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Obesity and long-term mortality risk among living kidney donors

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ABSTRACT

Background: Body mass index of living kidney donors has increased substantially. Determining candidacy for live kidney donation among obese individuals is challenging because many donation-related risks among this subgroup remain unquantified, including even basic postdonation mortality.

Methods: We used data from the Scientific Registry of Transplant Recipients linked to data from the Centers for Medicare and Medicaid Services to study long-term mortality risk associated with being obese at the time of kidney donation among 119,769 live kidney donors (1987–2013). Donors were followed for a maximum of 20 years (interquartile range 6.0–16.0). Cox proportional hazards estimated the risk of postdonation mortality by obesity status at donation. Multiple imputation accounted for missing obesity data.

Results: Obese (body mass index $\geq$ 30) living kidney donors were more likely male, African American, and had higher blood pressure. The estimated risk of mortality 20 years after donation was 304.3/10,000 for obese and 208.9/10,000 for nonobese living kidney donors. Adjusting for age, sex, race/ethnicity, blood pressure, baseline estimated glomerular filtration rate, relationship to recipient, smoking, and year of donation, obese living kidney donors had a 30% increased risk of long-term mortality compared with their nonobese counterparts (adjusted hazard ratio: 1.32, 95% CI: 1.09–1.60, $P = .006$). The impact of obesity on mortality risk did not differ significantly by sex, race or ethnicity, biologic relationship, baseline estimated glomerular filtration rate, or among donors who did and did not develop postdonation kidney failure.

Conclusion: These findings may help to inform selection criteria and discussions with obese persons considering living kidney donation.

Introduction

Since the year 2004, there has been a 13% decline in living kidney donation in the United States,[1] and this observed trend differs significantly from recent increases in living donation seen in other parts of the world, including the United Kingdom, Japan, the Netherlands, Mexico, and Australia.[1] The reasons for declining rates of living donation in the United States are likely multifactorial[1] but correspond with an increasingly unhealthy US general population[2–12] and questions surrounding donation-related health risks, particularly among living kidney donors with isolated medical abnormalities at the time of donation, such as obesity (body mass index [BMI] $\geq$ 30kg/m^2).[13]

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The prevalence of obesity in the United States has increased from 27.5% in 1999 to 36.5% in 2014,[2] and, along with the general population, the BMI of living kidney donors has also risen, with more than 25% of all contemporary living kidney donors with obesity at time of donation compared with fewer than 8% in the 1970s.[14] As newer data emerge on donation-related health risks, the transplant community continues to debate the optimal acceptable BMI threshold for living donors. Guidelines have suggested that live donor candidates with BMI $\geq$ 35kg/m^2 should be discouraged from donating,[15] and others have suggested that patients with BMI > 30kg/m^2 should reduce their weight before donation.[16] Currently, the 2017 Kidney Disease Improving Global Outcomes clinical practice guidelines suggest that the decision to approve living donor candidates with BMI > 30kg/m^2 should be individualized based on patients' demographic and health profiles in relation to the transplant program's acceptable risk threshold.[17]

Within the general population, obesity is strongly associated with an increased risk for cardiovascular disease, diabetes, chronic kidney disease, end-stage renal disease (ESRD)[3–7,11,18] and mortality.[19,20] Studies among obese living donors, however, have primarily focused on the risk of ESRD, demonstrating a 1.16-fold and a 1.86-fold higher ESRD risk among obese potential living donor candidates (adjusted hazard ratio [aHR]: 1.16; 95% CI: 1.04–1.29)[21] and actual obese living kidney donors (aHR: 1.86; 95% CI: 1.05–3.30),[22] respectively. The 2 major studies addressing mortality risk among living donors failed to risk-stratify by BMI[23,24] and therefore no study to date has specifically quantified the long-term mortality risks faced by obese donors.

Not surprisingly, tremendous variation in BMI thresholds for living donation exist across US transplant centers, highlighting persistent knowledge gaps in our current understanding of living-donor risks among obese donors and the need for continued focused research among this at-risk subgroup.[25] To improve our understanding of the risk of mortality in obese living kidney donors to enhance donor selection practices, we utilized a national registry to examine the association between BMI and postdonation risk of long-term mortality among living kidney donors, adjusting for potential confounders and exploring the presence of effect modification.

