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Obesity and cardiac risk after kidney transplantation: Experience at one center and comprehensive literature review [1]

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Abstract

Background—The cardiac implications of obesity in kidney transplant recipients are not well-described.

Methods—We examined associations of body mass index (BMI) at transplant with post-transplant cardiac risk among 1,102 renal allograft recipients at a single center in 1991-2004. Cumulative post-transplant incidences of congestive heart failure (CHF), atrial fibrillation (AF), myocardial infarction (MI), and a composite of these cardiac diagnoses were estimated by the Kaplan-Meier method. Bivariate (hazards ratio, HR) and covariate-adjusted (aHR) relationships of BMI increments with cardiac risk were modeled by Cox's regression. We also systematically reviewed the literature on BMI and cardiac events after transplant.

Results—In the local data, 5-year cumulative incidence of any cardiac diagnosis rose from 8.67% to 29.35% across the lowest to highest BMI quartiles (P=0.02), driven primarily by increases in CHF and AF. In contrast, the rate of MI did not differ by BMI quartile (P=0.56). Each 5 U BMI increase predicted 26 % higher risk of the cardiac composite (HR 1.26, 95% CI 1.06 −1.48 2.14, P=0.008), a relationship that persisted with significance after covariate adjustment (aHR 1.19, 95% CI 1.00 −1.43, P=0.049). BMI independently predicted cardiac risk in sub-cohorts with pre-transplant heart disease and with non-diabetic renal failure. Data from 26 original articles support BMI as a risk factor for post-transplant CHF and AF, whereas findings for coronary/ischemic outcomes are inconsistent and predominantly negative.

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Conclusions—High BMI at transplant predicts increased cardiac risk, especially of CHF and AF. Further research should examine whether obesity treatment modifies cardiac risk after kidney transplantation.

Keywords

Atrial fibrillation; Body mass index; Congestive heart failure; Ischemic heart disease; Kidney transplant; Myocardial infarction; Obesity

Introduction

Elevated body mass index (BMI) is an established marker of unfavorable health outcomes including cardiovascular disease events in the general population, reflecting statistically independent associations as well as clustering with other risk factors such as hypertension, dyslipidemia and insulin resistance (1-4). In end-stage renal disease, the outcome implications of BMI are complex. High BMI has been linked with a mortality benefit in dialysis patients, a relationship that may be at least partially confounded by underlying comorbidities and malnutrition that both reduce BMI and increase death risk (5-8). Patients selected for transplantation are, at least at the time of transplant, deemed healthy enough for surgery and immunosuppression and thus are generally free of conditions such as active infections, malignancy, symptomatic cardiovascular disease and severe malnutrition. As in the general population, obesity in kidney transplant recipients predicts increased mortality along with an array of adverse events including peri-operative complications, delayed graft function, increased transplant costs, and allograft loss (9-11). Cardiovascular disease is the leading cause of death both before and after transplant, but the relationship of BMI with cardiovascular disease events specifically after transplant is not well described.

To advance understanding of the relationship of obesity with post-transplant cardiac risk, we performed a retrospective study of kidney transplant recipients at a large Midwestern center. Using an electronic clinical record, we examined the risks of congestive heart failure (CHF), atrial fibrillation (AF) and myocardial infarction (MI) in relation to BMI. The potential for variations in BMI-related cardiac risk according to the status of selected classical cardiovascular risk factors were investigated. We also performed a systematic literature review to frame our results in the context of current knowledge and identify questions warranting further study.

Methods

Data Sources and Participant Selection

After Institutional Review Board approval, data were drawn from the electronic records of the kidney transplant program at Washington University, St. Louis, MO, USA. Information describing the clinical course for the center's transplant recipients is prospectively entered into a secured research database by trained nurse coordinators. Data from ambulatory encounters and in-center hospitalizations are tracked at point-of-care. Outpatient assessments are scheduled at least bimonthly for the first month after transplant, then at least monthly through the first quarter, then at least quarterly until the one-year post-transplant anniversary, and then quarterly to annually depending on patient stability. Records from hospitalizations and encounters reported by treating providers in the community are also summarized in the database, either at the time of an event (if available), or based on follow-up contact. For the current analysis, we retrospectively sampled adult (>18 year old) patients transplanted in 1991 to 2004 with available information on height, weight and other clinical covariates at the time of transplantation.

Outcome Definitions

The primary outcome of interest was time to first post-transplant cardiac event, defined as a composite of congestive heart failure (CHF), atrial fibrillation (AF) and myocardial infarction (MI). Individual event types were considered as secondary outcomes. Cardiovascular disease events are among the pre-specified clinical complications of interest tracked in the database. Guidelines incorporate clinical judgment based on history, physical examination, supporting radiolographic, echocardiographic, an laboratory data into the diagnosis of heart failure (12). Accordingly, an indication of CHF within the database requires physician-reported diagnosis plus objective evidence of cardiac dysfunction (eg, echocardiography or other forms of ventriculography, chest radiograph, and/or B-natriuretic peptide). MI events included those classified as “definite” or “probable” by Minnesota code electrocardiographic and biomarker criteria, as adapted by the American Heart Association for use in clinical research (13). Diagnosis of AF was based on diagnostic electrocardiographic findings. Fatal and non-fatal events were included in the individual outcomes. We also separately defined cardiac-related death as physician-reporting of myocardial infarction, atherosclerotic heart disease, pericarditits including tamponade, heart failure, cardiomyopathy, pulmonary edema or cardiac arrhythmia as primary or secondary causes of death.

