Consequences of Recipient Obesity on Postoperative Outcomes in a Renal Transplant: A Systematic Review and Meta-Analysis

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Abstract

Objectives: The prevalence of obesity is increasing rapidly and globally, yet systemic reviews on this topic are scarce. Our meta-analysis and systemic review aimed to assess how obesity affects 5 postoperative outcomes: biopsy-proven acute rejection, patient death, allograft loss, type 2 diabetes mellitus after transplant, and delayed graft function.

Materials and Methods: We evaluated peer-reviewed literature from 22 medical databases. Studies were included if they were conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology criteria, only examined postoperative outcomes in adult patients, only examined the relation between recipient obesity at time of transplant and our 5 postoperative outcomes, and had a minimum score of > 5 stars on the Newcastle-Ottawa scale for nonrandomized studies. Reliable conclusions were ensured by having our studies examined against 2 internationally known scoring systems. Obesity was defined in accordance with the World Health Organization as having a body mass index of > 30 kg/m². All obese recipients were compared versus “healthy” recipients (body mass index of 18.5-24.9 kg/m²). Hazard ratios were calculated for biopsy-proven acute rejection, patient death, allograft loss, and type 2 diabetes mellitus after transplant. An odds ratio was calculated for delayed graft function.

Results: We assessed 21 retrospective observational studies in our meta-analysis (N = 241,381 patients). In obese transplant recipients, hazard ratios were 1.51 (95% confidence interval, 1.24-1.78) for presence of biopsy-proven acute rejection, 1.19 (95% confidence interval, 1.10-1.31) for patient death, 1.54 (95% confidence interval, 1.38-1.68) for allograft loss, and 1.01 (95% confidence interval, 0.98-1.07) for development of type 2 diabetes mellitus. The odds ratio for delayed graft function was 1.81 (95% confidence interval, 1.51-2.13).

Conclusions: Our meta-analysis clearly demonstrated greater risks for obese renal transplant recipients and poorer postoperative outcomes with obesity. We confidently recommend renal transplant candidates seek medically supervised weight loss before transplant.

Key words: Renal, Transplantation, Obesity, Diabetes, Surgery

Introduction

Perhaps 2 of the most commonly discussed topics within the medical field are the global epidemic of obesity and the vast shortage of organ availability for transplant. However, these 2 topics have very rarely been evaluated together. Within the United States and Europe, 42% of adults are classified as obese.1,2 Obesity, with no shortage of media attention, has been an uncontrollable epidemic. With a significant number of studies done exclusively on each respective topic, there have been very few that have evaluated the effect of obesity on transplant recipients, especially renal transplant recipients. As shown by the World Health Organization, the number of renal transplant recipients defined as obese (having a body mass index [BMI] of ≥ 30 kg/m²) has increased 10-fold within the past 19 years, and the numbers of obese recipients are projected to double every 9 years as of 2014.3–5 As evidenced, there is a great need for a meta-analysis comparing the effects of recipient obesity on postoperative outcomes in renal transplant.

In the general population, when obese individuals undergoing abdominal surgery have been compared with individuals with a normal BMI (18.5-24.9 kg/m²) who are undergoing abdominal surgery, the obese individuals have been shown to have greater risk for...
anesthesia-related complications, greater incidence of surgical site infections, increased incidence of urinary tract infections, increased susceptibility to incisional hernias, and longer duration of hospitalization.6,7 Studies have shown that, in renal transplant, the degree of recipient obesity is directly correlated with increased complications after transplant and longer operative durations.8,9

Pathophysiologically, obesity can be detrimental to renal allografts. Obesity has been shown to result in a decreased glomerular filtration rate, ultimately leading to proteinuria. If left untreated, this proteinuria will eventually lead to obesity-related chronic kidney disease. The mechanism by which obesity-related chronic kidney disease develops is not well known; however, studies have suggested that it is a result of an immunologic phenomenon combined with other pathophysiologic mechanisms such as diabetic nephropathy, hyperfiltration, and cytokine-induced inflammatory damage to the renal allograft via leptin and interleukin 6 (both pro-inflammatory cytokines, released by adipose tissue, acting on the renal allograft).10-13 This pathophysiologic mechanism is responsible for damaging both native kidneys and transplanted renal allografts.14

Obesity also has been evidenced to modify the degradation and bioavailability of induction immunosuppression regimens, particularly rabbit antithymocyte globulin, interleukin 2 receptor antagonist, and calcineurin-based therapies.15,16 This altered metabolism exposes the renal allograft to native T lymphocytes, B lymphocytes, and natural killer lymphocytes, significantly increasing the risk for acute and chronic allograft rejection.17

In our meta-analysis, we examined the consequences of recipient obesity on 5 postoperative outcomes: biopsy-proven acute rejection (BPAR), patient death, allograft loss, type 2 diabetes mellitus after transplant, and delayed graft function (DGF).

