Obesity and kidney transplantation

Jae-Hyung Chang, Vladimir Mushailov and Sumit Mohan

Purpose of review
Obesity has reached epidemic proportions in the United States. It is a risk factor for developing, among others, heart disease, stroke, type 2 diabetes, and chronic kidney disease (CKD), and thus a major public health concern and driver of healthcare costs. Although the prevalence of obesity in the CKD/end-stage kidney disease population is increasing, many obese patients are excluded from the benefit of kidney transplant based on their BMI alone. For this reason, we sought to review the experience thus far with kidney transplantation in obese patients and associated outcomes.

Recent findings
Obesity is associated with a lower rate of referral and waitlisting, and lower likelihood of kidney transplantation. Despite increased risk for early surgical complications and delayed graft function, experience from multiple centers demonstrate a clear survival benefit of transplantation over dialysis in most obese patients, and comparable graft and patient survival rates to nonobese recipients.

Summary
Data suggest that long-term transplant outcomes among obese recipients are similar to those among nonobese. Strategies to achieve pretransplant weight reduction and minimally invasive surgical techniques may further improve results of kidney transplantation in obese recipients.

Keywords
kidney transplantation, obesity, outcome, weight loss

INTRODUCTION
Obesity defined as a BMI of at least 30 kg/m² is increasingly common in the United States. In 2015–2016, approximately 39.8% of the United States adult population was obese [1]. It is a major public health concern that is associated with heart disease, stroke, type 2 diabetes, and certain cancers as well as chronic kidney disease (CKD). As a result, the prevalence of obesity among the CKD/end-stage kidney disease (ESKD) population is also increasing [2]. A United Network for Organ Sharing (UNOS) data analysis of 1,084,816 waitlisted adults showed that mean BMI of incident dialysis population in the United States increased from 28.1 kg/m² in 2007 to 29.2 kg/m² in 2016 whereas the adjusted prevalence of class 1 obesity (BMI of 30–34.9 kg/m²) or higher increased from 31.9 to 38.2% [3*]. The rapid increase in the prevalence of obesity among waitlisted patients has occurred despite the fact that many transplant centers continue to use BMI as a single criterion to exclude obese patients with advanced kidney disease from the benefit of kidney transplant because of concerns about higher perioperative and postoperative complications despite evidences that obese individuals with ESKD also experience a significant survival advantage with a kidney transplantation [4**,5]. Currently, in the United States, there is no single universally accepted BMI cutoff across transplant programs allowing centers to determine their own thresholds thus adversely impacting access to transplantation in a manner that is often opaque to patients. Herein, we review the experience thus far with transplantation in obese patients as well as associated outcomes (Table 1).

SURVIVAL BENEFIT OF KIDNEY TRANSPLANTATION
Transplantation is considered the best treatment for ESKD in the general setting given the dramatic
improvement in long-term survival and quality of life compared with dialysis. Using data from the United States Renal Data System (USRDS) between 1995 and 2007, Gill et al. [6] demonstrated a clear survival benefit of transplantation over remaining waitlisted in obese patients. The survival benefit varied by BMI and donor type: while the reduction in the risk of death was at least 66% in all BMI groups for living donor transplantation, even in the heaviest patients with a BMI of at least 40 kg/m², they noted a 48% reduction in mortality with the use of a standard criteria deceased donor kidney – and 46% with the use of the erstwhile expanded criteria donor kidneys underscoring the clear benefit of transplantation in these individuals [6]. Concerningly, this analysis failed to demonstrate a survival benefit for black patients with BMI at least 40 kg/m² but the reasons for this remain unclear and may be the result of residual confounding rather than a true absence of a survival benefit. In another retrospective analysis from the United Kingdom, a survival benefit of transplant over remaining on the waiting list was observed in patients with all BMI categories (from <18.5 to ≥40 kg/m²), even when living donor transplants were excluded [7]. In Cox proportional hazards adjusted analyses, there was no significant effect of recipient gender or ethnicity on patient survival [7]. In contrast, a recent French time-dependent propensity score-matching study reported no significant life expectancy gain for patients with BMI at least 35 kg/m² who were transplanted versus those who remained on dialysis [8]. However, this conclusion was based on a small sample size (n = 212 per group). Also, possible confounders, such as ethnicity and socioeconomic status may have been missed as these were not collected in this registry study [8]. Together, these results support the notion that most obese patients also experience a survival benefit from transplantation and while there is a paucity of quality-of-life data in this population, presumably elimination of dialysis provides a significant improvement in quality of life for all individuals.

