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Obesity and Outcome Following Renal Transplantation

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Single institution series have demonstrated that obese patients have higher rates of wound infection and delayed graft function (DGF), but similar rates of graft survival. We used UNOS data to determine whether obesity affects outcome following renal transplantation.

From the UNOS database, we identified patients who underwent primary kidney-only transplantation between 1997 and 1999. Recipient and donor body mass index (BMI) was categorized as underweight (BMI $<$ 18.5), normal (BMI 18.5–24.9), overweight (BMI 25–29.9), obese (BMI 30–34.9) or morbidly obese (BMI $\geq$ 35). We correlated BMI with intermediate measures of graft outcome and overall graft survival, and created multivariate models to evaluate the independent effect of BMI on graft outcome, adjusting for factors known to affect graft success.

The study sample comprised 27 377 recipients. Older age, female sex, African American race and increased comorbidity were associated with obesity ($p < 0.001$). Compared with normal weight patients, morbid obesity was independently associated with an increased risk of DGF ($p < 0.001$), prolonged hospitalization ($p < 0.001$), acute rejection ($p = 0.006$) and decreased overall graft survival ($p = 0.001$). Donor BMI did not affect overall graft survival ($p \geq 0.07$).

Recipient obesity is associated with an increased risk of DGF and decreased graft survival following renal transplantation.

Key words: Graft function, kidney transplantation, obesity

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Introduction

Obesity has been labeled a nutritional epidemic (1). Based on the data from the Centers for Disease Control and Prevention, in 1991, no state had a prevalence of obesity above 20%. By 2003, over 20% of the population was obese in 35 states (2). Currently, 65% of the U.S. population is overweight based on the body mass index (BMI) criteria (3). Trends among renal transplant recipients mimic trends in the general population. Between 1987 and 2001, the proportion of renal transplant recipients categorized as obese increased by 116% (4).

Although most investigators have associated recipient obesity with an increased risk for delayed graft function (DGF) and local wound complications, the impact of obesity on long-term graft survival has been incompletely characterized. Results from single institution retrospective series have been equivocal and interpretation of results from these series is often limited by insufficient sample sizes (5–16). Analysis of over 50 000 renal transplant recipients in the United States Renal Data System (USRDS) demonstrated adverse graft survival among underweight and obese recipients independent of factors predictive of graft outcome (17). However, this analysis incorporated subjects that predated the calcineurin inhibitor era and included limited follow-up for subjects transplanted in the late 1990s. Furthermore, presentation of the multivariate models of graft survival was limited to data for the BMI variable, restricting comparison of the effect of BMI relative to covariates.

We analyzed recipient outcomes for subjects who underwent kidney-only transplantation between 1997 and 1999, with follow-up through 2004. Adjusting for factors known to affect graft function and overall graft survival, we evaluated the independent association between BMI and measures of renal transplant outcome.

Methods

An analytic file was created from the United Network for Organ Sharing (UNOS) Standard Transplant and Research (STAR) files based on OPTN data as of July 16, 2004. We identified all patients over 18 years old who underwent renal transplantation from January 1, 1997 through December 31, 1999. Subjects with complete anthropometric data as well as follow-up graft outcome data were included in the analysis. Exclusion criteria included multi-organ transplantation or a history of prior renal transplantation. Recipient BMI was abstracted from height and weight recorded at the time of transplantation or registration. We categorized BMI according to National

Table 1: Characteristics of the study sample (n = 27 377)

