blood pressure; CI, confidence interval; eGFR, estimated filtration rate; HR, hazard ratio.
*From October 1, 1987 to June 30, 2013.

The primary strengths of our approach were the inclusion of every known LKD in the United States since the establishment of the Organ Procurement and Transplantation Network (OPTN) in 1987 and the highly reliable linkage-based ESRD ascertainment. The large samples size of >100,000 actual LKDs enabled us to estimate the incidence of a rare event and to make inferences specific to the subgroup of obese living donors. These data provide critical information for those considering donation and the >100,000 individuals known to have already donated a kidney for the purposes of living donor transplantation. Despite these strengths, our study does have some important limitations. One-third of the cohort was missing information on predonation BMI, and as such, multiple imputation was used to allow us to include those who donated in years before when BMI was routinely captured for LKDs. This methodology

Table 4 | Adjusted risk of end-stage renal disease among living kidney donors estimated from complete case (two-thirds of donors in whom no baseline risk factors were missing) analyses*

Characteristic	HR	95% CI	*P* value
Obese (ref, nonobese)	2.26	1.30–3.92	0.004
Age, per 1-yr increase	1.00	0.98–1.03	0.74
Female	0.56	0.32–0.98	0.04
African American (ref, non-African American)	3.17	1.72–5.86	< 0.001
Systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg	1.64	0.83–3.24	0.6
eGFR, per 1 ml/min/1.73m^2 increase	0.99	0.97–1.00	0.09
Related to recipient	1.27	0.67–2.41	0.47

BP, blood pressure; CI, confidence interval; eGFR, estimated filtration rate; HR, hazard ratio.
*From October 1, 1987 to June 30, 2013.

generated 20 data sets for analysis in which some donors with missing BMIs were imputed as obese but might not have been in other imputations. As such, the median time to development of postdonation ESRD could not be estimated. However, it is important to note that the inferences presented from the imputed data set were confirmed in the complete case analyses (two-thirds of donors in whom no baseline risk factors were missing). Moreover, median follow-up for the study was only 10.7 years, and might not have permitted us to fully understand the long-term risk of postdonation ESRD. It was likely that the overall, lifelong risk for ESRD among obese donors observed in our study was an underestimate. In addition, the data lacked granularity with regard to predonation lipids; therefore, we were not able to identify those obese donors with metabolic syndrome, a condition known to be associated with increased risk for CKD.[34] As with any other retrospective cohort study, there might be residual confounding from failing to include factors not collected or not reliably captured by the OPTN (e.g., socioeconomic status, medication use). Finally, the incremental risk of ESRD directly attributable to living donation was not assessed in this study, and it remains to be determined what additional risk for development of ESRD, if any, kidney donation poses in the setting of obesity.

This is the first national study to examine risk for ESRD among a cohort of obese LKDs. Our findings indicate that, although the absolute risk for postdonation ESRD remains low, obese LKDs have a 1.9-fold higher risk for ESRD compared with their nonobese counterparts. These data have important implications for donor selection, predonation management of living donor candidates, and informed consent discussions with obese persons considering living donation. Further research is needed to better understand the relationships between living donor pre- and postdonation weight trajectories and long-term risk for ESRD postdonation.

MATERIALS AND METHODS

The study used data from the Scientific Registry of Transplant Recipients (SRTR), which includes data on all donor, wait-listed candidates, and transplantation recipients in the United States, submitted by members of the OPTN. The Health Resources and Services Administration of the US Department of Health and Human Services provides the oversight to the activities of the OPTN and SRTR contractors. All adult LKDs reported to the OPTN between October 1, 1987 and June 30, 2013 were included in this study (N = 119,769). Maximum time at risk was 20 years (median: 10.7 years, interquartile range [IQR]: 6.0−16.0), with a maximum of 26.8 years since donation.