**ACCESS TO KIDNEY TRANSPLANTATION**

Despite the obvious benefits, obese patients experience a lower rate of referral and waitlisting, longer waiting time, and a lower likelihood of transplantation when compared with the nonobese [3,9]. In the United States, between 2012 and 2014, nearly 40 000 dialysis patients had obesity reported as the sole contraindication to waitlisting [10]. In a recent analysis of over a million incident dialysis patients between 2007 and 2016 in the United States, class 2 obesity [subhazard ratio (SHR) 0.92; 95% CI 0.90–0.95] and class 3 obesity (SHR 0.41; 95% CI 0.40–0.43) were associated with dramatically lower access to the waitlist [3,9]. Given differences in the prevalence of obesity across racial groups in the United States, these BMI thresholds likely exacerbate existing racial disparities in access to transplantation. Similar barriers to transplantation exist in other countries as well. For example, in a national survey sent to all transplant centers in Germany (n = 39), 96% considered obesity an important issue, and 69% reported an absolute BMI threshold for waitlisting, with at least 35 kg/m² as the most commonly applied threshold [11].

Once listed, obese candidates continue to have decreased access to transplantation. In an analysis of a prospective cohort of 132 353 adults who were listed for deceased donor kidney transplantation in the United States between 1995 and 2006, the likelihood of receiving a transplant decreased with increasing BMI (adjusted hazard ratio 0.93, 0.72, and 0.56 for class 1, class 2, and class 3 obesity, respectively, when compared with a reference group of patients with a normal BMI) [9]. At the same time, the likelihood of being bypassed when an organ became available increased with BMI (adjusted incidence rate ratios 1.05, 1.11, and 1.22 for class 1, class 2, and class 3 obesity, respectively, when compared with nonobese candidates). Another UNOS data analysis on 702 456 adult incident ESKD patients showed that a higher BMI is associated with a lower

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**KEY POINTS**

- Although the prevalence of obesity among general population and patients with kidney disease continues to rise, obese CKD and ESKD patients have decreased access to transplantation including lower rate for referral and waitlisting, longer waiting time, and a lower likelihood of transplantation when compared with the nonobese candidate.

- There is currently no universal consensus for exclusion of obese patients from receiving kidney transplants. Many transplant centers establish their own threshold for BMI to use it as a contraindication to transplantation.

- Although obesity represents a risk factor for DGF and surgical complications, kidney transplantation still provides survival benefit over dialysis in most obese patients, with comparable graft and patient survival rates to nonobese recipients.

- Modern minimally invasive surgical techniques including RAKT allow an improved surgical complication rate with comparable graft and patient survival outcome in obese patients when compared with open kidney transplants; RAKT may represent a promising alternative for obese candidates.
BMI at least 40 kg/m² and at least 35 kg/m² was 95% CI 0.72–0.77). In contrast, among men, only a
0.77), and from a living donor (hazard ratio 0.75; 95% CI 0.72–
0.75; 95% CI 0.73–0.77), from a
dead donor (hazard ratio 0.74; 95% CI 0.72–
educated donor, respectively [12]. Further studies
are needed to understand the factors contributing
to the differential association of BMI with access to
transplantation in men and women.

SURGICAL COMPLICATIONS
Performing transplant procedure on obese patients
can be technically more difficult and may result in
longer total procedure time and longer warm ischémia time [13]. Complications in the perioperative
period are a significant concern in obese recipients,
especially concerns for increased risk of surgical site
infections (SSI), wound dehiscence, need for re-
exploration, development of lymphoceles and vas-
cular complications such as venous or arterial thrombosis [14]. Several studies have identified an
increased risk for surgical complications associated