	Underweight	Normal	Overweight	Obese	Morbidly obese	P-value
Number of recipients	1042	12 089	8765	3891	1590	
Age, mean ± SD	38.5 ± 13.3	43.7 ± 13.2	47.9 ± 12.5	48.3 ± 11.7	45.8 ± 11.7	<0.001
Sex, no. (%)						
Male	321 (30.8)	7018 (58.1)	5879 (67.1)	2309 (59.3)	812 (51.1)	<0.001
Female	721 (69.2)	5071 (41.9)	2886 (32.9)	1582 (40.7)	778 (48.9)	
Race, no. (%)						
White	606 (58.2)	7322 (60.6)	5254 (59.9)	2289 (58.8)	922 (58.0)	<0.001
African American	175 (16.8)	2458 (20.3)	2046 (23.3)	1074 (27.6)	479 (30.1)	
Hispanic	118 (11.3)	1442 (11.9)	1091 (12.4)	407 (10.5)	144 (9.1)	
Other	143 (13.7)	866 (7.2)	374 (4.4)	120 (3.1)	45 (2.8)	
Comorbidity, no. (%)						
Diabetes mellitus	113 (11.8)	2661 (23.3)	2514 (30.0)	1269 (34.1)	493 (32.6)	<0.001
Hypertension	665 (74.4)	8702 (80.0)	6559 (82.1)	2930 (81.9)	1227 (82.8)	<0.001
Coronary artery disease	47 (5.2)	1006 (9.2)	1003 (12.5)	460 (13.0)	163 (11.1)	<0.001
COPD	11 (1.2)	88 (0.8)	63 (0.8)	46 (1.3)	16 (1.1)	0.046
PVD	12 (1.3)	404 (3.7)	336 (4.2)	161 (4.5)	64 (4.4)	<0.001
Cerebrovascular disease	20 (2.2)	210 (1.9)	175 (2.2)	79 (2.2)	29 (2.0)	0.71
HLA 0 mismatch, no. (%)	81 (7.9)	859 (7.2)	570 (6.6)	277 (7.2)	124 (7.9)	0.19
Donor type, no. (%)						
Deceased	681 (65.4)	7994 (66.1)	5925 (67.6)	2749 (70.7)	1083 (68.1)	<0.001

COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; HLA: human leukocyte antigen.

Institutes of Health (NIH) and World Health Organization (WHO) guidelines as follows: underweight (less than 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–34.9 kg/m^2) and morbidly obese (35 or higher kg/m^2). For a subset of subjects, information on donor BMI at the time of recovery was available and was similarly categorized. Race/ethnicity was subdivided into whites, African Americans, Hispanics and others (Asian Americans, Pacific islanders, Native Americans, Alaskan natives, etc.).

Graft outcomes analyzed included the need for blood transfusions post-operatively, the incidence of DGF defined by dialysis requirement in the first week following transplantation, prolonged hospitalization defined as a length of stay greater than 14 days, and early graft loss or recipient mortality, defined as any graft failure or patient death within 30 days of transplantation. Immunologic outcomes included treatment for acute rejection, as reported in the UNOS STAR files, either prior to discharge, within the first 6 months following transplantation, or within the first post-operative year. Overall patient and graft survival were separately analyzed. Follow-up was available through July 2004. We defined graft failure as a permanent return to dialysis dependence or death with a functioning graft.

Statistical analysis

Demographic data were compared among transplant recipients stratified by BMI category with the chi-squared test for categorical variables and analysis of variance for continuous variables. We performed univariate analyses to determine the association between BMI and early graft and immunologic outcome. For outcomes with a statistically significant association ($p < 0.05$), we created multivariate models using logistic regression. Covariates included age, sex, race/ethnicity, comorbidity (coronary artery disease, peripheral vascular disease and diabetes mellitus), the level of human leukocyte antigen (HLA) matching, cold ischemia time and donor type (living or deceased). Graft survival was compared among subjects across BMI categories with univariate Cox proportional Hazards analysis and the log rank test. Multivariate Cox regression models were created to determine the independent association between BMI and graft survival, controlling for the above covariates.

Results

Of 30 597 subjects who underwent kidney-only transplantation from 1997 through 1999, we identified 27 377 recipients (89.5%) with complete anthropometric data. Characteristics of the study sample are presented in Table 1. Obese recipients tended to be older, and a disproportionate number of females was underweight or morbidly obese. With each successive BMI category, an increasing proportion of recipients was African American and a decreasing proportion was of the other race/ethnicity. Likewise, subjects in the obese and morbidly obese groups had a higher prevalence of comorbid conditions than those in the normal and underweight categories, with the exception of cerebrovascular disease, which affected a similar proportion of recipients regardless of body habitus. Obese and morbidly obese subjects were less likely to undergo living donor renal transplantation compared with underweight and normal weight recipients.