Body Mass Index and other baseline clinical factors

Body mass index (BMI, kg/m^2) at transplantation, the exposure of interest, was computed based on height and weight information recorded at the time of hospital admission for transplantation. Other clinical characteristics recorded at transplantation included: recipient age, race, sex, cause of end-stage renal disease (diabetes, hypertension, glomerulonephritis, other), and duration of pre-transplant dialysis; donor source (living, standard criteria deceased, expanded criteria deceased); use of induction immunosuppression, maintenance immunosuppression regimen at transplant discharge, and year of transplantation. An indication of cardiac disease prior to transplant reflects diagnoses of coronary artery disease, heart failure and/or arrhythmias during the clinical assessment for transplant candidacy, or as reported during the pre-transplant waiting period.

Statistical Analyses

We report means and standard deviations to describe normally distributed continuous variables, and describe categorical variables with counts and proportions. Continuous values of BMI were ranked into quartiles for selected analyses. We estimated the cumulative incidence of cardiac events after transplant by the Kaplan-Meier method (standard error (SE)), with stratification by BMI quartile and by other baseline clinical characteristics classically related to cardiac risk in general populations (gender, diabetes, pre-existing cardiac disease). Observation time was censored at the date of the last clinical data review recorded in the database, or at death unrelated to a study event.

We examined associations of continuous increases in BMI (per 5 units) with the risk of post-transplant cardiac events by Cox's proportional hazards regression. Multivariable models including baseline factors were also constructed to adjust BMI-related effect estimates. We assessed the proportionality of hazards over time by graphical methods. Final multivariable models were selected retaining BMI regardless of statistical significance, and applying stepwise selection for model reduction among other clinical covariates recorded at transplant with $p=0.10$ as the significance level for variable entry and retention. Maintenance immunosuppression at discharge was modeled as triple-drugs regimens of: cyclosporine, azathioprine and prednisone (reference); cyclosporine, mycophenolate and prednisone; tacrolimus, mycophenolate and prednisone; tacrolimus, azathioprine and prednisone; or other combinations/regimens. Regression models were stratified by year of transplant to minimize potential confounding by secular trends in the risk of the modeled outcomes.

To assess possible variations in the association of BMI with post-transplant cardiac risk according to baseline comorbidity, we individually stratified the study sample according to two major classic cardiac risk factors – diabetic renal failure and pre-transplant cardiac disease history. Kaplan-Meier estimates of the incidence of cardiac diagnoses according to BMI rank were performed within comorbidity-stratified sub-samples. Due to the smaller number of participants in sub-samples, the first and second BMI quartiles were compared to the third and fourth in these analyses. We estimated the adjusted associations of continuous increases in BMI with risk of any cardiac diagnosis in comorbidity-stratified sub-samples by multivariable Cox's regression. All analyses were performed with SAS for windows software, version 9.1 (SAS Institute Inc., Cary, NC).

Systematic Literature Review

In order to frame our results in the context of the published literature, we performed a systematic literature review of studies describing the association of BMI with cardiovascular outcomes among kidney transplant recipients. Two investigators independently conducted electronic queries of MEDLINE bibliographic database for relevant articles published from January 1st 1996 to July 31st 2007. Our search strategy included the following medical subject heading (MeSH) terms: “Kidney transplantation”, “Obesity”, “BMI”, “Overweight”, “Body Weight”, “Metabolic Syndrome X”, “Cardiovascular diseases”, “Heart diseases”, “Arrhythmia”, “Heart failure, congestive”, “Myocardial ischemia”, “Coronary disease”, “Myocardial infarction”, “Atrial Fibrillation”. Articles written in languages other than English, not related to humans or specific to the pediatric population were excluded. We also excluded studies that considered only non-cardiac vascular disease events (e.g., only cerebrovascular or peripheral vascular disease). Manuscripts listing BMI among study variables in the methods section but which did not report findings on cardiovascular events in relation to BMI were discarded. Full-text articles were retrieved for further evaluation when the investigators independently agreed about their potential relevance. Manual search of the reference lists of relevant articles and reviews supplemented electronic findings. Any disagreement regarding study inclusion was resolved by a third investigator. The descriptive and outcome data elements abstracted from the final sample of articles are shown as column headings in Tables 2–5.

Results

Characteristics of the local sample

We identified 1,102 individuals within the local clinical data who satisfied inclusion criteria. The distributions of baseline characteristics at transplantation are shown in Table 1. The majority of participants were white race (73.7%) and 59.4% were men. Mean age at transplantation was 47.3 ± 13.5 years. Mean BMI at transplant was 26.6 ± 5.3 kg/m^2, and ranged from 14.2 to 46.9 kg/m^2. Twenty five percent of the sample was obese by World Health Organization criteria (BMI ≥30 kg/m^2). Diabetes and glomerulonephritis were the leading causes of end-stage renal disease (23.8% and 22.7%, respectively). Cardiac disease prior to transplant was reported for 19.2%. Maintenance immunosuppression at transplant discharge during the study period predominantly comprised prednisone (93.9%), cyclosporine (70.8%) and azathioprine (59.4%).

Relationships of BMI and cardiac event rates in the local sample

The 5-year cumulative incidence of any cardiac diagnosis after transplant in the single-center full cohort was 18.52% (SE 1.98%), which included diagnoses of CHF in 10.90% (SE 1.75%), MI in 6.83 % (SE 1.15%) and AF in 4.50 % (SE 1.07%). In the presence of diabetic renal failure or a pre-transplant diagnosis of heart disease these incidence estimates rose to 25.72 % (SE 4.64 %) and 39.61% (SE 5.67%) at 5 years. The cumulative incidence of any cardiac event did not differ by patient sex (18.53% in men vs. 18.06% in women at 5 years, P=0.71)