| Study | Study year | Country | Design | Patients (n) | BMI (kg/m²) | Outcomes in obese recipients |
|-------|------------|---------|--------|-------------|-------------|-------------------------------|
| Tsapepas et al., 2022 | 2004-2020 | US | Retrospective | 2806 | ≥35 | Higher DGF rate; higher incidence of surgical site infection; no difference in graft survival. |
| Zhang et al., 2022 | 2016-2019 | China | Retrospective | 831 | >24 | Higher incidence of abnormal graft function in early posttransplantation period. |
| Yemini et al., 2022 | 2005-2019 | Israel | Retrospective | 1403 | ≥30 | Higher DGF rate; worse 1-year, 5-year, and 10-year graft and patient survival. |
| Buemi et al., 2022 | 2010-2018 | Belgium | Retrospective | 306 | ≥30 | Higher DGF rate; higher incidence of surgical site infection and surgical complications; worse patient survival; no difference in graft survival. |
| Castelli et al., 2022 | 2005-2018 | France | Time-dependent propensity score matching study | 27 037 | 30–35 | Increased 10-year life expectancy in kidney transplantation group versus awaiting-kidney transplantation group. |
| Dobrzycka et al., 2022 | 2014-2017 | Poland | Retrospective | 433 | ≥30 | Higher DGF rate; higher incidence of early surgical complications; worse 1-year death-censored graft survival. |
| Scheuermann et al., 2022 | 1993-2017 | Germany | Retrospective | 578 | ≥30 | Higher DGF rate; higher incidence of surgical site infection and surgical complications; worse death-censored graft survival. |
| Axelrod et al., 2022 | 2005-2016 | US | Retrospective | 193 984 | ≥30 | Higher incidence of posttransplant DM. |
| Yin et al., 2021 | 1991-2019 | Multinational | Meta-analysis | 326 550 | BMI with the lowest risk of graft loss: 25.2 kg/m². BMI with the lowest risk of patient death: 24.7 kg/m². |
| Fouche et al., 2021 | 2005-2016 | France | Retrospective | 4691 | ≥30 | Higher incidence of serious bacterial infections and cardiac complications; worse patient survival. |
| Sureshkumar et al., 2021 | 2001-2016 | US | Retrospective | 44 560 | >35 | Higher DGF rate; worse death-censored graft survival in recipients with BMI ≥30. |
| Jarv et al., 2021 | After 2000 | Estonia | Retrospective | 706 | ≥25 | Worse 5-year graft survival; worse 5-year and 10-year patient survival. |
| Bellini et al., 2017 | 2014-2016 | UK | Prospective | 370 | 30 | No difference in DGF rate and graft survival. |
| Lafranca et al., 2015 | 2014 | Multinational | Meta-analysis | 209 000 | ≥30 | Higher DGF rate; higher incidence of surgical site infection and surgical complications; higher incidence of posttransplantation DM; higher incidence of acute rejection; worse graft and patient survival. |
| Nicoletto et al., 2014 | 1990-2013 | US | Meta-analysis | 9296 | | Higher DGF rate; no difference in graft and patient survival for patients who received kidney transplant after year 2000. |
| Gill et al., 2013 | 1995-2007 | US | Retrospective | 208 498 | ≥40 and <40 | Survival benefit in kidney transplantation group versus nonkidney transplantation group; no survival benefit in Black patients with BMI ≥40. |

**Table 1.** Summary of published reports of kidney transplant outcomes in obese recipients

**DGF**, delayed graft function; **DM**, diabetes mellitus.
with obesity [13,14*,15–18]. However, experiencing these complications was not associated with adverse long-term graft survival [15,16]. Despite the increase in perioperative complications, observational analyses have suggested no clinically meaningful differences in the length of stay during the transplant admission [19*,20].

Minimally invasive surgical techniques allow minimized trauma related to surgical access, reduced wound complications, and earlier onset of patient mobilization [21,22]. Robotic surgery allows minimally invasive approach while maintaining higher resolution visual system, and the ability to maneuver within a three-dimensional orientation. The global experience to date with robotic-assisted kidney transplantation (RAKT) is promising and shows a lower incidence of SSI and comparable graft and patient survival outcome in obese patients when compared with open kidney transplants [23*,24].

**DELAYED GRAFT FUNCTION**

Obesity is associated with increased risk for delayed graft function (DGF), defined as the need for dialysis within 7 days after transplantation but the underlying cause for this remains unclear [13,14*,15–18,19*,25–29]. Although obesity is associated with a proinflammatory environment with elevated levels of cytokines and chemokines, technical challenges encountered in performing the transplantation may lead to a longer warm ischemic time and other anatomical challenges. Together, these can lead to an increased risk of DGF. A retrospective analysis reported that DGF rates were 51% higher for patients with BMI greater than 36 kg/m² when compared with recipients with BMI 24–26 kg/m² [30]. Another UNOS database analysis showed the highest risk of DGF among the heaviest patients (BMI >35 kg/m²) and a graded association of lower DGF risk with decreasing BMI, with adjusted odds ratio for DGF of 0.73 (95% CI 0.64–0.83), 0.55 (95% CI 0.48–0.62) and 0.42 (95% CI 0.36–0.48) for patients with BMI greater than 30–35, greater than 25–30, and 18–25 kg/m², respectively (P < 0.001 for all) [19*]. Prospective studies are needed to evaluate impacts of minimally invasive surgical techniques and different types of induction immunosuppression therapies on DGF risk in obese recipients.