Linkage to medical evidence Form 2728 CMS permitted ascertainment of ESRD.[23] ESRD was defined as the earliest of initiation of maintenance dialysis, placement on the renal transplantation waiting list, or receipt of a living or deceased donor kidney transplantation. The OPTN did not begin collecting social security numbers (SSNs) until April 1, 1994; for donors whose date of donation occurred on or after April 1, 1994, linkage was performed using a combination of SSN, last name, first name, middle name, or all 3 names; date of birth; and sex. For donors whose date of donation occurred before April 1, 1994, linkage to CMS was performed using identifiers listed other than SSN. Ascertainment of ESRD outcomes via the CMS 2728 form began in April 1994; therefore, donors whose date of donation occurred before April 1, 1994 were considered late entries. These donors were assumed to be free of ESRD before that date, and as such, were left truncated (e.g., did not begin contributing time at risk until April 1, 1994).

Data collection on living donor registration forms by the OPTN has varied over time, with changes to the number and format of variables collected, resulting in a wide range in the prevalence of missing data. The probability of a particular set of variables missing for an individual was assumed to not depend on the values themselves, which was conditional on the observed values of other variables. Therefore, multiple imputation using chained equations[35,36] was used to impute values that were missing for BMI, preoperative systolic and diastolic blood pressures, baseline eGFR, insurance status, relationship to the recipient, and smoking status. Missing values were imputed based on outcome, age, sex, year of donation, and baseline hazard, with imputed values of BMI restricted to the range of 10 to 70 kg/m^2. Twenty imputations were run, each with 20 burn-in periods, and trace file plots were used to assess convergence of the imputations.

Donors were defined as obese at the time of donation if their BMI was $\geq$30 kg/m^2. Donor characteristics were compared by obesity status at donation in the nonimputed data set. Continuous variables were analyzed using analysis of variance, and categorical variables were examined using χ^2 tests of independence. Martingale residuals, spline terms, and stratification were used in the complete case data to examine the functional form of BMI and to explore the presence of a point at which BMI became significantly hazardous. eGFR was calculated using the CKD-epi equation. Although there are limitations associated with assessing renal function using calculated eGFR, particularly in an obese population, data reported to the OPTN on kidney function are limited; therefore, the calculated eGFR was the most reliable method available for assessing donor baseline kidney function (a factor known to be associated with risk for ESRD). Furthermore, CKD-epi has been demonstrated to be superior to the Modification of Diet in Renal Disease equation for eGFR among individuals with creatinine clearance expected to be between 60 and 120 ml/min (which represents the typical LKD). During the development and validation of the CKD-epi equation, it was determined that the addition of weight did not significantly improve model performance.[37]

All survival analyses were performed using imputed data, estimating the parameters from all imputed data sets and adjusting coefficients and SEs for the variability between imputations. Cumulative incidence of ESRD was estimated using Kaplan-Meier methods and compared between obese and nonobese donors using log-rank tests, and displayed graphically using Loess smoothed survival curves. Risk of ESRD by obesity status at donation was estimated using Cox proportional hazards models, adjusting for donor age, sex, race, blood pressure, baseline eGFR, and the relationship to the recipient.

Potential effect modification was investigated by testing for interactions, although no interaction terms were included in the final model due to lack of statistical significance. The proportional hazards assumption was assessed and verified using time-dependent variables.

The final model was then applied to the complete case cohort (two-thirds of donors in whom no baseline risk factors were missing). Inferences from both the imputed and complete case data

were congruent. Multiple additional sensitivity analyses were also performed. Full models were produced using all factors examined on univariate analysis; systolic and diastolic blood pressures and BMI were examined as continuous measures; blood pressure was examined as an ordinal variable; and donation year was accounted for. Results across all models were congruent, and inferences were confirmed.

All analyses were performed using Stata 12.0 (Stata Corp, College Station, Texas), and all hypothesis tests were 2-sided, with a significance level of $\alpha = 0.05$.

DISCLOSURES

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIALS

Table S1. The number of postdonation end-stage renal disease events by donation year

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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