The 5-year cumulative incidence of the composite cardiac outcome increased significantly across BMI quartiles, rising from 8.67% (SE 2.41%) in the lowest BMI group to 29.35% (SE 5.44 %) in the upper BMI quartile (P=0.02; Figure 1A). This was driven primarily by increases from the first to fourth BMI quartile in the incidences of CHF (3.56% vs. 18.43%, P=0.007) and AF (1.00% vs. 10.71%, P=0.12). In contrast, the cumulative incidence of MI did not differ by BMI quartile (P=0.56). By unadjusted Cox's regression, each 5 U increase in BMI predicted an approximate 25% increase (HR 1.25, 95% CI 1.07 −1.47, P=0.005) in the risk of any cardiac diagnosis. This composite risk was mediated by significant associations of each 5 U increase in BMI with the risk of CHF (HR 1.31, 95% CI 1.05 −1.64, P=0.02) and AF (HR 1.55, 95% CI 1.14 −2.11, P=0.005). In contrast, the risk of MI was not significantly associated with continuous 5U BMI increments (HR 1.06, 95% CI 0.82 −1.38 , P=0.6).

Upon multivariate adjustment for baseline factors, the relationship of BMI (per 5U increase) with AF (adjusted HR (aHR) 1.64, 95% CI 1.11 −2.42 , P=0.01) and the cardiac composite (aHR 1.19, 95% CI 1.00 −1.43 2.48, P=0.049) were significant at $p<0.05$, and the relationship of BMI with CHF was nearly significant (aHR 1.27, 95% CI 0.99–1.63, P=0.06). Congruent with large registry-based analyses (Table 2), BMI>28 was associated with approximately 60% higher risk of post-transplant CHF compared to BMI<28, although the risk relationship with this dichotomized BMI exposure did not reach statistical significance in the single-center data (aHR 1.62, 95% CI 0.91–2.89, P=0.10). As in the unadjusted model, BMI was not related to MI risk after covariate adjustment. Other baseline factors significantly associated with risk of the cardiac composite in the multivariable model included recipient age at transplant (aHR per decade 1.40, 95% CI 1.18–1.67), diagnosis of pre-transplant heart disease (aHR 2.42, 95% CI 1.62–3.32), and ESRD due to diabetes (aHR 1.83, 95% CI 1.12–2.99) or hypertension (aHR 2.02, 95% CI 1.22–3.32). Adjusted CHF risk was higher among black compared to white race recipients (aHR 2.12, 95% CI 1.16–3.86).

Analysis of cardiac event rates by BMI category and cardiac history suggested relative amplification of BMI-related risk among patients with pre-transplant cardiac disease. Specifically, in patients with prior cardiac history there was a trend towards >150% increase in the 5-year incidence of any cardiac event if BMI was above the median compared to the lower quartiles (57.66% (SE 8.80%) versus 20.94% (SE 5.05%), P=0.06) (Figure 1B). In patients without baseline heart disease the 5-year incidence of any cardiac event also trended higher across BMI ranks, but the magnitude of change was smaller (9.33% (SE1.98%) to 18.75 % (SE 3.68%), P=0.06). BMI-related cardiac risk was less apparent in subjects with diabetic ESRD compared to renal failure from other causes. The 5-year incidence of any cardiac event more than doubled across BMI ranks in those without diabetic ESRD (9.49% (SE 1.98%) to 24.98% (SE 4.14%), P=0.008), whereas BMI-related incidence change in those with diabetic ESRD was smaller and did not approach significance (18.37% (SE 4.69%) versus 35.94% (SE 8.76%), P=0.44). In multivariable regression adjusted for other baseline factors, each 5 U increase in BMI was significantly associated with increased risk of the cardiac composite in patients with pre-transplant heart disease (aHR 1.40, 95% CI 1.06–1.82, P=0.02) and non-diabetic renal failure (aHR 1.33, 95% CI 1.08–1.64, P=0.006) (Figure 2). BMI was a not a significant adjusted predictor of cardiac risk in the sub-groups without baseline heart disease or with diabetic ESRD.

There was a trend towards higher cumulative incidence of all cardiac-related death with increasing BMI category in the local clinical data. Five-year cumulative incidence of cardiac-related death was 1.75% (SE 1.07%), 3.54% (SE 1.61%), 8.37% (SE 3.14%) and 8.61% (SE 4.31%), respectively, in the four BMI quartiles but this graded increase was not statistically significant (P=0.30). In multivariable regression, continuous increases in BMI at transplant were not independently associated with the risk of cardiac-related death after transplant (P=0.80).

Literature review

The search algorithm yielded 848 original articles potentially relevant to the association of BMI and cardiovascular outcomes in kidney transplant recipients, of which 26 met complete selection criteria (10,14-38). The study sample was organized according to the reported cardiac outcome: CHF, AF (Table 2), coronary disease events/ischemic heart disease (Table 3), cardiac death and composite outcomes (Table 4). Most (24/26) of the selected articles employed historic cohort or nested case-control designs; two were prospective observational investigations (27,38). Approximately half (14/26) the studies were performed at single centres and 16/26 were conducted in the United States. Sample sizes ranged from 100 to 53,297 patients (median: 1,028). Observation periods, where specified, ranged from a minimum of 1 month to a maximum of 14 years. BMI was ascertained before or at transplantation in 20 studies. Obesity prevalence at transplantation (BMI >30 kg/m^2) ranged from 9.5% to 29%.

Elevated BMI was a significant independent predictor of CHF in 3/3 studies (14-16), with BMI>30 versus ≤30 predicting up to 59% relative risk increase (Table 2). All 3 studies were based in the United States Renal Data System Registry, but varied in case definitions (only hospitalized CHF versus combined inpatient and outpatient diagnoses) and years of transplant for participants (ranging from 1995-2001). Two registry studies examined AF risk in relation to BMI, one of which found that BMI >28.3 independently predicted a 79% relative increase in the risk of hospitalized AF compared to lower BMI (17). In the second study of AF including outpatient events, obesity was a significant correlate in bivariate analyses but the association was not significant in the final multivariable model (18).