**ACUTE REJECTION**

The association between obesity and acute rejection is controversial. Although some groups have suggested an association with an increased risk of acute rejection [17,26], others have not [18,25,27]. A retrospective single-center study reported that while the main reason for graft failure were acute and chronic rejection for all three BMI groups (18.5–24.9, 25–29.9, and ≥30 kg/m²), no statistical difference could be observed between the three groups with regard to graft loss secondary to rejection [18]. Higher rate of DGF with initiation of immune response toward the graft, a ‘state of chronic low-grade inflammation’, and a more difficult maintenance of an appropriate level of immunosuppression in obese patients could be reasons for the enhanced rate of acute rejection. Observed discrepancies in rejection rates in different cohorts may be in part related to differences in how centers approach dosing for immunosuppressive agents, in particular dosing of induction agents such as thymoglobulin. Although some centers use ideal body weight given the expected volume of distribution, other centers continue to use actual body weight for dosing.

**MEDICAL COMPLICATIONS**

Obesity leads to physiologic changes in the kidney, including renal hyperfiltration and increased tubular reabsorption of sodium, leading to the development of glomerular hypertension and podocyte hypertrophy. This is not any different after transplantation, especially given that patients receive in most instances only a single allograft thus exaggerating the potential impact of obesity leading to possible allograft injury [31]. A UNOS data analysis showed higher incidence of posttransplant diabetes mellitus (PTDM) in obese (BMI ≥30 kg/m²) recipients, regardless of the immunosuppression regimen [32]. Inflammation and altered immune response may contribute to the insulin resistance. Another meta-analysis reported that every five-unit increment of BMI was associated with a 43% higher risk of PTDM. In a French study, a BMI at least 30 kg/m² was associated with a 1.2-fold increase in the risk of PTDM within 2 years after transplantation compared with nonobese patients. After the 2 years, the hazard ratio increased to 4.24 (95% CI 2.46–7.29, P < 0.0001) [27]. Another single-center study in 1102 kidney transplant recipients showed that each five-unit increment increase in BMI was associated with a 19% increase in relative risk of composite cardiac events including myocardial infarction, congestive heart failure, and atrial fibrillation [33]. Together, these findings underline the importance of close follow-up care with intensive control of diabetes and hypertension in obese recipients.

**GRAFT AND PATIENT SURVIVAL**

Conflicting data have been published about the association of BMI with posttransplant outcomes
in obese recipients. The higher prevalence of comorbidities such as cardiovascular disease, dyslipidemia, diabetes, and hypertension in obese individuals may negatively affect long-term allograft survival. Although some studies reported a negative impact of obesity on graft and patient survival [13,17,26–28], others found no association [15,20,34,35]. A meta-analysis that compared outcomes of obese and nonobese patients who underwent kidney transplantation suggested that obesity was associated with increased risks for graft loss and death only in the analysis of studies that evaluated patients who received a transplant before year 2000 [25]. No such association was found in the analysis of studies that evaluated patients who received a graft after year 2000. It is conceivable that this is because of improvement in general posttransplant care including advances in immunosuppressive therapy. A recent single-center study reported that recipients with a BMI greater than 30 kg/m² had higher risk of both graft and patient loss at 1, 5, and 10 years after transplantation compared with control group (BMI ≤30 kg/m²) [28]. This is in contrast to the retrospective study by Jarv that reported that obesity (BMI ≥25 kg/m²) was associated with worse short-term (5-year) graft (BMI <25 versus ≥25 kg/m², 67 versus 61%, P < 0.05) and patient survival (BMI <25 versus ≥25 kg/m², 80 versus 70%, P < 0.05), but no statistically significant difference in long-term (10-year) graft survival, and only minimal difference in long-term patient survival [36]. A U-shaped relationship between BMI and both graft loss and patient death was suggested by a meta-analysis of 50 observational studies which showed that, referring to a BMI of 22 kg/m², the risk of graft loss was 1.088, 0.981, 1.003, and 1.685 for a BMI of 18, 24, 28, and 40 kg/m², respectively [17]. Similarly, referring to a BMI of 22 kg/m², the death risk was 1.115, 0.981, 1.032, and 2.634 for a BMI of 18, 24, 28, and 40 kg/m², respectively. Using UNOS database, Sureshkumar et al. [19*] found that death-censored graft failure at a median follow-up of 3.9 years, when compared with recipients with a BMI greater than 35 kg/m² as a reference, was less frequent for BMI 25 or less and greater than 25–30 kg/m² [hazard ratio 0.66 (95% CI 0.59–0.74) and 0.79 (95% CI 0.70–0.88)] whereas there was no significant difference for patients with a BMI greater than 30–35 kg/m². Patient survival did not differ by recipient BMI. Together, these data implicate that patients with obesity and kidney disease have acceptable transplant outcomes if they are otherwise suitable candidates.