Table 2 displays the univariate models of graft outcomes associated with recipient BMI. Morbidly obese recipients were significantly more likely to incur adverse graft events, including bleeding, DGF, prolonged hospitalization, early graft loss, acute rejection episodes and a trend toward increased post-operative mortality compared with normal weight subjects, although this was not statistically significant. Furthermore, morbidly obese recipients were significantly more likely to die with a functioning allograft, and had significantly worse long-term graft survival than normal weight recipients. For DGF, prolonged hospitalization, early graft loss and death with a functioning graft, a trend was observed where each higher recipient BMI category suffered an increased risk of the adverse outcome. In multivariate

Table 2: Univariate analysis of recipient BMI and post-operative graft outcome

		Underweight		Overweight		Obese		Morbidly obese	
	Normal	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Recipient transfusions[1]	1.00	1.20 (0.96–1.50)	0.11	0.87 (0.78–0.97)	0.01	1.02 (0.89–1.17)	0.79	1.23 (1.02–1.47)	0.03
DGF[1]	1.00	0.86 (0.72–1.03)	0.11	1.21 (1.12–1.30)	<0.001	1.49 (1.36–1.64)	<0.001	1.91 (1.69–2.16)	<0.001
Prolonged hospitalization[1]	1.00	1.06 (0.88–1.27)	0.56	1.10 (1.01–1.19)	0.03	1.23 (1.12–1.36)	<0.001	1.57 (1.37–1.80)	<0.001
Early graft loss[1]	1.00	1.17 (0.98–1.40)	0.09	1.06 (0.98–1.15)	0.14	1.23 (1.11–1.36)	<0.001	1.47 (1.27–1.69)	<0.001
Post-operative mortality[1]	1.00	0.83 (0.36–1.91)	0.67	1.10 (0.80–1.52)	0.56	1.15 (0.76–1.74)	0.52	1.54 (0.91–2.60)	0.10
Acute rejection[1]									
Prior to discharge	1.00	0.90 (0.69–1.17)	0.44	1.08 (0.97–1.20)	0.16	1.19 (1.04–1.36)	0.014	1.56 (1.30–1.86)	<0.001
6 months	1.00	1.03 (0.86–1.24)	0.76	0.98 (0.90–1.06)	0.57	1.03 (0.93–1.15)	0.55	1.28 (1.11–1.49)	0.001
1 year	1.00	1.12 (0.94–1.34)	0.22	0.98 (0.90–1.06)	0.60	1.0 (0.90–1.10)	0.92	1.20 (1.04–1.39)	0.014
Death with functioning graft[1]	1.00	0.81 (0.62–1.04)	0.10	1.14 (1.03–1.26)	0.009	1.32 (1.16–1.49)	<0.001	1.30 (1.09–1.55)	0.004
Overall graft failure[2]	1.00	1.09 (0.96–1.24)	0.19	1.04 (0.99–1.10)	0.13	1.19 (1.11–1.28)	<0.001	1.38 (1.26–1.52)	<0.001

OR: odds ratio; CI: confidence interval.
[1]Univariate logistic regression with normal BMI subjects as the referent.
[2]Univariate Cox regression with normal BMI subjects as the referent.

analysis (Table 3), the association between morbid obesity and an increased risk of DGF, prolonged hospitalization and acute rejection remained, independent of covariates known to affect graft outcome. After controlling for demographic characteristics and comorbid conditions, obesity was not independently associated with an increased risk of death with a functioning graft.

Long-term graft survival is displayed in Figure 1. Although underweight, normal weight and overweight recipients had a similar graft survival profile, obese and morbidly obese recipients had worse longitudinal graft survival trends. Table 4 presents the multivariate model of factors associated with graft failure over time. Extremes of body habitus, independent of factors known to affect graft survival and confounding factors, especially those common among obese patients such as diabetes mellitus, are associated with decreased long-term graft survival.

Of the recipients studied, 19 882 subjects (72.6%) had donor BMI information available. In univariate analysis, the only measures of graft outcome associated with donor BMI were DGF (OR 0.88, $p = 0.047$ for underweight donors; OR 1.30, $p < 0.001$ for overweight donors; OR 1.52, $p < 0.001$ for obese donors and OR 1.96, $p < 0.001$ for morbidly obese donors compared with normal weight donors) and prolonged hospitalization (OR 1.01, $p = 0.94$ for underweight donors; OR 1.19, $p < 0.001$ for overweight donors; OR 1.23, $p = 0.001$ for obese donors and OR 1.28, $p = 0.002$ for morbidly obese donors compared with normal weight donors). In multivariate logistic regression analysis, donor BMI remained an independent predictor of DGF (OR 0.74, $p = 0.001$ for underweight donors; OR 1.34, $p < 0.001$ for overweight donors; OR 1.65, $p < 0.001$ for obese donors and OR 1.92, $p < 0.001$ for morbidly obese donors compared with normal weight donors) and prolonged hospitalization, although when DGF was included as a covariate in the prolonged hospitalization model, donor BMI became nonsignificant ($p \geq 0.62$). Donor BMI was not associated with graft survival on univariate analysis ($p \geq 0.07$).