Among 12 articles focused on coronary disease events/ischemic heart disease, 2 detected significant associations with ischemic heart disease – 1 from Egypt using BMI (19) and 1 from Spain using weight in kg (20) as predictors (Table 3). An Iranian study identified increasing BMI as a risk factor for acute coronary syndromes, although the incremental BMI change examined was not defined (21). DeMattos et al. also found BMI>30 independently predicted a 190% increase in the adjusted relative risk of a composite outcome combining angina, MI, coronary revascularization and cardiac death in American patients (36) (Table 4b). The 9 studies that failed to detect significant associations of BMI with coronary/ischemic events included single-centre and large-registry based investigations from North America, Europe and/or China, with follow-up ranging from 1.6 to 14 years.

The largest of 8 studies examining cardiac mortality identified BMI as a significant risk factor (10) (Table 4a). In this study of nearly 52,000 patients in the United States Renal Data System registry, the adjusted risk of cardiac death increased at both low BMI (RR ˜1.3 if <20) and high BMI (RR ˜1.2 if 30-32; RR ˜1.4 if >36) compared to the reference group with BMI 22-24. Seven studies reporting cardiac mortality did not detect associations with BMI; however, the total number of observed outcomes was very small (3 to 54 cardiac deaths) in these studies. (27,30-35).

Two studies combining cerebral and peripheral vascular disease events into a composite end-point with cardiac events reached differing conclusions on risk in relation to BMI (37,38) (Table 4b). Aker et al in Germany found that the risk of their composite outcome increased >150% in those with BMI qualifying as overweight or higher (BMI >25) compared to lower BMI (37). In contrast, BMI did not differ in those who did and did not develop events from a composite outcome in a small Spanish study (38). None of the studies in the literature sample considered variation in the associations of BMI and cardiac events according to other recipient characteristics, nor did any of the sampled studies analyze association of BMI changes over time in relation to cardiac outcomes.

Discussion

Obesity predicts all-cause mortality and peri-surgical complications among kidney transplant recipients, but the cardiovascular implications of obesity in this population are not well-described. We examined associations of BMI at transplant with post-transplant cardiac diagnoses at one center, and performed a systematic literature search to compare our results with available published data.

Among transplant recipients at our institution, we found that raw risk of any cardiac diagnosis rose with increasing BMI due to graded increases in rates of CHF and AF events. After covariate adjustment, increasing BMI at transplant was independently predictive of AF and the cardiac composite, and bore a nearly significant relationship with CHF. In contrast, post-transplant MI risk appeared unrelated to BMI in the local data. Subanalyses suggest that BMI-related cardiac risk may be particularly important in patients with pre-transplant heart disease and in those with non-diabetic renal failure. The comprehensive literature review supports consistent associations of BMI with CHF and AF. One large registry study also found associations of BMI with cardiac death, while remaining studies included too few total cardiac deaths to support inferences and our local data suggest a trend that was not statistically significant. Conclusions from prior studies with respect to coronary/ischemic heart disease risk were mixed, with the majority finding no link to BMI.

Community-based studies have established obesity as an independent risk factor for CHF in the general population (1,39). In a recent analysis of participants in the Framingham Heart Study, overweight and obese BMI predicted 34% and 104% relative increases in the risk of heart failure compared to normal BMI after adjustment for an array of potential mediating factors including diabetes, hypertension and coronary disease (2). Putative mechanisms for an obesity-CHF link independent of these comorbidities include altered ventricular remodeling from hemodynamic overload, neurohormonal activation, and/or oxidative stress (40,41). Reduced levels of natriuretic peptide have been demonstrated in obese compared to non-obese patients with heart failure of similar severity, suggesting a pathway for exacerbated symptoms of fluid overload and congestion in obese CHF patients (42). Notably, purposeful weight loss has been associated with improvements in systolic function, diastolic function and heart failure classification in a small study of morbidly obese patients without kidney transplants (43). Data from the Framingham cohort identify BMI as a risk factor for AF in the general population, as obese persons of both genders faced approximately 50% higher hazards of AF compared to normal weight individuals (3). Proposed explanations for pro-arrhythmic effects of obesity include alterations of myocardial structure, autonomic tone, and diastolic function (41,44). Left atrial enlargement is an important precursor of AF, and increasing BMI is in turn a powerful predictor of atrial enlargement (45). Adiposity may also contribute to electrical instability though oxidative stress (46). To date, the impact of purposeful obesity treatment on the risk of these cardiac complications after transplant has not been prospectively investigated.

In contrast with the increased risk of CHF and AF in high-BMI transplant recipients, we did not observe a significant association of BMI at transplant with the risk of subsequent MI in our local data. Similarly, the majority of prior publications found no independent relationships of BMI with coronary artery/ischemic heart disease events after transplant. Evaluation for ischemic heart disease risk is a focus area of the pre-transplant evaluation (47), and it is possible that obese candidates are subject to differential scrutiny such that selection bias mediates an unexpectedly low risk of coronary disease events in obese patients chosen for transplant. A recent registry-based analysis found that obese candidates are less likely to receive an organ and more likely to be bypassed for an offer when an organ becomes available, suggesting possible selection bias in organ allocation to obese candidates even after listing (48).

Alternatively, factors other than BMI at transplant (which could include post-transplant weight change) may be dominant in promoting clinical coronary artery disease events after transplant.