**Materials and Methods**

Our meta-analysis evaluated peer-reviewed published literature from 22 medical databases: AccessMedicine, Cinahl Plus, ClinicalKey, Cochrane Library, Embase, Emerald, ERIC, Evidence Based Medicine Reviews, Global Health, Health Business Elite, Journal Citation Reports, Justis, Leadership Foundation for Higher Education, Medicines Complete, MEDLINE through PubMed, MEDLINE from Ovid, MEDLINE through EBSCOhost, PsycINFO, Scifinder Scholar, Scopus, TOXLINE, and Web of Science.

The keywords used were obesity, renal transplant and transplantation, postoperative outcomes, and surgical complications. No date, country of publication, or language limits was applied. June 12, 2015, was the final date for literature research.

Only retrospective observational studies were included in our meta-analysis. Only studies that assessed posttransplant-related outcomes in adult patients (age ≥18 years) were included. The primary outcome our meta-analysis set out to examine was BPAR. We also evaluated 4 secondary outcomes: patient death, allograft loss, type 2 diabetes mellitus, and DGF. Our primary outcome (BPAR) was defined, according to the Banff classification scale for assessment of renal allograft pathology and function, as having a Banff grade of > 1.

The primary inclusion criterion for the observational studies evaluated in our meta-analysis was for studies to have been conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria. Every study evaluated in our meta-analysis strictly met the MOOSE criteria, meaning they were classified as “good methodological quality studies.”18-20 The MOOSE criteria is the most commonly used international reporting system to examine the methodologic quality of clinical observational studies.18-20 Our inclusion criteria further specified the sole use of studies that examined the relation between recipient obesity at time of transplant with our defined transplant-related outcomes (BPAR, patient death, allograft loss, type 2 diabetes mellitus, and DGF). Our final inclusion criteria necessitated the use of studies that scored a minimum score of > 5 stars on the Newcastle-Ottawa scale for nonrandomized studies.

Exclusion criteria included studies that reported on pediatric posttransplant outcomes, studies that defined obesity not in accordance with the WHO definition, studies that analyzed BMI as a continuous variable, studies that examined postoperative outcomes in patients undergoing simultaneous pancreas and kidney transplants, and studies that did not meet the MOOSE reporting criteria. To avoid the risk of using duplicated data, such that the same patient would be included in 2 or more studies, when 2 or more studies had a similar or identical sampling period, we only included data from the larger study. This ensured that
the sampling periods of 2 or more studies did not select the same patient. Important to note, this also encompassed those recipients classified as grade 2 obese (BMI of 35.0-39.99 kg/m²) and grade 3 obese (BMI > 40 kg/m²).

Because our meta-analysis solely evaluated retrospective observational studies, we expected there to be a degree of heterogeneity. As a result, pooled estimates were calculated using random effects selection models. Heterogeneity among the studies was evaluated using Cochran Q test, the I² statistic, and the chi-square test. Begg test, Egger test, and trim and fill analysis were used to ensure a minimal level of publication bias. Statistical analysis was done via Cox proportional hazards regression model. This was used to calculate the probability of BPAR, patient mortality, allograft loss, and type 2 diabetes mellitus. In calculating hazard ratios, patients with a BMI of 18.5-24.9 kg/m² (a healthy BMI), were used as the reference point. As previously done in many observational studies on this topic, an a priori sensitivity analysis was done to calculate the risk of recipient obesity on DGF. To exhibit the risk of recipient obesity on DGF, an odds ratio was calculated. In calculating the odds ratio for obesity and DGF, patients with a healthy BMI (18.5-24.9 kg/m²) were used as the reference point.