WEIGHT LOSS BEFORE TRANSPLANT

Although obesity is clearly a barrier to access to kidney transplantation, higher BMI might confer survival benefits to ESKD patients treated with dialysis [37]. In dialysis patients, weight loss may signal protein-wasting malnutrition and progressive sarcopenia, which are associated with increased mortality. Although some literature suggests pretransplant weight reduction to the BMI less than 30 kg/m² might allow a better short-term course of transplantation as well as long-term graft survival [13], there are no prospective studies to date to demonstrate clear benefit of weight loss before kidney transplantation on posttransplant outcomes [38,39]. In a prospective cohort study, unintentional, but not intentional, weight loss prior to transplant was associated with higher graft loss and mortality [39].

Bariatric surgery is the most effective treatment to achieve long-term weight loss. The most commonly performed procedures are laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass (RYGB). In a single-center retrospective study of 13 patients with BMI at least 35 kg/m² who underwent bariatric surgery as preparation for kidney transplantation, the authors reported that gastric bypass procedures (RYGB, n = 6; laparoscopic RYGB, n = 1; omega loop GB, n = 3; laparoscopic omega loop GB, n = 3) did not increase complications after transplantation or negatively affect graft and patient survival [14*]. In this study, DM underwent remission in 67% of cases after bariatric surgery, and PTDM was not observed. As RYGB is a restrictive/malabsorptive procedure, it may affect intestinal drug absorption, which can lead to significant changes of pharmacokinetics of tacrolimus and mycophenolate mofetil. Thus, RYGB patients may need higher doses of these medications [40]. In contrast, sleeve gastrectomy is mainly a restrictive procedure, and therefore, does not affect the oral bioavailability of immunosuppressive drugs.

In the absence of prospective, randomized controlled trial data to date to support weight loss before kidney transplantation, the decision on timing of weight loss and surgical procedure of choice should account for the need to decrease peri-transplant risks, but not at the expense of delaying or excluding the patient from transplant which confers survival benefit to the recipient.

CONCLUSION

As the risk of dialysis, even for obese patients, far exceeds those of transplantation, it is crucial to address any existing bias and/or barriers that cause nephrologists to delay or forgo kidney transplantation. BMI is
a simple index of weight-for-height, and does not take into account age, ethnicity, muscle mass, fat distribution, and body fluid accumulation. Currently, there is no common BMI cutoff across transplant programs to exclude obese candidates from transplantation, but instead, arbitrary thresholds are applied unevenly across transplant centers. This raises several controversies; should BMI be used as a sole parameter to exclude patients from life-saving transplantation, and what would be the ideal threshold? There is an imminent need for transplant communities to redefine transplant eligibility for obese patients by including individualized patient assessment of health and weight status rather than establishing absolute contraindications based on BMI alone as kidney transplantation confers a significant survival advantage over dialysis even for obese patients.

Although current data on graft and patient survival in obese recipient are encouraging, further long-term and multidisciplinary management strategies are needed to improve outcomes. These include healthcare professional (HCP)-patient engagement, training of HCP in obesity counseling techniques (such as motivational interviewing), integration of digital technology (such as electronic reminders to prompt BMI measurement), and integration of community resources for obesity management. Also, prospective multicenter trials are required to examine the impact of pretransplant versus posttransplant medical and surgical weight loss, and minimally invasive techniques such as RAKT on the early surgical complication rate and long-term transplant outcomes.

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Conflicts of interest
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