Prospective, large-sample data from the general population have shown incremental, covariate-adjusted increases in the risk of cardiovascular death at BMI levels both above and below normal (4). One large study among kidney transplant recipients also found a U-shaped risk relationship for cardiovascular death according to BMI at transplant (10), and similar U-shaped risk patterns for all-cause death and death with functioning graft after transplant according to BMI category have been reported (8,10). We observed a non-significant trend towards higher cardiac-related death with increasing BMI quartile in our local clinical data. In contrast, studies in dialysis patients have consistently observed inverse relationships, with graded reductions in risk of both all-cause and cardiovascular death with higher BMI (5-7). Proposed mechanisms for this “obesity paradox” in dialysis include confounding by underlying causes of malnutrition, sequestration of uremic toxins in adipose tissue, and more stable hemodynamics in high-BMI dialysis patients (5). Transplant recipients are selected for adequate general health to predict tolerance of surgery and benefit from the allograft. Further, transplantation markedly alters the physiology of end-stage renal disease by restoring renal function and reducing inflammation. These factors may cause reversion of the obesity-mortality paradox of dialysis to patterns more akin to the general population after transplantation.

Secondary analyses of our local data imply that the prognostic importance of BMI for post-transplant cardiac risk may be dampened in certain subgroups such as those with diabetic renal failure. Notably, obesity and physical inactivity did not predict cardiovascular disease among patients with type-2 diabetes without kidney failure in the large UKPDS cohort (49). Obesity and sedentary lifestyle are risk factors for diabetes, and the relative impact of these factors may diminish once diabetes is established. In contrast, as various forms of heart disease such as heart failure, ischemia and arrhythmias are often related, prior cardiac pathology may establish substrate for amplification of obesity-related risk in the onset of other cardiac conditions. These hypotheses require external investigation, particularly as interactions of obesity with other clinical factors were not examined in studies of post-transplant cardiac risk published to date.

The current analysis of single-center medical records is limited by the retrospective design. While consistent methods were used for BMI classification at our center, some clinical cardiac events may have been missed due to under-reporting. We also lacked information in our database on some clinical exposures that may be relevant to cardiac risk including smoking, family history, blood pressure, laboratory values and use of medications aside from immunosuppression – these factors would not impact bivariate associations of BMI and cardiac events but may represent sources of uncontrolled confounding if related to both BMI and outcomes. Residual confounding does diminish the importance of high BMI as a risk marker but is relevant to the causality underlying associations. A comprehensive literature review was included to compare consistency of our findings with other studies. The majority of articles reporting data on associations of BMI with post-transplant cardiac events are also retrospective and some are limited by small sample sizes, short observation periods, and/or absence of data for potentially relevant clinical covariates. Nonetheless, consistency of result patterns across studies, as found for the risk of CHF and AF with high transplant-BMI, support reliability. An important issue not addressed in prior publications or the current analysis relates to the potential impact of post-transplant weight change on cardiovascular risk. Weight gain and onset or exacerbation of obesity are common after transplant due to side effects of immunosuppression such as corticosteroids and to reversal of dialysis-related malnutrition (50). BMI at transplant may be a limited measure of BMI exposure over time, and investigations of the cardiovascular consequences of weight change and obesity control are needed.

In conclusion, data from our center and the published literature implicate high BMI as a risk marker for CHF, AF, and possibly cardiac death after kidney transplant. Evidence on associations of transplant BMI with subsequent coronary events is inconsistent, with most studies finding no relationship – however, selection bias due to more rigorous consideration of ischemic heart disease risk in obese transplant candidates may explain the apparent lack of association of BMI with coronary disease events after transplant. The value of BMI as a cardiac risk predictor may be particularly important in certain sub-groups, but this hypothesis requires additional study. Further research should examine whether the reduction and prevention of post-transplant obesity modifies cardiac risk among renal allograft recipients.

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Abbreviations

ACS, Acute coronary syndrome; AF, Atrial fibrillation; BMI, Body mass index; CHF, Congestive heart failure; HR, Hazards ratio; IHD, Ischemic heart disease; MI, Myocardial infarction; SE, Standard error.

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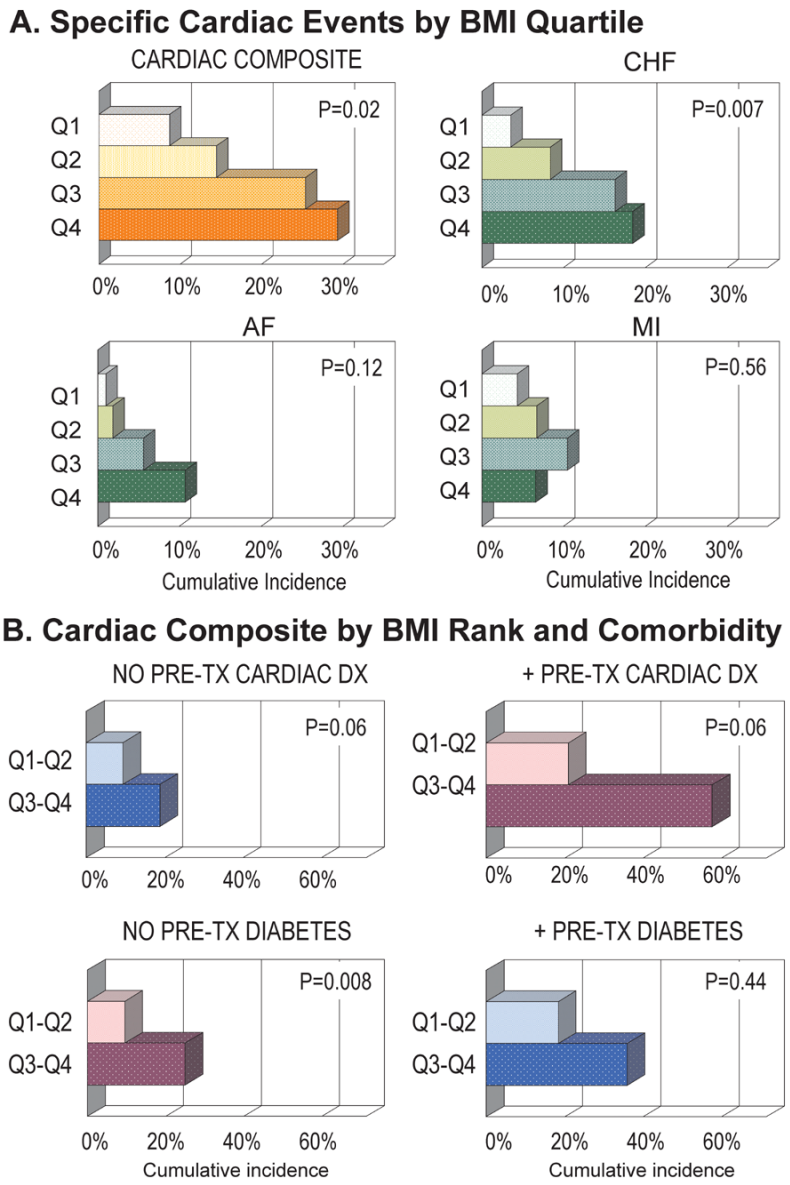