**Publication bias**

When assessed, we found minimal publication bias in the studies used in our meta-analysis. Funnel plots (Egger test and Begg test) were used to calculate publication bias for all 5 outcomes (BPAR, patient death, allograft loss, type 2 diabetes mellitus, and DGF). When the outcomes of BPAR, patient death, allograft loss, and DGF were examined, publication bias was not likely to have been present, as evidenced by minimal asymmetry and average Begg test scores of P = .41 and Egger test scores of P = .09. Asymmetry was observed in the plot comparing recipient obesity with type 2 diabetes mellitus. This indicates that broad studies were evaluating the minor effects of recipient obesity on type 2 diabetes mellitus. Begg test score of P = .87 and Egger test score of P = .04 further evidenced these results. These results illustrate modest publication bias in the case of recipient obesity and type 2 diabetes mellitus; however, we strongly believe that, despite the effect size changing, the key findings remain in force.

**Results**

In the 22 medical databases that we accessed, our literature search brought up 435 pertinent studies conducted on the topic of recipient obesity and its effects on postrenal transplant outcomes. However, only 21 studies met our inclusion criteria. The 21 retrospective observational studies gave us a patient sample size of 241 381. All patients assessed in our meta-analysis were ≥ 18 years old. All 21 studies evaluated conformed to the MOOSE criteria. When we assessed the 21 retrospective observational studies using the Newcastle-Ottawa scale for nonrandomized studies, all studies obtained a score of ≥ 5 stars. The lowest score given to any study was 5 stars, with the highest score being a perfect 9 stars.

**Biopsy-proven acute rejection**

The presence of BPAR after renal transplant was evaluated in 7 studies. The 7 studies assessed 52 238 patients. Biopsy-proven acute rejection was defined in accordance with the Banff classification scale for assessment of renal allograft pathology and function as “the presence of foci of moderate tubulitis (5-10 mononuclear cells per tubular cross section/10 tubular epithelial cells) in cases with significant interstitial infiltration (> 25% of parenchyma affected).” This definition was applied universally to all 7 studies assessed. The hazard ratio (HR) for the presence of BPAR in obese recipients was calculated to be 1.51 (95% confidence interval [CI], 1.24-1.78). Our evaluation showed that obese transplant recipients had a significantly greater risk of BPAR after renal transplant (heterogeneity, P = 17%; P < .01).

**Patient death**

Overall, 14 studies assessed the association between recipient obesity and its effects on patient mortality rates. The 14 studies assessed 63 383 patients. Patient death was defined to include cessation of heartbeat, cessation of respiratory system, and complete loss of brain activity. In comparison with healthy renal transplant recipients (BMI of 18.5-24.9 kg/m²), obese renal transplant recipients had an HR of patient death of 1.19 (95% CI, 1.10-1.31). These results show obese transplant recipients have a small but higher risk of death compared with healthy transplant recipients (BMI of 18.5-24.9 kg/m²) (heterogeneity, P = 38%; P < .01).
Allograft loss
Thirteen studies examined the effects of recipient obesity on allograft survival rates.\textsuperscript{21,23,30-40} The 13 studies assessed 48,719 patients. Allograft loss was defined in accordance with the journal *Kidney International* as “either the need to re-transplant, resume chronic hemodialysis, or undergo a nephrectomy.”\textsuperscript{43} The HR for allograft loss in obese recipients was 1.54 (95% CI, 1.38-1.68).\textsuperscript{21,23,30-40} This HR represents statistically significant evidence of greater allograft loss in obese transplant recipients (heterogeneity, $I^2 = 3\%$; $P = .49$).

Type 2 diabetes mellitus after transplant
Type 2 diabetes mellitus was reported in 5 studies.\textsuperscript{22,25,31,37,41} The 5 studies assessed 29,921 patients. Type 2 diabetes mellitus was defined clinically as “the requirement of insulin for a minimum period of 30 days posttransplant and/or a fasting blood glucose level > 125 mg/dL posttransplant.”\textsuperscript{45} In comparison with healthy renal transplant recipients (BMI of 18.5-24.9 kg/m$^2$), obese renal transplant recipients had an HR of developing type 2 diabetes mellitus of 1.01 (95% CI, 0.98-1.07).\textsuperscript{22,25,31,37,41} These results indicate essentially no statistically significant difference in the risks of developing type 2 diabetes mellitus between healthy transplant recipients and obese transplant recipients (heterogeneity, 74%; $P < .01$).

