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Obesity, Transplantation, and Bariatric Surgery: An Evolving Solution for a Growing Epidemic

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Abbreviations:

ASTS: American Society of Transplant Surgeons

BMI: body mass index

CKD: chronic kidney disease

DAA: direct-acting antiviral

D-LT: delayed sleeve gastrectomy after liver transplant

DM: diabetes mellitus

EBWL: excess body weight loss

ESLD: end-stage liver disease

ESRD: end-stage renal disease

GFR: glomerular filtration rate

HCV: hepatitis C virus

KT: kidney transplantation

(L)RYGB: (laparoscopic) Roux-en-Y gastric bypass

(L)SG: (laparoscopic) sleeve gastrectomy

LT: liver transplantation

MELD: Model for End-Stage Liver Disease

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

PGD: primary graft dysfunction

S-LT: simultaneous sleeve gastrectomy with liver transplant

SRTR: Scientific Registry of Transplant Recipients

SSI: surgical site infections

UNOS: United Network for Organ Sharing

(L)VAD: (left) ventricular assist device

ABSTRACT

The increasing obesity epidemic has major implications in the realm of transplantation. Patients with obesity face barriers in access to transplantation as well as unique challenges in perioperative and postoperative outcomes. Due to comorbidities associated with obesity along with the underlying end-stage organ disease leading to transplantation candidacy, these patients may not even be referred for transplant evaluation, much less be waitlisted or actually undergo transplantation. However, the utilization of bariatric surgery in this population can help optimize the transplant candidacy of patients

with obesity and end-stage organ disease as well as improve perioperative and postoperative outcomes. In this paper, we will review the impact of obesity on kidney, liver, and cardiothoracic transplant candidates and recipients, as well as explore potential interventions to address obesity in these populations.

1. INTRODUCTION

Obesity is a worldwide epidemic. In 2005, 25% of the world population was overweight (as defined by body mass index [BMI] 25-29.9 kg/m^2) and 10% was obese (BMI >30 kg/m^2).[1] By 2030, the prevalence is projected to reach 38% overweight and 20% obese. In the U.S., the rates of obesity in 2014 were 35% of men and 40% of women.[2] The health-related ramifications of obesity have been well-documented, including but not limited to cardiovascular disease, diabetes mellitus (DM), and cancer.[3-5] In patients with end-organ disease, obesity-related comorbidities can influence access to transplantation, technical aspects of the transplant operations, and post-transplant outcome. While Class 1 obesity (BMI 30-34.9 kg/m^2) is not typically a contraindication, Class 2 (BMI 35-39.9 kg/m^2) and Class 3 (BMI >40 kg/m^2) obesity can be relative or absolute contraindications to transplantation. Findings from a survey of American Society of Transplant Surgeons (ASTS) members administered by our task force showed that for kidney transplant candidates, the average BMI cutoff considered to be a relative and absolute contraindication was 38 and 41 kg/m^2, respectively. For liver transplant candidates, these cutoffs were 40 and 45 kg/m^2 and for thoracic transplant candidates, they were 35 and 38 kg/m^2.

Optimal post-transplant outcomes are desirable for the individual recipient and from the perspective of responsible stewardship of limited donor organs. Studies examining the impact of obesity on transplant outcomes are limited by a lack of consensus not only of a commonly accepted definition of obesity, but also of a standard approach to assessment of obesity. Despite these limitations, known comorbidities associated with obesity, such as DM, cardiovascular disease, obstructive sleep apnea, metabolic syndrome, and impaired pulmonary function can impact transplant outcomes. These cardiometabolic risks are compounded by the increased incidence of hyperlipidemia, hypertension, and DM observed with immunosuppressive drugs. Other considerations include the challenges of dosing immunosuppressive and other medications, especially lipophilic agents that are impacted by the variability in the volume of distribution in patients with obesity.

Given the impact of obesity on transplant outcomes, many transplant centers have incorporated interventions targeting obesity in their transplant candidates. Dietary education and interventions can be helpful, but are resource intensive for a relatively modest level of impact.[6] For those failing nutritional intervention and medical therapy, bariatric surgery can be helpful. Currently, the two predominant procedures include laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB). While both procedures achieve 60%–80% excess body weight loss (%EBWL) within 18–24 months, the mechanism differs insofar as LSG is a restrictive procedure involving resection of the greater curve of the stomach, and LRYGB is a restrictive/malabsorptive procedure that entails creation of a gastric pouch and formation of a Roux-en-Y gastrojejunostomy.