Discussion

Previous studies, predominantly from single institutions, have reported findings that make it difficult to assess the impact of body habitus on transplant outcomes. Some investigators have demonstrated no association between obesity and adverse graft survival, despite increased risk among obese recipients for wound infections and DGF (5–13). Conversely, others have shown decreased graft survival rates among obese recipients when compared with normal weight subjects (14–16). The majority of these investigations are limited by small sample sizes. Yamamoto et al. analyzed recipients of paired kidneys in whom one of the kidneys was placed in an obese subject, and the other in a nonobese subject (11). Although differences in graft survival were not statistically significant, serum

Table 3: Multivariate analysis of factors associated with post-operative graft outcome

	DGF		Prolonged LOS		Early graft loss		Acute rejection		Death, functioning graft	
	Parameter estimate	p-value	Parameter estimate	p-value	Parameter estimate	p-value	Parameter estimate	p-value	Parameter estimate	p-value
Body mass index (vs. normal)										
Underweight	−0.05	0.69	0.10	0.42	0.26	0.04	−0.27	0.14	0.25	0.14
Overweight	0.13	0.01	<0.001	0.99	–0.09	0.08	0.05	0.50	−0.14	0.03
Obese	0.34	<0.001	0.10	0.14	–0.01	0.95	0.16	0.07	–0.05	0.52
Morbidly obese	0.58	<0.001	0.31	<0.001	0.15	0.10	0.32	0.006	0.03	0.81
Recipient age	–0.002	0.25	0.01	<0.001	0.01	<0.001	–0.01	0.001	0.05	<0.001
Recipient sex (vs. male)										
Female	−0.17	<0.001	0.04	0.41	0.03	0.47	0.13	0.03	0.01	0.84
Recipient race (vs. white)										
African American	0.38	<0.001	0.39	<0.001	0.38	<0.001	0.22	0.001	0.02	0.77
Hispanic	0.05	0.48	–0.05	0.48	−0.35	<0.001	−0.28	0.01	−0.32	0.001
Other	0.07	0.45	−0.13	0.25	−0.22	0.05	−0.13	0.36	–0.35	0.01
Recipient comorbidities										
Diabetes mellitus	0.25	<0.001	0.20	<0.001	0.22	<0.001	0.14	0.04	0.74	<0.001
Coronary artery disease	0.08	0.22	0.03	0.70	0.09	0.22	−0.09	0.36	0.27	<0.001
Peripheral vascular disease	0.08	0.42	0.09	0.43	0.25	0.02	−0.04	0.80	0.33	0.002
HLA 0 mismatch (vs. any mismatch)	−0.47	<0.001	−0.49	<0.001	−0.39	<0.001	−0.98	<0.001	0.08	0.47
Cold ischemia < 24 h (vs. > 24 h)	−0.47	<0.001	−0.29	<0.001	−0.09	0.11	−0.22	0.002	−0.10	0.14
Living donor (vs. deceased)	−1.60	<0.001	−0.64	<0.001	−0.60	<0.001	−0.16	0.02	−0.38	<0.001

LOS: length of stay; HLA: human leukocyte antigen

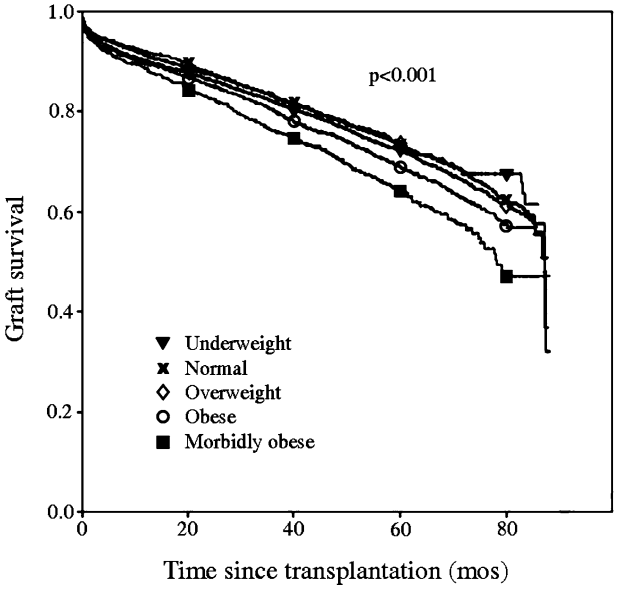

Figure 1: Graft survival following renal transplantation stratified by recipient BMI at the time of transplantation.