Delayed graft function
Delayed graft function was evaluated in 16 studies.\textsuperscript{21-30,33-38} The 16 studies assessed 47,120 patients. Delayed graft function was defined as “the use of dialysis in the first postoperative week following transplant.”\textsuperscript{46} After calculation, the odds ratio for DGF was an elevated 1.81 (95% CI, 1.51-2.13). An odds ratio so elevated clearly denotes a greater risk of DGF occurring in obese transplant recipients (heterogeneity, 65%, $P < .01$).

Discussion
In our thorough search of 22 medical databases, we obtained 435 pertinent studies on the topic of recipient obesity and its effects on outcomes after renal transplant. After the application of our strict inclusion criteria, 21 retrospective observational studies were included in our research.\textsuperscript{21-41} These 21 studies gave us a patient sample size of 241,381. All patients evaluated in our meta-analysis were adults, defined as age $\geq 18$ years. To ensure credibility of our results, all of these studies were examined against 2 internationally known scoring systems for retrospective observational studies. All studies used in our meta-analysis met the strict standards of the MOOSE criteria, and all studies received a score of $\geq 5$ stars on the Newcastle-Ottawa scale for nonrandomized studies. With each study being evaluated against such high standards, authentic and dependable conclusions can be drawn from our data.

In summary of the results, our meta-analysis demonstrated a noticeably greater risk of obese transplant recipients suffering BPAR after renal transplant than healthy transplant recipients (HR = 1.51; 95% CI, 1.24-1.78). Patient mortality rates were also greater in obese transplant recipients. Although not a statistically large difference, the risk of patient mortality was still greater in obese recipients (HR = 1.19; 95% CI, 1.10-1.31). The risk of having allograft loss was significantly greater in obese transplant recipients (HR = 1.54; 95% CI, 1.38-1.69). The risks of developing type 2 diabetes mellitus was nearly identical in both patient groups examined (HR = 1.01; 95% CI, 0.98-1.07). The final outcome evaluated, DGF, was much more prevalent after transplant in obese recipients (odds ratio = 1.81; 95% CI, 1.51-2.13).

As of January 1, 2015, an estimated 1.71 billion people are obese.\textsuperscript{47} The majority of these individuals are from high-income (high gross domestic product) countries; however, rates are also increasing at an alarming rate in many poor and middle-income countries.\textsuperscript{47} This epidemic of obesity has a profound effect on many potential transplant recipients. As stated in a report by the *American Journal of Nephrology*, 18% of transplant recipients within the United States were defined as “obese at the time of transplant” in 2012.\textsuperscript{48} When compared with that shown in 1995, only 7.8% of transplant recipients were obese at the time of transplant.\textsuperscript{9} These ever-increasing statistics on obesity and its increasing prevalence in renal transplant recipients mandates a study on the postoperative effects of obesity in this patient group.

Our results show that, in obese recipients, the risk of BPAR is significantly higher. A possible explanation for these results is the excessive inflammation and altered immune response characteristic of obese individuals. Inflammation in the white adipose tissue, characteristic of obese individuals, results in
increased accumulation of cytotoxic CD8-positive T cells. These accumulated CD8-positive T cells result in the subsequent recruitment, differentiation, and activation of macrophages globally within the body. Natural killer cells then infiltrate the white adipose tissue and contribute to acute rejection. B lymphocytes in turn infiltrate the white adipose tissue and begin producing antibodies against the allograft. These pathways combined contribute to the acute rejection seen in obese recipients.49,50

The risk of patient death was slightly higher in obese recipients. Although a small difference, it was nonetheless statistically significant. The explanation behind this finding is perhaps found in the surgical complications associated with obesity.51 In all patients, obese recipients had longer surgical durations, and this directly correlated with increased surgical complications. These complications included fatal complications, which occurred in 9 patients of the 241,381 total patients studied. Although obesity itself did not confer a negative outcome on patient survival, its complications did. Therefore, we can confidently recommend transplant candidates to engage in a weight loss program before the time of transplant.

There have been few high-impact studies on this topic, with 2 theories as to why DGF is more likely to occur in obese recipients. The first theory blames ischemic injury to the allograft. Ischemic injury occurs via vasoconstriction and the lengthier surgical time associated with obese patients.63 The second theory as to why there is a greater incidence of DGF in obese recipients credits immunologic injury. This theory is the weaker of the 2, with many questions still unanswered.64 Although we cannot definitively state why DGF is more likely to occur in obese recipients, we can boldly state DGF is more likely to occur in obese recipients. The outcome of DGF again brings up the importance of weight loss before transplant.