Figure 1.

Five-year cumulative incidence estimates of cardiac events in the single-center sample, by BMI rank and baseline comorbidity

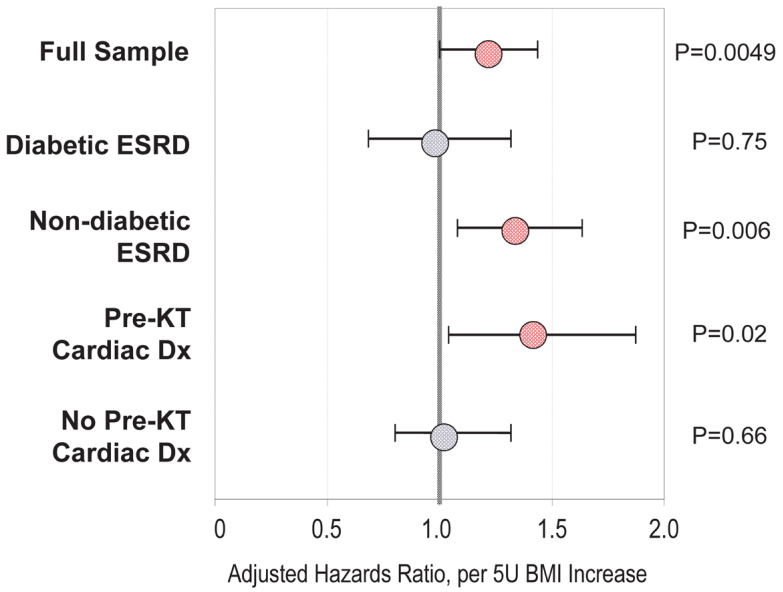

Figure 2.

Adjusted BMI-related cardiac risk per 5 unit BMI increase within the full sample and subgroups from the single center*.

*Stepwise Cox's regression in the full sample was performed to adjust for the following potentially confounding variables: recipient age, race, gender, ESRD etiology, pre-transplant dialysis duration, pre-transplant cardiac history; donor type (living, standard criteria deceased, or expanded criteria deceased); use of induction and maintenance immunosuppresion at discharge; and transplant year. All variables except the subgroup classification factor were included in stepwise regression in the subgroup analyses.

Table 1

Demographic and clinical characteristics of the sample of kidney transplant recipients examined in local clinical data (N= 1,102).

Characteristic		
Recipient demographic and clinical traits		
Age (years), mean ± SD		47.3 ± 13.5 (Range: 18 – 81)
Female gender, n (%)		448 (40.6%)
Race, n (%)		
	White	812 (73.7%)
	Black	265 (24.0%)
	Other	25 (2.3%)
ESRD cause, n (%)		
	Diabetes	262 (23.8%)
	Hypertension	217 (19.7%)
	Glomerulonephritis	250 (22.7%)
	Other	373 (33.8%)
ESRD duration (mo)		
	None (pre-emptive transplant), n (%)	156 (14.2%)
	Median (intra-quartile range) among those with dialysis	19.8 (IQR: 10.2–34.9)
Pre-transplant cardiac disease, n (%)		212 (19.2%)
BMI distribution (kg/m^2)		
	mean ± SD	26.6 ± 5.3 (Range: 14.2 – 46.9)
	1st Quartile	14.2 – 22.9
	2nd Quartile	23.0 – 26.0
	3rd Quartile	26.1 – 29.7
	4th Quartile	29.8 – 46.9
Transplant factors		
Donor type, n(%)		
	Living	344 (31.2%)
	Standard criteria deceased	688 (62.3%)
	Expanded criteria deceased	72 (6.5%)
Induction immunosuppression		739 (67.1%)
Immunosuppression at discharge, n (%)		
	CSA	780 (70.8%)
	Tacrolimus	266 (24.2%)
	Mycophenolate mofetil	404 (36.6 %)
	Azathioprine	655 (59.4%)
	Prednisone	1035 (93.9 %)
	Sirolimus	22 (0.2%)
Transplant year, n (%)		
	1991-1996	318 (28.9%)
	1997-2000	426 (38.7%)
	2001-2004	358 (32.5%)

Table 2

Published studies (1996-2007) reporting relationships of BMI with Congestive Heart Failure or Atrial Fibrillation in renal allograft recipients.