While the literature on patients with end-stage renal disease and concurrent obesity has generally shown bariatric surgery to have a positive impact on access to kidney transplant as well as post-transplant outcomes, uncertainties remain regarding optimal timing of bariatric surgery, either pre- or post-transplant. For kidney transplant candidates, 62.3% of transplant surgeons surveyed preferred bariatric surgery pre-transplant, whereas 23.6% preferred post-transplant bariatric surgery. For liver transplant candidates, however, only 29.0% and 30.3% of surgeons preferred bariatric surgery either pre- or post-transplant, respectively. This likely reflects the less robust evidence base for bariatric surgery in this patient population, with questions remaining regarding overall impact on transplant outcomes as well as appropriate timing of bariatric surgery. For cardiothoracic transplant candidates, literature is more limited regarding the use of bariatric surgery, as evidence is only beginning to emerge in this population. One potential benefit for early bariatric surgery, particularly for patients with chronic organ disease, is the potential for weight loss to prevent progression to end-stage organ failure.[7] However, the focus of this manuscript is that of patients who already have end-stage organ failure, and will not cover the scope of chronic disease prior to organ failure.

With the pervasiveness of obesity in potential transplant candidates, there is need for increased awareness and further education of all providers who care for this patient population. Of ASTS members surveyed, 64.2% of respondents even expressed interest in attending a course to learn more about bariatric surgery and how to set up a bariatric transplant center. In this paper, we will review the impact of obesity on kidney, liver, and cardiothoracic transplant candidates and recipients, as well as explore potential interventions to address obesity in these populations.

2. KIDNEY TRANSPLANTATION

2.1 Access to kidney transplantation

Like the rest of the U.S. population, the end-stage renal disease (ESRD) population is becoming progressively more obese.[8] Obesity-related comorbidities including cardiovascular disease, DM, and cancer can all affect progression of chronic kidney disease (CKD) as well as morbidity preventing potential listing for kidney transplantation (KT).[3-5] However, there is an "obesity paradox" for patients on hemodialysis. There are data suggesting that patients with higher BMIs (>27 to 27.8 kg/m^2) have better outcomes on dialysis compared to patients with lower BMIs (<21.8 to 23.1 kg/m^2).[9,10] In ESRD patients, higher BMI associated with visceral fat or abdominal obesity (potential indicators of metabolic syndrome) increases risk of DM and cardiovascular disease, whereas higher BMI with normal to high muscle mass or favorable waist circumference may confer some protection.[4,11-17] Further complicating the picture, it has been suggested that subcutaneous fat may be a marker of nutritional status in patients on hemodialysis, while visceral fat may be associated with a more inflammatory state.[18,19]

Despite the potential protective effect of obesity in patients on dialysis, KT still provides a clear survival advantage over dialysis.[20] Given these interacting factors, a more nuanced approach to the management of obesity is desirable to increase access to transplantation, as well as increase the likelihood of operative technical success and long-term post-transplant outcomes. The use of weight assessment, often using BMI, is common, although controversial, and can occur even at the referral level.[21-23]

Once listed, patients with obesity continue to face lower rates of transplant and higher likelihood of organ offer bypass, and this is further compounded by gender-related differences, with women less likely to be transplanted with BMI >25 kg/m^2.[8,24] Paradoxically, programs that have become "more conservative" after receiving a low-performance Scientific Registry of Transplant Recipients (SRTR) report are more likely to remove patients with BMI ≤24 kg/m^2, rather than higher BMI patients, suggesting an underlying appreciation for reasonable outcomes in patients with obesity who are otherwise considered good surgical candidates.[25]

