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Longitudinal trends and influence of BMI mismatch in living kidney donors and their recipients

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Abstract

Background and objectives—Age and body mass index (BMI) of kidney donors and recipients affect kidney allograft outcomes. Moreover, while deceased donor and recipient body size mismatch have been reported to influence allograft outcomes, how BMI mismatch in living kidney donor–recipient pairs affect graft survival is not well defined.

Design, setting, participants, and measurements—We investigated trends in characteristics of 90,815 US. living kidney donors and their recipients between 1987 and 2008.

Results—Median ages of donors and their recipients have risen over time, and the proportion of living donors age ≥ 50 years increased from 11 to 25%. Median BMI of recipients increased from 22.6 to 26.6 kg/m²; median BMI of kidney donors for the past 5 years has been 26.4 kg/m². Only 35% of living donor–recipient pairs were in the same BMI category (<25 , 25–29.9, 30–34.9, or ≥ 35 kg/m²). BMI mismatch where the living donor was three categories heavier than the recipient was associated with a significant adjusted risk for death-censored allograft loss (HR 2.31, 95% CI 1.05–5.08).

Conclusions—Living kidney donors are donating at more advanced ages, and the majority are overweight or obese in recent years. In summary: (1) previous longitudinal studies of living kidney donor outcomes may not be generalizable to recent donors, and studies of contemporary living kidney donor cohorts may be informative, (2) the majority of living donor–recipient pairs have BMI mismatch, and (3) extreme BMI mismatch where the living donor is heavier may confer an independent risk for allograft loss.

Keywords

Living kidney donation; Donor/recipient BMI mismatch; Donor age

Introduction

Population aging and epidemic rates of obesity [1] in the United States have led to increasing incidences of diabetes and hypertension in recent years. Consequently, these factors have led to a dramatic rise in the prevalence of chronic kidney disease (CKD) progression and end-stage renal disease (ESRD) either directly as an independent risk factor [2, 3] or mediated by the development of diabetes mellitus [4].

The growing demand for kidney transplant in the United States in the setting of the persistent deceased donor organ shortage necessitates increased utilization of living donors. In turn, this raises questions as to how demographic and clinical characteristics of living donors and their recipients might also be changing over time. Long-term health outcomes of these kidney donors, as well as renal transplant outcomes in their recipients, are presumably influenced by the characteristics of each at the time of donation. We hypothesized based on our clinical observations and experience that living kidney donors in the recent years would be older and have higher BMI than previous donors. We were also interested in examining the influence BMI mismatch in living kidney donor-recipient pairs on allograft outcomes and hypothesized that kidneys from smaller donors transplanted into larger recipients would confer an increased risk for allograft loss. We therefore undertook an analysis of the United Organ Sharing Network (UNOS) database to examine trends in living kidney donor-recipient pairs over time as well as the influence of BMI mismatch between living donors and recipients.

Materials and methods

We obtained unidentified kidney donor and recipient data through United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) Standard Transplant Analysis and Research files obtained in November 2008. These data include living kidney donor and recipient information submitted up through August 2008. In these analyses, we included available data for living kidney donors and their recipients ($n = 91,493$ pairs). We excluded donors of combined kidney- pancreas (and their recipients; $n = 47$ pairs), as well as those with missing procedure type ($n = 24$ pairs). After inspection of the distribution of donor age and plasma creatinine, we also excluded donors (and their recipients) reported to be ≤ 16 years ($n = 11$ pairs) or ≥ 80 years ($n = 5$ pairs), as well as those with reported plasma creatinine < 0.5 mg/dl ($n = 117$ pairs) or > 1.5 mg/dl ($n = 474$ pairs) as extreme values. After these exclusions, a total of 90,815 living kidney transplant pairs were available for analysis for trends over time.

Ethnicity was categorized as White, African-American, Hispanic, or Asian/Other where "Other" represented American/Alaskan natives, Hawaiian/other Pacific Islanders, and multiracial categories where there were low numbers observed. For body mass index (BMI) analyses, donors with height < 150 cm ($n = 161$) or > 200 cm ($n = 35$) and weight < 45 kg ($n = 390$) or > 120 kg ($n = 199$) were excluded as implausible values likely from data entry errors. BMI was then calculated among the remaining donors as $\text{weight (kg)}/\text{height (m)}^2$. Because recipients included minors and children, we did not apply exclusions based on weight or height, but instead excluded those (and their donors) with implausible values. After examination of the distribution, we exclude recipient BMI ≤ 12 ($n = 172$ pairs) or ≥ 50 ($n = 282$ pairs).