Study Reference	Study Design & Data Source	Sample Size & Country	Distribution of BMI (kg/m^2)	Cohort Outcome Frequency and Follow-up time	BMI and CV outcomes: significant associations
Congestive Heart Failure					
Abbott, 2002 (14)	Historic Cohort Billing claims	33,479 USA*	Mean at Tx: 26.6 ± 4.8 (29.8% with BMI >28) in group that developed CHF; 24.7 ± 4.6 (17.0% with BMI >28) in group that did not develop CHF (p<0.01)	Incidence density over mean follow-up of 1.65 ± 1.14 yrs: 13.3/1,000 PY	aOR for BMI >28 vs. ≤28: 1.57, 95% CI 1.31–1.88
Abbott, 2003 (15)	Historic Cohort Billing claims	29,597 USA*	Mean at Tx: 25.9 ± 24.8 (19.2% with BMI >30)	Incidence density over mean follow-up of 2.11 ± 0.9 yrs: 14.2/1,000 PY	aHR for BMI >30 vs. ≤30: 1.59, 95% CI 1.10–2.30
Lentine, 2005 (16)	Historic Cohort Billing claims	27,011 USA*	At Tx: <25, 36.6%; 25 ≤ to <30, 53.6%; ≥30, 15.5%	Incidence density over maximum follow-up of 3 yrs: 77.6/1,000 PY	aHR for BMI ≥30 vs. <25: 1.43, 95% CI 1.30–1.57
Atrial Fibrillation					
Abbott, 2003 (17)	Historic Cohort Billing claims	39,628 USA*	Mean at Tx: 25.2 ± 5.3	Incidence density over maximum follow-up of 3 yrs: 5.8/1,000 PY	aHR for BMI >28.3: 1.79, 95% CI 1.30–2.47
Lentine, 2006 (18)	Historic Cohort Billing claims	31,136 USA*	At Tx: <25, 41.8%; 25 ≤ to <30, 38.8%; ≥30, 19.3%	Incidence density over maximum follow-up of 3 yrs: 27.4/1,000 PY	Age-adjusted 3yr incidence 6.7% if BMI ≥30 vs. 5.4% if BMI <25 (P=0.0004). BMI category not significant in full multivariable model.

aHR, adjusted hazards ratio; aOR, adjusted odds ratio; PY, person-years; Tx, transplant.

*Refers to studies performed on the United States Renal Data System.

Table 3

Published studies (1996-2007) reporting relationships of BMI with Coronary Artery Disease Events (Acute Myocardial Infarction, Acute Coronary Syndrome) or Ischemic Heart Disease in renal allograft recipients.

Study Reference	Study Design & Data Source	Sample Size & Country	Distribution of BMI(kg/m^2)	Cohort Outcomes Frequency and Follow-up time	BMI and CV outcomes: significant associations
El-Agroudy[‡], 2004 (19)	Historic Cohort Clinical records	650 Egypt	At 6 mo after Tx: <25, 57.8%; 25 ≤ to <30, 28.9%; ≥30, 13.2%	37 (5.7%) developed IHD over minimum follow up of 2 yrs	4.5% if BMI <25, 5.3% if BMI 25 ≤ to <30, 11.6% if BMI ≥30 (p<0.05)
Marcen, 2006(20)	Nested Case-Control Clinical records	2,382 Spain	Body weight (kg) assessed at Tx (height not reported)	IHD incidence density over 1 yr: 15.7/1,000 PY[§]	RR for 1 kg increase: 1.02; 95% CI 1.01–1.03
Fazelzadeh, 2006 (21)	Historic Cohort Clinical records	1,200 Iran	Mean at Tx: 22.2 ± 4.6	30% developed ACS over mean follow-up of 5.7 ± 2.4 yrs	aOR 6.11, 95% CI 1.70–20.2 for an unspecified BMI increase
Kasiske, 1996 (22)	Historic Cohort Clinical records	706 USA	*Not reported*	85 (12%) developed IHD over a mean follow up of 7.0 ± 4.2 yrs	Not significant (*data not reported)*
Hernandez, 2001 (23)	Nested Case-Control Clinical records	1,004 USA	Mean at Tx: 23.3 ± 4.0 in IHD cases, 24.2 ± 4.7 in controls (p=0.045)	116 (11.6 %) developed IHD over a maximum follow up of 14 yrs[§]	Not significant (*data not reported)*
Abbott, 2002 (24)	Historic Cohort Billing claims	14,237 USA[*]	Mean at Tx: 25.5 ± 5.2; BMI ≥ 30 in 11%	ACS incidence density over mean follow-up of 1.6 ± 0.9 yrs: 9.0/1,000 PY	Not significant – HR for BMI ≥30 vs. <30: 1.27, 95% CI 0.77–2.09
Abbott, 2003 (15)	Historic Cohort Billing claims	29,597 USA[*]	Mean at Tx: 25.9 ± 24.8 (19.2% with BMI >30)	ACS incidence density over mean follow-up of 2.1 ± 1.0 yrs: 8.9/1,000 PY	Not significant (*data not reported)*
Lufft, 2004(25)	Historic Cohort Clinical records	154 Germany	Mean at Tx: 23.3 ± 3.4 (diabetic patients) and 24.6 ± 3.3 (non-diabetic patients)	28 (18%) developed IHD over a maximum follow up of 10 yrs	Not significant (*data not reported)*
Chuang, 2004 (26)	Nested Case Control Clinical records	780 USA	Mean at Tx: 26.4 in cases (n=28) and 26.8 in 56 controls (n=56) (p>0.4)	28 (3.7%) developed ACS over 2 yrs follow-up[§]	No difference in mean BMI between cases and controls
Jardine, 2005 (27)	Prospective Cohort	1,052 EU/Canada	Mean at trial enrollment: 25.8 ± 4.6	Non-fatal MI incidence density over mean follow-up of 5.4 yrs: 12.1/1,000 PY	Not significant – HR per 1unit BMI increase: 1.04, 95% CI 0.99–1.09 for MI)
Lentine, 2005(28)	Historic Cohort Billing claims	35,847 USA[*]	At Tx: BMI ≥30 in 14.4%	MI incidence density over maximum 3 yrs follow-up: 45/1,000 PY	Not significant (*data not reported)*
Kasiske, 2006 (29)	Historic Cohort Billing claims	53,297 USA[*]	Distribution at Tx not provided	MI incidence over maximum follow-up of 3 yrs: 6.1% after deceased donor Tx and 4.2% after living donor Tx	Not significant – aHR for BMI ≥30 vs. <30: 0.92, 95% CI 0.71–1.18

ACS, acute coronary syndrome; IHD, ischemic heart disease; MI, myocardial infarction

Articles reporting a significant association between BMI and the outcome of interest are listed first.