As with any study, there are strengths and limitations. A primary strength of our study was the number of patients evaluated. A sample size of 241,381 makes our meta-analysis one of the largest...
Our study intentionally evaluated patients from 17 countries. This makes our results credible among an international audience and allows for increased inclusion in global transplant programs. Another strength of our meta-analysis was the number of postoperative outcomes that we examined. Most studies on this topic were only able to investigate 3 posttransplant outcomes. Here, we investigated 5 posttransplant outcomes and were able to do so on a global scale. Another strength of our meta-analysis is our strict inclusion criteria. This allowed all of our outcomes to have 1 set definition that allowed for the most accurate results when comparing data among studies evaluated. This identical definition for posttransplant outcomes among all studies evaluated minimizes bias and keeps heterogeneity low. Perhaps one of the most prominent strengths in our study was the minimal publication bias of our 21 studies evaluated. To ensure minimal publication bias, funnel plot analysis was used.

Our study had limitations. Most of the studies examined did not state whether the renal allograft was from a deceased or living donor. For those that were from deceased donors, the studies did not mention the exact cause of death of the patient. Although not expected to have an effect, it would be interesting to assess whether the cause of death of the donor (circulatory, respiratory, brain death) would affect any posttransplant outcomes. No studies examined by our meta-analysis stated whether donors were on hemodialysis or peritoneal dialysis. This finding also would be interesting to assess and to observe whether it had any effect on the recipient’s outcomes after transplant. A limitation of our meta-analysis and research in the whole medical community is that no study has thus far assessed waist circumference, hip-to-waist ratio, or fat distribution in transplant recipients. We have all defined obesity as a BMI of ≥ 30 kg/m². These additional parameters could have easily resulted in differing results for our outcomes.

Our meta-analysis has clearly demonstrated an injurious effect of obesity on posttransplant outcomes. Whether it is a higher risk of BPAR, death, allograft loss, or DGF, obese patients clearly have poorer outcomes after transplant compared with healthy BMI patients. With the results of our study, we strongly recommend potential renal transplant recipients to take part in strict weight loss regimens before transplant. Weight loss regimens have been initiated recently in this patient group in an effort to improve posttransplant outcomes. As evidenced by many studies, undertaking dietary restrictions in an effort to lose weight before the date of transplant is rather ineffective and often unsuccessful. In obese transplant candidates who lose weight via dietary restrictions, it was noted they were likely to gain that weight back after transplant; therefore, essentially undoing the benefits of weight loss before the surgical procedure. Posttransplant weight is gained primarily because of the improved metabolic conditions of the patient, resulting in increased nutrient absorption. Weight also can be gained back in this patient group from decreased energy expenditure that occurs after transplant.

Another method for weight loss before transplant in obese recipients, and perhaps the most effective, is bariatric surgery. Many high-profile studies have documented the benefits of bariatric surgery in this patient group and its effect in lowering posttransplant complications. Bariatric surgery gives relatively prompt results and results that last after transplant. In accordance with American and European guidelines for bariatric surgery, any potential renal transplant recipient with a BMI > 35 kg/m² and with comorbidities or any potential renal transplant recipient with a BMI > 40 kg/m² is recommended to undergo bariatric surgery. Bariatric surgery has been exhibited to treat and/or decrease the risk of many obesity-related comorbidities such as asthma, mortality rates, hypertension, diabetes, and sleep apnea. With mortality and complication rates of bariatric surgery on patients with renal failure at a minimal 0.27%, we strongly recommend potential obese renal transplant candidates to consider bariatric surgery as a way to improve posttransplant outcomes and quality of life.

In conclusion, our results have clearly demonstrated the greater risks in obese renal transplant recipients and the poorer outcomes posttransplant versus healthy patients. Obese recipients showed a greater risk of having BPAR, death, allograft loss, and DGF compared with their healthy BMI counterparts. We recommend that obese renal transplant candidates not be excluded because of their BMI alone, as the survival rate of obese patients after renal transplant is far greater than that shown in obese patients on dialysis treatment. Where obese renal transplant candidates should be placed on the organ wait list is a highly controversial issue yet to be
resolved. Second, we recommend that obese renal transplant candidates with a BMI > 35 kg/m² and with comorbidities or candidates with a BMI > 40 kg/m² to be carefully assessed for bariatric surgery before transplant. Third, we recommend informed consent for potential obese renal transplant candidates to document the risks associated with obesity on postoperative outcomes in renal transplant.

References

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