2.2 Graft and patient outcomes

The survival benefit of transplant over dialysis for patients with obesity has been established (Figure 1), although the benefit is lower at higher BMIs, particularly BMIs >40 kg/m^2, and there are suggestions that certain subgroups have inferior outcomes.[20,26,27] It is similarly well-established that graft and patient survival in patients with obesity are inferior.[28] This pattern follows a U-shaped distribution, as patients with either lower or higher than normal range BMI (either ≤20 or ≥26 kg/m^2) have worse outcomes following transplant.[6,29] These results are likely due to some combination of visceral fat effect, lean muscle mass or sarcopenia, frailty, propensity for diabetes, and other obesity-related comorbidities.[30,31] Interestingly, significant post-transplant weight gain (>20% in the first year or 10% in the second year) or weight loss (>5%) has been associated with decreased patient survival, suggesting that unintentional nutritional or metabolic states that result in large swings in weight are deleterious.[32] Pre-existing DM prior to transplant has also been associated with increased mortality in the first 10 years after transplant.[33]

Consistent with the model of obesity as an inflammatory state, obesity has been associated with increased biopsy-proven rejection, as well as delayed graft function.[34-37] Post-transplant obesity or visceral adiposity is further associated with the development of cardiovascular disease, hypertension, and post-transplant DM.[38,39] Many of these comorbidities have an inflammatory component, which may be partially mitigated by controlled weight management. Complicating this issue, obesity can also impact immunosuppression, with tacrolimus overdosing more common among patients with obesity.[40]

There are technical aspects to KT that can be more difficult with obesity. Some techniques, such as caval extensions in deceased donor right kidneys, have been developed to address these issues. However, particularly for those with obesity and significant iliac arterial disease, the operation is technically more challenging and occasionally prohibitive. Morbidity is affected—recipients with BMIs >30 kg/m^2 may have up to a 4-fold increase in surgical site infections (SSI) and a nearly 3-fold increase in hernias.[41] The incidence of SSIs has been reported to range from 20%-40% in recipients with BMIs >40 kg/m^2.[42] Despite these complication risks, overall physical quality of life is similar for those who are overweight or obese following transplant, although costs are higher for those with BMIs >40 kg/m^2.[43,44] Nonetheless, it is important to note that the presence of SSIs correlates with worse graft survival.[45]

The application of minimally invasive techniques to KT, such as robotic surgery, has shown promising results compared to open KT.[46] Robot-assisted KT (RAKT) has resulted in statistically significant reduction in SSIs in a cohort of recipients with obesity.[47,48] Additionally, a matched-pair cohort study comparing recipients of robotic KT and a historical open KT cohort (28 patients each arm) found comparable patient and graft survival.[46] RAKT seems to be a safe approach with a reduced complication rate in patients with obesity.

2.3 Treatment options for kidney transplant patients with obesity

Weight loss is difficult, particularly for those with ESRD. For patients with obesity and CKD, particularly if on dialysis, pharmacological options are limited and usually ineffective. Traditionally, bariatric surgery has been thought to be risky for patients with CKD.[49] However, as the preferred approach has migrated from LRYGB to LSG,[50] there has been increased interest, particularly for patients requiring dialysis.[51] For those patients with CKD who are pre-dialysis, bariatric surgery may also improve effective renal function, with acceptable morbidity and mortality.[52,53] Furthermore, pre-transplant LSG increases access to the transplant waitlist and improves post-transplant outcomes (Figure 2).[54-56] Granular studies on post-transplant bariatric surgery are small, but the risk profile appears to be acceptable, with similar improvement in comorbidities seen in solid-organ transplant recipients as compared with the general population.[57] A retrospective study evaluating bariatric surgery before and after KT compared to propensity-matched non-bariatric surgery controls from the OPTN database found that those who underwent bariatric surgery (either before or after KT) had significantly decreased allograft failure and mortality.[58] However, the risks of complications and mortality after bariatric surgery in solid organ transplant recipients remain unclear and need further investigation.

2.4 Conclusions and Recommendations

- Kidney transplantation results in a survival benefit compared to dialysis or waitlisted patients in all classes of obesity.
- Patient and graft survival after kidney transplant exhibit a U-shaped phenomenon, where those at either extreme of BMIs have impaired outcomes, although survival benefit is still maintained.
- Pre-transplant sleeve gastrectomy and Roux-en-Y gastric bypass have been shown to be safe and efficacious, in addition to increasing access to the transplant waitlist and improving post-transplant outcomes.
- As the survival benefit of kidney transplantation exists across BMIs, timing of kidney transplantation relative to obesity intervention may be influenced by anticipated time on the transplant waitlist (or availability of living donors). For candidates with shorter anticipated wait times, proceeding with transplant followed by bariatric surgery is reasonable, but with longer anticipated wait times, the candidate may benefit from bariatric surgery first.