Methods

The study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by members of the Organ Procurement and Transplantation Network (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. We included all adult kidney-only living donors reported to the OPTN between October 1, 1987, and June 30, 2013 (N = 119,769), with a maximum time since donation of 28.2 years.

To determine postdonation mortality, donors were linked to the Social Security Death Master File. We also assessed whether donors developed postdonation ESRD by linkage to Centers for Medicare and Medicaid Services (CMS) data. To perform the linkage, we used a combination of Social Security number (SSN), last name, first name, middle name (or all three), date of birth, and sex for those who donated on or after April 1, 1994, because the OPTN did not begin collecting SSN until that date. For donors before April 1, 2004, linkage to CMS occurred using identifiers other than SSN. We considered donors whose date of donation was before April 1, 1994, to be late entries and assumed they had not developed ESRD before that date, as CMS ascertainment of ESRD via the 2728 form began in April 1994. Therefore, these donors were left truncated, and their time at risk began on April 1, 1994. All donors were followed until date of death or administrative end of study on December 31, 2015.

Given changes over time to the variables collected in the OPTN living-donor registration forms, there was a high prevalence of missing data. These data were assumed to be missing at random, wherein the probability of missing variables was assumed to not depend on the unobserved values, conditional on observed values of other variables. We used multiple imputation by chained equations to impute missing BMI (in the range of 10–70 kg/m^2), preoperative blood pressure, baseline estimated glomerular filtration rate (eGFR), insurance type, donor's relationship with the recipient, and history of smoking. We imputed missing values based on completely observed variables of outcome, age, sex, year of donation, race or ethnicity, and baseline hazard of both ESRD and mortality. We ran 20 imputations with 20 burn-in periods, and we checked convergence of imputations using trace file plots.

Using the World Health Organization classification of BMI, donors were defined as obese if their BMI at donation was $\geq$30 kg/m^2. We calculated baseline eGFR, using the chronic kidney disease–EPI equation, which was the most reliable method available to assess donor preoperative kidney function and 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 greater than 60 ml/min/1.73m^2 (the typical lower threshold of a living kidney donor), as described elsewhere.[26] We compared donor characteristics by obesity at donation in the nonimputed data set among all those with observed values.

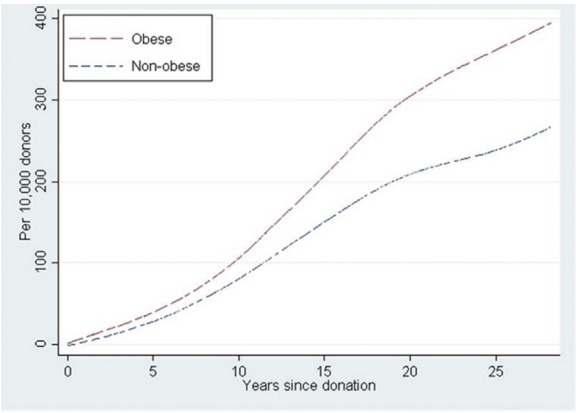
We performed survival analyses among the imputed datasets, using Rubin's rules to combine estimates from all imputations and adjusting coefficients and standard errors for the variability between imputations. To illustrate absolute risk of obesity, we estimated the cumulative incidence of mortality from baseline hazards in a regression model and displayed the estimates with Loess curve fitting. We used Cox proportional hazards regression to estimate risk of mortality by obesity at donation, adjusting for the following donor characteristics: age, sex, race, blood pressure, baseline eGFR, relationship to recipient, history of smoking at donation, and year of donation. Given that ESRD development is a time-variant factor, we also generated an extended Cox model that allowed ESRD status to vary over time. This was achieved using the *mi stsplit* command in the imputed data, and robust standard errors were used to account for multiple observations for donors who developed ESRD.

We explored the potential for effect modification by testing for interactions and with stratification, although because of a lack of statistical significance, interaction terms were not included in the final model. We assessed the proportional hazards assumption using time-dependent variables. In the case of nonproportionality, a model was generated to include a strata statement for the violating variable. Inferences were consistent with the primary analysis, and as such, the primary analyses are presented.