Table 4: Multivariate Cox regression of factors associated with graft failure

	HR (95% CI)	P-value
Body mass index (vs. normal)		
Underweight	1.21 (1.03–1.42)	0.02
Overweight	0.98 (0.92–1.05)	0.61
Obese	1.07 (0.98–1.17)	0.13
Morbidly obese	1.22 (1.09–1.38)	0.001
Recipient age	1.00 (1.00–1.01)	0.01
Recipient sex (vs. male)		
Female	1.03 (0.97–1.09)	0.38
Race (vs. white)		
African American	1.49 (1.39–1.60)	<0.001
Hispanic	0.83 (0.75–0.93)	0.001
Other	0.78 (0.67–0.91)	0.002
Recipient comorbidities		
Diabetes mellitus	1.28 (1.19–1.36)	<0.001
Coronary artery disease	1.17 (1.07–1.28)	0.001
Peripheral vascular disease	1.19 (1.04–1.36)	0.01
HLA 0 mismatch (vs. any mismatch)	0.76 (0.66–0.86)	<0.001
Cold ischemia < 24 h (vs. > 24 h)	0.90 (0.84–0.97)	0.003
Living donor (vs. deceased)	0.65 (0.60–0.70)	<0.001

HLA: human leukocyte antigen.

creatinine at 1 year was 2.0 mg/dL in the obese group compared with 1.4 mg/dL in the nonobese group. Marks et al. presented 3-year deceased donor graft survivals of 75% in morbidly obese recipients and 90% in nonobese recipients that were not different statistically (13). The lack of statistical significance in these disparities likely reflects inadequate power and does not confirm that a clinically meaningful difference does not exist between these recipient groups.

Analysis of national databases has overcome sample size limitations of single institution series. Meyer-Kriesche et al. identified 51 927 renal transplant recipients in the USRDS with inclusion and exclusion criteria similar to our analysis and demonstrated similar associations between extremes of body habitus and graft survival (17). Primary outcomes were restricted to patient and graft survival, with limited analysis of intermediate outcomes. Furthermore, although multivariate modeling evaluated the independent effect of BMI on graft survival in their cohort, presentation of the models included tests of significance for BMI only, limiting interpretation of the clinical impact of BMI relative to covariates. Inclusion of subjects managed with outdated immunosuppressive regimens further limits generalization of their findings.

We identified 27 377 subjects who underwent renal transplantation in the contemporary era of immunosuppression, with follow-up through 2004. From this cohort, we derived several important findings. First, obesity was associated with an increased risk of DGF following renal transplantation. Our data corroborates prior investigations (7,8,14,16–18). The association between morbid obesity and DGF was more profound than all covariates, with the exception of the inverse correlation between living donor transplantation and DGF. Although DGF may not affect overall graft survival, DGF is associated with increased radiographic and pathologic monitoring of the allograft and prolonged hospitalization, which increases health care costs and the risk for complications (19). Furthermore, DGF confounds diagnoses of acute rejection in the post-operative period. The association between obesity and DGF may be immunologically-mediated; however, at the present this remains purely speculative (19).

Second, morbidly obese subjects were more likely to be treated for acute rejection independent of covariates that increase the risk for acute rejection episodes, including African American race and the level of HLA matching. Although a disproportionate fraction of African Americans were obese and morbidly obese, both factors were independently associated with acute rejection episodes. An increased risk for acute rejection may relate to difficulty achieving adequate immunosuppression in obese recipients. In obese patients, the relationship between the oral cyclosporine dose and the area under the concentration (AUC) versus time curve follows a nonlinear relationship complicating dosage adjustments in these recipients (20). The inability to accurately monitor immunosuppressive levels in these recipients may predispose them to acute rejection episodes.

Third, adjusting for comorbidities common among obese patients, obesity did not increase the likelihood of recipient death with a functioning graft. This finding contrasts that

of Meyer-Kriesche et al. in which underweight and morbidly obese recipients were significantly more likely to die with a functioning graft than normal weight recipients (17). Our model adjusted for comorbidities that may account for the increased risk of mortality seen in prior analyses. Comorbid conditions common among these recipients include diabetes mellitus, hypertension and hyperlipidemia, all independent risk factors for ischemic heart disease.