3 LIVER TRANSPLANTATION

3.1 Access to liver transplantation

The U.S. obesity epidemic has led to a dramatic rise in obesity-related liver disease and the number of patients who require liver transplantation (LT) for decompensated non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), or associated hepatocellular carcinoma.[59] While only a minority of patients with obesity-related liver disease (4% of NAFLD and 20% of NASH) will progress to cirrhosis and potential consideration for LT, the vast number of patients affected by obesity drives the increased demand.[60,61] In fact, NAFLD has become the second most common indication for listing and the third most common indication for transplantation.[62,63]

Despite the increased incidence of NAFLD and resultant need for transplantation, an analysis of waiting list outcomes from 2002-2006 demonstrated that patients with obesity were less likely to be listed for or undergo transplantation.[64] More detailed analysis demonstrated that this was at least partly due to fewer Model for End-Stage Liver Disease (MELD) exceptions being granted, along with a higher likelihood of offer rejections, resulting in a nearly 30% lower transplant rate.[64] The reluctance to consider patients with obesity for transplantation may have been driven in part by initial SRTR data which indicated reduced post-transplant survival for LT recipients with obesity.[65] Importantly though, this study had a relatively small proportion of patients in the higher BMI cohorts (5% with BMI 35-40 kg/m^2 and 2% with BMI >40 kg/m^2), with no adjustment for ascites. Subsequent analyses also using SRTR data based on a more contemporary data set, as well as a multi-center prospective database, demonstrated similar outcomes for both patient and graft survival for transplant recipients with and without obesity.[26,66-68]

3.2 Graft and patient outcomes

Patients with obesity tend to gain weight after transplant and a significant proportion develop metabolic syndrome.[69] LT recipients who develop post-transplant metabolic syndrome have higher risk of vascular events (stroke, transient ischemic attacks, myocardial infarction, acute coronary syndrome, and sudden cardiac death).[70] The increased incidence of post-transplant DM is also associated with decreased survival rate after LT.[71]

Surgical complications, including wound infections, dehiscence, biliary complications, and overall infection rate after LT are increased (in some studies 4-6-fold) in patients with BMI >35 kg/m^2.[72,73] A number of studies have reported longer ICU and hospital lengths of stay (LOS), as well as increased rates of discharge to a skilled nursing or rehabilitation facility in LT recipients with obesity.[65,72,74,75] Other studies have shown mixed outcomes in terms of both short-term morbidity and long-term survival.[65,68,76-78] Regardless of these varied results, recent cohorts suggest similar post-transplant survival between recipients with and without obesity.[73,79] Furthermore, a survival benefit with LT is observed in candidates with all categories of obesity.[26]

Patients with obesity and NASH are reported by some groups to have equivalent graft and patient survival compared to those with other causes of liver disease.[80,81] However, NASH recipients also had increased operative time, blood loss, and hospital LOS.[81] Another study noted that mortality within 4 months of LT was twice as high in patients with NASH compared to those without, and that patients with obesity and NASH, along with a high-risk phenotype (age >60 years, BMI >30 kg/m^2, concomitant hypertension, and DM) had lower 5-year survival rates compared to NASH recipients without the phenotype.[82]

Future directions for research to guide patient selection and interventions to optimize short- and long-term outcomes after LT in patients with obesity may benefit from a consensus conference to establish uniform 1) categories of obesity, 2) approaches to measure type (visceral/peripheral) and degree of obesity in patients with end-stage liver disease (ESLD), 3) assessment of key comorbidities associated with obesity and liver disease, 4) pre- and post-transplant interventions to enhance muscle mass and mitigate metabolic syndrome including recurrent disease post-transplant and 5) criteria to measure post-intervention success.