We applied the final model to the complete case cohort (among the 2/3 of donors without missing predonation risk factors). Inferences from both the imputed and complete case data were congruent. In addition, we explored BMI as both a continuous variable and according to the World Health Organization classification categories, and our inferences were confirmed. All analyses were performed using Stata 12.0 (StataCorp, College Station, TX), and all hypothesis tests were 2-sided with a significance level of $\alpha = 0.05$.

Results

We identified 119,769 living kidney donors from October 1, 1987, to June 30, 2013. Of these, 78,592 had BMI data reported at donation. Obese living donors were more often male (43.1% vs 39.2%) and African American (16.4% vs 11.1%). Predonation blood pressures



Obesity status	5-year	10-years	15-years	20-years
Obese (BMI ≥ 30 kg/m^2)	39.3	105.6	206.7	304.3
Non-obese (BMI < 30 kg/m^2)	28.2	80.3	150.0	280.9

Figure. Cumulative incidence of postdonation mortality among living kidney donors by obesity status at the time of donation.

were higher in obese living donors (mean systolic 124.4 mmHg vs 119.9 mmHg and mean diastolic 75.6 mmHg vs 72.9 mmHg) than in nonobese donors. Obese donors did not differ significantly from nonobese donors regarding age, baseline eGFR, type of insurance, their relationship with the recipient, or history of smoking.

Compared with nonobese donors, the cumulative incidence of long-term mortality per 10,000 living donors was higher among obese living kidney donors, and this increased risk was observed as early as 5 years postdonation (39.3/10,000 vs 28.2/10 000, respectively). At 20 years postdonation, obese living kidney donors had a cumulative incidence of mortality of 304.3/10,000 compared with 208.9/10,000 among their nonobese donors (Figure).

Table I presents results from multivariable models. After adjustment for donor age, ethnicity, gender, baseline eGFR, baseline blood pressure, smoking history, year of donation, and relationship to the recipient, and not accounting for postdonation ESRD development, obesity and smoking (modifiable risk factors) were independently associated with increased risk of postdonation mortality. Compared with nonobese donors, obese living kidney donors had a 1.3-fold increased risk of mortality postdonation (aHR: 1.32, 95% CI: 1.09–1.60, $P = .006$; Table I). These results were consistent with analyses that limited the cohort only to donors with complete data (aHR: 1.47, 95% CI: 1.09–1.98, $P = .01$; Table II).

Postdonation ESRD was then included as a time-varying exposure. Even among obese donors who did *not* develop postdonation ESRD, there remained a 1.28-fold increased risk for mortality (aHR: 1.28, 95% CI: 1.04–1.57, $P = .02$; Table I). Overall long-term mortality risk was greatest among donors who developed postdonation ESRD regardless of obesity status (nonobese aHR: 27.11, 95% CI: 16.72–43.94, $P < .001$; obese aHR: 26.15, 95% CI: 15.13–45.19, $P < .001$). As demonstrated in our effect modification analyses, this finding was not modified by BMI (aHR: 0.77, 95% CI: 0.39–1.54, $P = .46$). Moreover, there were no statistically significant interactions between obesity and age, eGFR, systolic or diastolic blood pressure, race or ethnicity, gender, relationship to the recipient, smoking history, or year of donation (Supplemental Table).

Table I
Multiple imputation in total cohort (119,769)*

Characteristic	aHR	95% CI	*P* value
Without adjustment for postdonation ESRD development			
Obese (ref: BMI < 30 kg/m^2)	1.32	1.09–1.60	.006
With time varying 4-level variable for postdonation ESRD development			
Obesity/ESRD			
Nonobese/no ESRD	Ref		
Obese/no ESRD	1.28	1.04–1.57	.02
Nonobese/ESRD	27.11	16.72–43.94	< .001
Obese/ESRD	26.15	15.13–45.19	< .001

ESRD, end-stage renal disease; *eGFR*, estimated glomerular filtration rate; *BMI*, body mass index; *aHR*, adjusted hazard ratio; *CI*, confidence interval.
* Adjusting for donor age, sex, race or ethnicity, baseline blood pressure, baseline eGFR, relationship to recipient, history of smoking, and year of donation.