Of note, living donor weight and height were not reliably recorded before 2004. Therefore, for the BMI mismatch outcomes analyses, we included only data from adult living donor-recipient pairs between May 1, 2004, and May 15, 2008, where BMI data were available for both the donor and the recipient. Data were compiled for 25,363 recipients receiving a transplant from a live donor after May 1, 2004, resulting in information on 25,435 transplants. Of these, 12,636 recipients and their donors had data on their BMI and age and ethnicity, as well as information on recipient diabetes, recipient dialysis dependency at time of transplant, delayed graft function (defined as necessity for dialysis during the 1 week after the transplant), and status of HLA matching. After excluding 32 pairs where it was not the recipient's first transplant, the final data set had 12,604 living donor-recipient pairs.

Categories of BMI were <25, 25–29.9, 30–34.9 and ≥ 35 kg/m². Magnitude of BMI mismatch was calculated for each pair and ranged from –3 (recipient heavier by 3 BMI categories) to +3 (donor heavier by 3 BMI categories) with 0 (donor and recipient with the same BMI category) as the referent category.

Descriptive statistics are presented as frequencies or medians as appropriate. Chi-square test was employed to test for statistical significance in frequencies of characteristics; two-tailed $P < 0.05$ was considered significant. Time-to-failure of the transplant analysis was first examined univariately using the Kaplan-Meier product limit method. Clinically, important variables as well as variables exhibiting significant association with the univariate outcome of death-censored allograft loss were combined in a Cox proportional hazards model. We adjusted for nonproportional hazards by including the interaction of diabetes status and time, and delayed graft function and time. SAS for Windows, version 9.1 (Cary, North Carolina) was used for all statistical analyses. This study was approved by the Partners' Health Care Institutional Review Board.

Results

Trends in living donor kidney transplantation over time

There was an increase in median age of living kidney donors from 35 years in 1987 to 40 years in 2008; the increase in median age in their recipients was even more marked (31–47 years). The proportion of older donors aged 50 years or above at the time of donation increased substantially over this same interval (12 to 25%; Fig. 1). Fewer than 2% of living donors were age 65 or older in any year.

The proportion of female living kidney donors increased from 55% in 1987 to $\geq 60\%$ in the years since 2006. In contrast, men consistently constituted 60% of the recipients of living donor nephrectomies. Unrelated (non-spousal) living kidney donation increased from 1% in 1987 to $>20\%$ in the years since 2003. The percentage of recipients of living kidney donations who had a previous transplant also increased from 1% in 1987 to 9% in 2007–2008. We observed consistent trends toward preferential use of left-sided versus right-sided living donor nephrectomies over time (59% in 1987 to 86% in 2007–2008); overall, 80% of donor nephrectomies were left-sided. The type of nephrectomy was only reliably recorded beginning in the year 2000, but between 2000 and 2008, the annual percent of laparoscopic nephrectomy increased from 49 to 92%.

Plasma creatinine was not routinely recorded in living donors until 2004; the median plasma creatinine was 0.9 mg/dl and remained unchanged between 2004 and 2008. Distribution of donor ethnicity between 1987 and 2008 was White 70.7%, African-Americans 13%, Hispanic 12%, Asian 2.4%, and Other 1.9%. Distribution of recipient ethnicity was White 69.2%, African-Americans 14%, Hispanic 12%, Asian 3.1%, and Other 1.7%. The frequency of White living donors decreased from 77% to 69% over the study period, whereas frequencies of African-American (10.3–12.5%), Hispanic (9.3% to 13%), and Asian (0.3% to 2.9%) increased. Only 7.4% of living transplants were between donor–recipient pairs of different ethnic categories.

BMI mismatch in living donor kidney transplantation

Median donor BMI between 2004 and 2008 was 26.4 and did not vary by year (donor data from prior years were not available). Almost two-thirds of the living donors had BMI > 25 ; similarly, approximately 60% of their recipients had BMI > 25 . BMI data for 81,580 recipients were available going back to 1987 and showed a clear trend of increasing median BMI over time from ~ 22.5 to 26.5 kg/m².

We examined categories of donor BMI (<25, 25–29.9, 30–34.5, and ≥ 35) stratified by ethnicity and found that Asians/Other were more likely to have BMI < 25 when compared to other ethnic groups. African-Americans and Hispanics were more likely to have BMI > 25 when compared to Whites and Asians/Other ($P < 0.001$). A similar pattern was observed in the kidney recipients.

Only 35% of living donors and their recipients were in the same BMI category; of these, 49.6% had BMI < 25, 37.1% had BMI 25 to 29.9, 11.4% had BMI 30 to 34.9, and 1.9% had BMI ≥ 35 . The frequency of BMI category match remained 35% when analysis was performed only in recipients 18 years or older. When stratified by ethnic categories, Asian/Other donors were more frequently in the same BMI category as their recipients and African-Americans the least frequently.