3.3 Treatment options for liver transplant patients with obesity

Currently, options for managing obesity in the transplant population similar to the non-transplant population and includes diet, exercise, and bariatric surgery. Given the effect of obesity on peri- and post-operative outcomes, weight loss is likely beneficial for LT recipients. However, optimal time for weight loss interventions and best method(s) remain unclear (Table 1).[83]

Pre-Transplant Obesity Management

Certainly, management of obesity before transplantation is beneficial as it can improve candidacy for transplantation and reduce both the technical challenges of operating in patients with obesity as well as the attendant peri-operative complications. While there is limited information regarding the effects of diet and exercise on pre-transplant weight loss, a few studies have demonstrated the beneficial effect of both aerobic exercise and caloric restriction in patients with compensated cirrhosis vis-à-vis improved insulin resistance and liver enzymes, as well as decreased body fat and BMI.[84-87] Two separate studies showed a loss of 10% total body weight to be associated with a reduction in fibrosis.[88,89]

Bariatric surgery may be feasible for patients with compensated cirrhosis, though it is less commonly an option for waitlisted patients given the risk of elective surgery for patients with decompensated liver disease. LSG has advantages over LRYGB in patients with compensated cirrhosis given 1) the technical ease of the procedure and therefore shorter operative time, and 2) preservation of the gastrointestinal tract for creation of a possible Roux-limb as part of a LT or maintenance of access for potential future therapeutic endoscopic interventions.[55] Studies have shown the safety and efficacy of LSG in patients with ESLD.[55,90] Short-term complications included bleeding, wound infections, staple line leak, and hepatic encephalopathy, though there were no associated 30-day mortalities. %EBWL was 50-62% at one year post-LSG and for those who underwent LT, this weight loss was maintained up to one year post-LT, suggesting a protective effect of pre-transplant LSG on post-transplant weight gain.

Perioperative Obesity Management

Simultaneous bariatric surgery and LT (S-LT) is another approach to managing obesity in this patient population. The advantage of this approach includes addressing both obesity and liver disease in one operation, with potentially less patient discomfort and lower costs. The disadvantage lies in the fact that combining both surgeries creates a more complicated procedure. To examine this, Heimbach et al. compared outcomes between LT candidates who lost weight pre-operatively using lifestyle modification (n=37) to those patients who underwent S-LT (n=7) due to failure of lifestyle modification.[87] Their results demonstrated that the cohort who had S-LT had non-inferior perioperative outcomes despite having a significantly higher pre-operative BMI. Specifically, in patients undergoing the combined procedures, there were no deaths or graft losses. Complications included one leak from the gastric staple line and one patient with excess weight loss. There were no patients who developed post-transplant DM or steatosis, and all patients maintained substantial weight loss out to an average of 17 months (Figure 3). Taken together, this study suggests a role for bariatric surgery at the time of LT in carefully selected patients. A recent report from the same group reported on longer term outcomes for 29 patients who underwent S-LT, including 13 patients more than 3 years out, demonstrating efficacy for achieving and maintaining weight loss as well as favorable metabolic profiles for those who underwent S-LT.[91] Two additional case reports of S-LT also supported safety and efficacy of the procedure.[92,93] The first reported case of simultaneous SG with a living donor LT recipient was described in 2017, resulting in post-transplant weight loss to BMI < 30 kg/m^2 within 2 months, as well as cure of DM.[94]

Post-Transplant Obesity Management

A non-invasive, structured multi-disciplinary weight loss program remains the foundation of obesity management even in the post-transplant setting. If not successful, which is more likely for patients with severe obesity, delayed bariatric surgery after LT (D-LT) may be considered. In a series of RYGB after LT (n=7), Al-Nowaylati et al. reported effective weight loss, but concerning results included one death and one reversal due to complications of bariatric surgery.[95] A matched case-control series of LSG in patients with (n=12) versus without prior LT (n=36) noted similar operative times and post-operative morbidity with no conversion to open surgery, though with a longer hospital LOS in those with a prior LT.[96] Other smaller series of D-LT note similar efficacy with weight loss and metabolic complications, though adhesions, bleeding issues, and longer operative time were described.[55,96-98]

3.4 Conclusions and Recommendations

- Obesity-related liver disease is projected to become the leading indication for liver transplantation in the next decade in the United States.
- Liver transplantation results in a survival benefit in all classes of obesity.
- Recommendations based on low-to-moderate grade evidence suggest sleeve gastrectomy as the preferred bariatric surgical technique in liver transplant candidates or recipients.
- Future studies should investigate comparative effectiveness of bariatric surgery timing in the LT population between S-LT and D-LT.