Table II
Complete case with time-varying covariate for ESRD development ($N = 46,133$)

Characteristic	aHR	95% CI	*P* value
Obese (ref: BMI < 30 kg/m^2)	1.47	1.09–1.98	.01
Age, per 1-year increase	1.04	1.02–1.05	< .001
Female	0.56	0.42–0.75	< .001
African American (ref = non-African American)	1.56	1.02–2.36	.04
Systolic blood pressure, per 1-unit increase	1.02	1.01–1.03	.003
Diastolic blood pressure, per 1-unit increase	1.00	0.98–1.01	.67
eGFR, per 1 mL/min/1.73m^2 increase	1.00	0.99–1.01	.80
Biologically related to recipient	0.94	0.71–1.25	.68
History of smoking at donation	2.76	2.08–3.66	< .001
Year of donation	0.88	0.83–0.94	< .001
Developed ESRD	28.43	3.71–217.71	.001

ESRD, end-stage renal disease; *eGFR*, estimated glomerular filtration rate; *BMI*, body mass index; *aHR*, adjusted hazard ratio; *CI*, confidence interval.

Discussion

In this national study of 119,769 living kidney donors, we calculated a postdonation long-term death rate at 20 years of 209/10,000 among nonobese donors and 304/10,000 for obese living donors. Although the absolute risk for postdonation mortality remains low, the magnitude of the mortality risk difference between these 2 donor groups is significant. After adjusting for age, ethnicity, gender, baseline eGFR, baseline blood pressure, smoking history, year of donation, and relationship to the recipient, donors with obesity had a 30% increased risk for postdonation mortality compared with nonobese living donors. This excess mortality risk was maintained even in models that accounted for the development of postdonation ESRD. In other words, obesity is very clearly independently associated with long-term mortality after a living donation.

This association between obesity and excess mortality risk is not entirely surprising. Studies from the general US population have also shown a negative association with obesity and mortality. Of note, although, these nondonor cohorts contained individuals with diabetes and hypertension, conditions correlated with increased mortality.[11,27] Living kidney donors are by definition, generally healthy, but even in this cohort of actual living donors we found that obesity was an independent risk factor for long-term mortality. Differences in mortality rate by obesity status were apparent as early as 5 years after donation and more pronounced by 10 years of follow-up. We found that this effect was not modified by the development of ESRD, age, eGFR, systolic blood pressure, diastolic blood pressure, African American ethnicity, gender, relationship to the recipient, smoking history, or year of donation, again highlighting that obesity is an independent risk factor for postdonation long-term mortality. These findings are useful for current living-donor selection practices and can be used to inform BMI thresholds for absolute contraindications for donation.

As with any study, there are important limitations. We used multiple imputation to include the one-third of the cohort who donated before BMI was routinely captured for donors. We confirmed our inferences from multiple imputation in the

complete-case analyses among donors who were not missing any baseline risk factors, underscoring the robustness of our findings. The relatively short time frame of the study (median follow-up of 10.7 years) may not have allowed for complete understanding of the long-term risk of mortality. However, it is likely that the risk observed here is underestimated. In addition, we are limited by the completeness and the nature of predonation and follow-up data collected by the OPTN. These data do not contain predonation lipid measurements, and, as such, we could not identify presence of predonation metabolic syndrome, which is known to be associated with an increased risk of mortality.[28] We are also unable to assess for postdonation development of hypertension, diabetes, or cardiovascular disease, all comorbidities associated with obesity in the general population. However, in single-center series, development of these comorbidities has not negatively impacted living-donor survival.[29] There is a strong possibility of residual confounding resulting from not including factors not collected reliably by the OPTN (eg, socioeconomic status, medication use). Finally, the incremental risk of mortality directly attributable to living donation and loss of nephron mass was not assessed in this study. Obesity in the absence of kidney donation confers an increased risk of premature mortality, but the additional risk of development of mortality conferred by living donation in the setting of obesity remains unknown.

In conclusion, although the absolute risk of postdonation mortality remains low, the risk of long-term mortality is 30% higher among obese living kidney donors compared with nonobese donors. These data can be used to inform donor selection, predonation management, and informed consent discussions with obese persons who are considering living donation. Further research is needed to better understand the relationships between changes in weight predonation and post donation and long-term risk for postdonation mortality.

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Conflict of interest

The authors have indicated that they have no conflict of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.03.016.

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