The degree and direction of BMI mismatch between donors and their recipients appeared to be symmetrical across all ethnic categories. Recipient dialysis status (yes/no) at the time of transplant was not associated with BMI mismatch (40% in each group had BMI mismatch, $P = 0.68$). Previous kidney transplant in recipients was also not associated with BMI mismatch ($P = 0.85$).

We compared the characteristics for those included ($n = 12,604$) and excluded ($n = 12,831$) in the BMI mismatch analyses and noted the groups were very similar. For example, 5.0% of recipients not included reached death-censored allograft failure compared with 4.1% of those included. Racial distribution was not meaningfully different in included versus excluded donors and recipients. Mean age of donors was 41 years and of recipients 47 years with identical mean BMI's of donors (26.8 kg/m²) and recipients (27.1 kg/m²) in included and excluded groups. The prevalence of diabetes was 14%, and the incidence of delayed graft function was 2% in both included and excluded recipients. Therefore, those pairs included in the BMI mismatch analyses appeared to be representative of the overall group between 2004 and 2008.

With a mean follow-up of 1.8 years, 503 recipients (4.1%) reach death-censored allograft failure. Upon adjusted analysis, BMI mismatch, where donors were three categories heavier than their recipients, was associated with greater risk for death-censored allograft rejection (HR 2.31, 95% CI 1.05–5.08); other BMI mismatch categories were not associated with significantly different risk relative to matched BMI (Table 1). Neither donor BMI ($P = 0.38$) nor recipient BMI ($P = 0.08$) was statistically associated with allograft loss in the multivariable model. Covariates that were also significantly associated with allograft failure included recipient age (HR 0.98 [0.97, 0.98] per year), donor age (HR 1.01 [1.005, 1.02] per year), donor African-American race (HR 2.01 [1.27, 3.20]), recipient on dialysis (HR 1.32 [1.09, 1.59]), and delayed graft function (HR 20.83 [16.0, 27.1]). When the analysis was limited to those donor-recipient pairs where it was a preemptive transplant for the recipient ($n = 5,044$), the results remained consistent and statistically significant (HR 6.27, 95% CI 1.34 to 29.3 for donors three categories heavier than recipients).

Discussion

We report that living donors and their recipients are older than previous, with a marked increase in donors 50 years or older. BMI has been steadily increasing among recipients, and the majority of donors are overweight or obese at time of donation. These data also indicate that scarcely one third of donor-recipient pairs fall into the same BMI category.

Importantly, we observed that extreme BMI mismatch by three categories where the living donor is heavier conferred a significantly elevated risk for death-censored allograft loss after adjustment for known potential confounders including donor and recipient BMI. We had

initially hypothesized that greater BMI mismatch where the donor was smaller than the recipient would confer a greater risk for allograft loss, but our results showed that extreme BMI mismatch where the living donors are larger was associated with greater risk for allograft loss. By definition, these donors were all in the morbidly obese category ($\text{BMI} \geq 35 \text{ kg/m}^2$); however, there may also be an effect of donor obesity although donor BMI was not associated with allograft loss in the adjusted model. These data may be consistent with previous observations that donor obesity is associated with higher rates of delayed graft function and acute rejection [5] and significantly lower rates of graft survival [6].

Furthermore, donor obesity may influence not only allograft outcomes in the recipient but also donor outcomes. Being overweight or obese have been identified as independent risk factors for the development of chronic kidney disease [2] and progression to end-stage renal disease [3], and it is possible that transplanted kidneys from overweight donors have a greater early focal segmental sclerosis as previously reported [7]. A study of 73 kidney donors has reported those with $\text{BMI} > 30$ had significantly greater risk for developing overt proteinuria or renal insufficiency (92% vs. 12%, $P < 0.001$) [8]. Obesity in living donors has also been identified as a risk factor for longer surgical times [9] and peri-operative complications [10].

In contrast to our findings, a previous analysis of cadaveric kidney transplants in the UNOS database reported that larger recipients of deceased female kidney donors had markedly lower rates of allograft survival at 1 and 3 years. The authors suggested that a mismatch in nephron number and/or mass between presumably smaller female donors and larger recipients may result in worse graft survival [11]. This study examined only cadaveric renal transplants and used body surface area instead of BMI for recipients and did not provide specific data on donor size, however, and may not be directly comparable this study.