4 CARDIOTHORACIC TRANSPLANTATION

4.1 Access to cardiothoracic transplantation

As all health care providers know, obesity is an epidemic worldwide and this is no different in thoracic transplantation. In a recent survey of thoracic transplant surgeons (2018 Obesity in Transplantation Task Force Survey), 60% of programs have a BMI threshold with 33% being an absolute and 50% a relative contraindication. Of survey responders, 75% have intervention programs for obesity, spanning the spectrum of interventions from dietary and lifestyle modifications to medical and surgical interventions. The presence of obesity thresholds, as well as hesitancy of certain centers to surgically intervene on patients with both obesity and end-stage cardiopulmonary failure significantly inhibits access to life-saving transplant therapies. If patients are able to be transplanted, their wait-time can be increased and access to suitable organs limited.[99]

4.2 Graft and patient outcomes

As with other transplants, there is a tendency of patients to gain weight post-cardiothoracic transplantation[100] and this can confound mobilization and infections. Functional status of patients with morbid obesity coupled with a risk for hidden sarcopenia drives a large portion of the concern. These patients with obesity have an increased risk for impaired sternal wound healing, with sternal non-union/dehiscence[101-103], which is a problem even without the added burden of immunosuppression. In patients with left ventricular assist devices (LVADs), obesity is correlated with driveline infections[104] which can also influence recovery after heart transplantation.

The impact of obesity on outcomes post-transplantation is not limited to the morbidity of wound healing, but on survival as well.[105] Obesity predisposes recipients to increased cardiac allograft vasculopathy, cardiovascular diseases, and metabolic syndrome after heart transplantation.[106] Patients with obesity are also at a higher risk of post-transplant mortality in both heart and lung transplantation.[107-110] These outcomes are accentuated in idiopathic pulmonary fibrosis patients where the risk of 90-day mortality is 1.71-fold higher with obesity, and this can significantly impact overall center performance.[107,108] Additionally, in lung transplant recipients, obesity is associated with a significant 2-fold increase risk of primary graft dysfunction (PGD)[111] within 72 hours post-transplant and there is an increased risk of 40% occurrence of PGD for each additional 5 kg/m^2 increase in BMI.[111]

4.3 Treatment options for cardiothoracic transplant patients with obesity

Treatment options for the patient with morbid obesity have relative pros and cons. Dietary, supplementation, and life style modifications were employed by all respondents in the ASTS Taskforce Survey. These approaches have some benefit, though the overall impact on the patient with end-stage cardiopulmonary failure can be limited. The relative sedentary nature of the disease courses, the impact on oxygen delivery, and limited mobility can hinder increased caloric expenditure (i.e., exercise). Socio-economic impacts compound the issues as well. For many patients, the time-sensitive nature of their disease means that the likelihood of losing meaningful weight prior to becoming transplant ineligible is prohibitive. Pre-lung transplant weight loss significantly improves survival and decreases days on the ventilator[112] so any intervention resulting in weight loss can have significant impacts on outcomes and survival. Patients with morbid obesity who are able to undergo LSG can facilitate weight loss and improve eligibility for transplantation.[113,114] In patients with end-stage lung disease, select patients with obesity undergoing bariatric surgery can have improvement of their lung disease and function, as well as pulmonary hypertension, through the weight loss.[115,116]

In summary, obesity has significant negative impact on access to thoracic transplantation. Furthermore, obesity also negatively impacts perioperative morbidity and mortality. When appropriate and feasible, LSG provides a strategy to facilitate weight loss and improvement in pre-transplant symptoms and function as well as enhancing access.

4.4 Conclusions and Recommendations

- Bariatric surgery prior to thoracic transplantation may lead to improved pulmonary function, access to transplant, and post-transplant outcomes.