[*] Refers to studies performed on the United States Renal Data System.

[§] In Nested Case Control studies the incidence rate refers to the cohort phase of the study.

Table 4a

Published studies (1996-2007) reporting relationships of BMI with Cardiovascular Death in renal allograft recipients.

Study Reference	Study Design & Data Source	Sample Size & Country	Distribution of BMI	Cohort Outcomes Frequency and Follow-up time	BMI and CV outcomes: significant associations
Meier-Kriesche‡, 2002 (10)	Historic Cohort Billing Claims	51,927 USA*	Mean at Tx: 25 ± 5.04	3,978 (7.7%) - *follow-up time not specified.*	aHR compared to BMI 22-24: ~ 1.2 if BMI 30-32, ~ 1.4 if BMI >36, and ~1.3 if BMI <20)
Halme‡, 1997 (30)	Historic Cohort Clinical Records	276 Finland	At Tx: ≥30, 16.7%; 20–25, 83.3%	3 (1.1%) at 1 mo after Tx.	Not significant – 0 if BMI ≥30 vs.1.3% if BMI between 20 and 25 (p ≥0.01)
Meier-Kriesche‡, 1999 (31)	Historic Cohort Clinical Records	405 USA	Mean at Tx: 25.6 ± 5.0. BMI <25 in 59.2%	3 (7.4%) over maximum follow-up of 7 yrs	Not significant – 3 events if BMI >30 vs. 0 if BMI ≤25 (p ≥0.05)
Howard‡, 2002 (32)	Historic Cohort Clinical Records	833 USA	At Tx: <25, 55%; 25 ≤ to <30, 33%; ≥30, 12%	44 (5.2%) over maximum follow-up of 5 yrs.	Not significant – 4% if BMI <25, 5% if BMI 25 ≤ to <30, and 5% if BMI >30 (p ≥0.05)
Jardine, 2005 (27)	Prospective Cohort	1,052 EU/Canada	Mean BMI at enrollment: 25.8 ± 4.6	54 over mean follow-up of .4 yrs	Not significant – HR per 1unit BMI increase: 1.02, 95% CI 0.96-1.08
Massarweh‡, 2005 (33)	Historic Cohort Clinical Records	193 USA	At Tx: BMI ≥30 in 29%	6 (3%) over mean follow-up of 2 ± 1.2 yrs	Not significant – 1 event if BMI ≥30 vs. 5 if BMI <30
Aalten‡, 2006 (34)	Historic Cohort Clinical Records	2,067 Netherlands	At Tx: BMI ≥30 in 9.5%	43 (2%) over median follow-up of 2 yrs.	Not significant – 43% if BMI ≥30 vs. 2.3% if BMI <30 (p ≥0.05)
Chow‡, 2006 (35)	Historic Cohort Clinical Records	150 China	Mean at Tx: 22.9 ± 4.0. BMI >25 in 75%	5 (3.3%) over median follow-up of 9 yrs	Not significant – 5% if BMI >25 vs. 3% if BMI< 25 (p=0.42)

Table 4b. Published studies (1996-2007) reporting relationships of BMI with Cardiovascular Disease Composite Outcomes in renal allograft recipients.

Study Reference	Study Design & Data Source	Sample Size & Country	Distribution of BMI	Cohort Outcomes Frequency and Follow-up time	BMI and CV outcomes: significant associations
Aker, 1998 (37)	Nested Case Control§ Clinical records	427 Germany	Mean BMI 24 mo after Tx: 24.9 ± 3.9 kg/m^2	50 (11.7%) developed composite outcome (MI, IHD by coronary angiography, cerebral or peripheral vascular disease) over mean follow-up of 2.4 ± 1.7 yrs	aRR for BMI >25 vs. < 25: 2.56, 95% CI 1.25-5.27
De Mattos, 2006 (36)	Historic Cohort Clinical records	922 USA	At Tx: <25, 54.6%; 25 ≤ to <30, 30.2%; ≥30, 15.2%	Incidence density of composite (angina, MI, revascularization, cardiac death) over 6,947 PY: 15.9 events/1,000 PY	aHR for BMI >30 vs. <25: 2.92, 95% CI 1.69–5.04
Laures, 2005 (38)	Prospective Cohort	100 Spain	Mean BMI 24 mo after Tx: 27 ± 5.6 kg/m^2 in group with cardiovascular events and 27 ± 4.6 in group without events (p=0.8)	14 (14%) developed composite outcome (coronary artery disease, CHF, AF, cerebrovascular or complicated peripheral vascular disease) over maximum follow-up of 2 yrs	No difference in BMI between patients who did and did not develop the primary composite outcome.

Article reporting a significant association between BMI and cardiovascular death is listed first.

Articles reporting a significant association between BMI and the composite outcome are listed first.

*Refers to studies performed on the United States Renal Data System

§In Nested Case Control studies incidence estimates refers to the cohort phase of the study.