Fourth, extremes of body habitus were associated with worse graft survival. Factors limiting graft survival in underweight recipients may include malnutrition and inappropriate immunosuppression leading to chronic allograft nephropathy (CAN) (17). Among obese recipients, the association with worse graft survival is likely multifactorial. Looking at Figure 1, the gap in graft survival between morbidly obese recipients and those of all other body habitus categories continues to widen with time, indicating a progressive deterioration in renal function. Changes common in the native kidneys of obese patients may explain the deleterious effects of obesity on transplant outcomes, although this has not been validated. Associated comorbidities may predispose obese subjects to CAN. Obesity-related hypertension either results from or results in chronic kidney disease (21). Obesity increases tubular reabsorption due to activation of both the sympathetic and renin-angiotensin-aldosterone axes (22). An increase in salt reabsorption increases glomerular filtration rate (GFR) in order to maintain salt homeostasis eventually leading to decompensated hydrostatic pressures in the glomeruli and glomerulosclerosis (23). Obesity-associated hyperlipidemia may promote glomerulosclerosis through oxidative stress and involvement of low density lipoprotein receptors on mesangial cells (24). Pathologic changes consistent with diabetic nephropathy are common among obese patients, regardless of whether there is a clinical history of diabetes mellitus (25). These changes may reflect subclinical hyperinsulinemia in the obese population.

Pathological levels of adipocytokines may play a pathogenic role in the development of CAN in the obese recipient. Leptin is a hormone secreted by adipose tissue that affects appetite. Serum concentrations of leptin are correlated with body fat stores (26). Effects in the kidney include stimulation of transforming growth factor β (TGF-β) leading to increased collagen deposition and mesangial proliferation (26). TGF-β is also directly secreted by adipocytes. Leptin infusion in rats results in proteinuria and progression to glomerulosclerosis (26). Leptin may also be implicated in obesity-related hypertension and hyperfiltration injury (27). Tumor necrosis factor α, secreted by adipocytes, also promotes inflammation within the kidney and may contribute to obesity-associated glomerulosclerosis (28). Other adipose-derived factors include angiotensin II and plasminogen activator inhibitor 1, both of which induce endothelial injury leading to renal arteriosclerosis and glomerulosclerosis (29,30).

Other mechanisms of CAN in the obese recipient include hyperfiltration injury and an increased incidence of acute rejection episodes. The size discrepancy that occurs when kidneys from normal weight donors are transplanted into obese recipients may induce hyperfiltration injury, eventually leading to proteinuria, glomerulosclerosis and CAN (31). We demonstrated an independent association between morbid obesity and post-operative acute rejection, itself a risk factor for CAN (32).

Finally, donor obesity may affect graft outcomes in the post-operative period, but does not impact overall graft survival. Very few investigators have examined the impact of donor body habitus on recipient outcome. Pesavento et al. found increased rates of wound infection and longer operative times for the donor among obese donors participating in living donor renal transplantation (33). Recipient outcomes were not examined in their analysis. Among subjects undergoing deceased donor renal transplantation, utilization of kidneys from small donors in large recipients resulted in decreased graft survival (34). However, donor obesity did not affect long-term graft function, similar to our findings.

Our study has several limitations. First, although using a national database affords increased statistical power, an overpowered study risks identifying associations that are statistically significant but clinically meaningless. With respect to our principle findings, the association between BMI and our outcomes of interest compared favorably with covariates known to impact graft outcome. Second, we examined the incidence of treatment for acute rejection as opposed to the incidence of biopsy-proven episodes. In obese individuals, body habitus may preclude biopsy, leading to increased treatment on a presumptive basis and biasing obese recipients toward worse acute rejection outcomes. Third, although our subjects were transplanted in the era of calcineurin inhibitors, immunosuppression in these recipients likely combined a full-dose calcineurin inhibitor with steroids. Current protocols that minimize steroid and calcineurin inhibitor dosages with the addition of sirolimus may ameliorate or exacerbate the disparities noted in our study. Finally, the retrospective nature of our study prohibited adjusting for unmeasured confounding factors that may eliminate the association between obesity and adverse graft outcome in a prospective, randomized trial.

Despite these limitations, we found that BMI impacts early and long-term renal transplant outcome. Morbid obesity increases the risk of DGF, prolonged hospitalization and treatment for acute rejection in the post-operative period, and adversely affects overall graft survival. Underweight recipients were similarly predisposed to worse graft survival. Although donor BMI is associated with DGF, long-term graft survival is not affected. In light of these findings and the scarcity of deceased donor allografts, morbidly obese patients should be counseled at the time of registration, with

attention to nutrition and weight loss programs and perhaps even bariatric surgery.

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