These data also show that unrelated living donation has also gained popularity since 1996 and may be due to a report of excellent graft outcomes in spousal and living unrelated donors published in the New England Journal of Medicine in 1995 [12]. Few studies are currently available on long-term outcomes in living donors, however, and usually include donors who were overall younger and had lower BMIs than current living donors. For example, one study of 339 Egyptian living donors published in 2007 reported excellent outcomes after a mean 10.7 years of follow-up, but the mean age at donation was 37.8 years and mean BMI was 23.7 [13]. The University of Minnesota reported preserved renal function and excellent quality of life among a subset of 255 of their center's living donors followed for a mean of 12.2 years. Although this study appeared to have a substantial representation of donors with $\text{BMI} \geq 30 \text{ kg/m}^2$ (~30%), these values were measured at the time of follow-up and likely do not reflect patients' BMI at donation. The mean age of this cohort at donation was 41.1 years, which is similar to that seen among the 2006–2008 cohorts in this study; the proportion of donors over the age of 50 was not reported [14].

Our result that older recipient age was associated with better allograft survival is the opposite of a previous analysis of >59,000 kidney recipients in the United States Renal Data System (USRDS), which reported lower rates of censored graft survival in older recipient age groups (67% for ages 18–49 vs. 61.8% for ages 50–64 vs. 50.7% for ages 65+, $P < 0.001$) [15]. These were unadjusted; however, whereas our model had confounders including BMI, diabetes, and dialysis status. Immune dysfunction may be more common in older individuals, a theory supported by the observation that the prevalence of panel reactive antibodies >10% is only 30% in recipients >60 years old compared with 40% in recipients <18 years [16].

Older donor age has been associated with higher rates of acute rejection and graft loss in the transplanted kidney, although the effect appears most significant in donors >65 years of age [17]. Consistent with this, we noted a small but statistically significant increased risk for allograft failure for higher living donor age (HR 1.01, 95% CI 1.001–1.02 per year) in our adjusted model. The residual kidney function after donor nephrectomy in older or obese donors is also of concern. A study of 178 consecutive living kidney donors who underwent predonation and postdonation renal functional reserve assessment (as measured by percent increase in iothalamate GFR with low-dose dopamine infusion) reported that both older age and higher BMI (the latter particularly in younger donors) were associated with greater loss in renal reserve after donor nephrectomy [18]. Therefore, the informed consent process for living kidney donation should include a discussion of how older age and higher BMI may be associated with decreased ability of the remaining kidney to compensate for GFR.

Notable limitations in this investigation include the sizable proportion of missing data, especially the absence of all donor BMI data prior to 2004, which prevents examination of trends in donor BMI. Based on the increasing BMI in the general US population over the past 30 years [19], as well as the increase in recipient BMI observed here, however, it is likely that donor BMI has similarly increased over time. Although data for BMI mismatch analyses were missing in approximately half of the living donor–recipient pairs in 2004–2008, we confirmed that those with BMI mismatch data were representative of the overall group. Very importantly, the mean 1.8 years of follow-up is relatively short.

In conclusion, the changing characteristics of living kidney donors and their recipients over time emphasize the need for new studies of donor and recipient outcomes following living kidney transplantation among a contemporary cohort, because previous longitudinal studies often included donors with ages and BMI substantially lower than those seen presently. This analysis of the UNOS database also further highlights areas where better quality longitudinal data are needed including tracking of change in BMI of living donors after donation and how this influences donor outcomes. Specific questions for future study include the incidence and risk factors for the development of hypertension, diabetes, and cardiovascular disease in living kidney donors.

The majority of living kidney donor–recipient pairs have BMI mismatch and donor–recipient BMI mismatch by 3 categories where donor being heavier is associated with significantly increased risk for allograft loss.

Because the volume and popularity of both living related and unrelated kidney donation have increased dramatically over the past two decades in the United States, better defining the risks and outcomes for this elective procedure represents an important public health issue.

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Fig. 1.
Proportion of living kidney donors ≥ 50 years of age at time of donation (1987–2008)

Table 1

Influence of BMI mismatch on living donor allograft outcomes

	Hazards ratio [95% CI] ^a for allograft failure
Recipient 3 categories heavier	0.88 [0.67, 1.91]
Recipient 2 categories heavier	0.94 [0.60, 1.47]
Recipient 1 category heavier	0.88 [0.68, 1.17]
BMI category match	1.0 [referent]
Donor 1 category heavier	1.06 [0.81, 1.41]
Donor 2 categories heavier	1.14 [0.71, 1.84]
Donor 3 categories heavier	2.31 [1.05, 5.08]

^a Adjusted for donor age, donor ethnicity, donor baseline BMI, recipient age, recipient ethnicity, recipient baseline BMI, recipient diabetes, recipient dialysis status, degree of HLA match, and delayed graft function