5 FINANCIAL CONSIDERATIONS FOR OBESITY INTERVENTION

The ASTS has previously shared the high cost of patients on the transplant waitlist. For example, the cost of maintenance pre-transplant hemodialysis can easily be as high as $260,000 per year per covered life.[117] Even after transplantation, average Medicare payments in the following three years after KT increase with higher BMI (Figure 4). LSG can have a significant positive financial and clinical impact in the KT population. Utilizing LSG in a patient with obesity and advanced CKD or early ESRD can potentially allow these patients to be listed for a deceased donor KT or even better, to receive a pre-emptive living donor KT. Additionally, small studies have shown that performing S-LT for patients with NASH prevents disease recurrence, thus avoiding the high cost of potential graft failure and re-transplantation, with the 1-year additional cost of liver graft failure over $150,000.[91] In summary, consideration of bariatric surgery in the transplant population has early potential to positively impact the transplant process financially. However, there is a need for well-designed clinical trials as well as cost-effectiveness studies to support broader payor coverage of bariatric surgery prior to, or even during, transplant surgery.

6 PHARMACOLOGY/PHARMACOKINETICS

Bariatric surgery may result in altered absorption of medications, including immunosuppressive agents that are crucial in the post-transplant setting. RYGB in KT candidates and recipients has been shown to result in higher requirements of cyclosporine as well as significant differences in pharmacokinetics of tacrolimus, sirolimus, mycophenolic acid, and mycophenolic acid glucuronide when compared to non-bypass patients.[118,119] KT candidates who underwent LSG did not appear to have significantly different pharmacokinetics of tacrolimus (immediate or extended release) or mycophenolic acid, suggesting that post-LSG patients may not require dose modification out of the norm for transplant recipients.[120] However, a larger series demonstrated that both RYGB and LSG could be performed without requiring significant dosage adjustments of tacrolimus, mycophenolic acid, or prednisone, and indeed, stability of blood trough levels increased after bariatric surgery.[57] Therefore, with appropriate monitoring, immunosuppression may be well maintained in recipients of both RYGB and LSG.

7 CONCLUSIONS AND FUTURE DIRECTIONS

Patients with obesity and concurrent end-stage organ failure face significant challenges in access to transplantation as well as negative impacts on outcomes after solid organ transplantation. Addressing obesity in select patients with bariatric surgery prior to transplantation may improve access, facilitate an easier operation, as well as improve benefits of transplantation. Bariatric surgery after transplantation may also help to enhance the benefits from transplantation under certain situations. Further investigation is needed to clarify optimal timing of bariatric surgery relative to transplantation, as well as to evaluate the role of bariatric surgery for chronic organ disease prior to development of end-stage organ failure, and to assess the role of bariatric surgery for potential living donors with obesity.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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9 TABLES

TABLE 1. Bariatric surgery and liver transplantation case series, including those with pre-transplant, simultaneous with transplant, and post-transplant bariatric surgery.

Author	**Time range**	**Cohort (n)**	**Bariatric procedure done**	**Timing of bariatric procedure to transplant**	**Endpoints and notable findings**
Lin et al	2006-2012	SG pre liver (n=20) and kidney (n=6) transplant	SG	Pre-transplant	7/20 transplanted, all met weight criteria. 1 staple line leak, 2 patients with transient hepatic decompensation
Safwan et al	2007-2017	Patients currently undergoing LT with remote history of prior bariatric surgery -Roux en Y (9) -Sleeve gastrectomy (1) -Jejunoileal bypass (1)	-LRYGB -SG -Jejunoileal bypass	Pre-transplant	30 day re-op rate, biliary complications, patient and graft survival at 1 and 2 years. No comparison group for complications, but similar patient/graft survival to those without bariatric surgery

Takata et al	2004-2007	Patients with cirrhosis (n= 6) who underwent SG	SG	Pre-transplant	Complications, excess weight loss, obesity related comorbidities, transplant candidacy. Excellent weight loss noted, though short follow-up. No major complications but transient hepatic decompensation noted peri-operatively.
Heimbach et al	2006-2012	Obese patients undergoing LT who had a combined LT and SG (n=7) and who had LT with no SG (N=37)	SG	Simultaneous	Death, graft loss, operative complications were similar in two groups. Post LT metabolic outcomes superior in the combined group.
Tariciotti et al	2016	N=1 obese patient with NAFLD and HCC undergoing combined LT + SG.	SG	Simultaneous	Weight loss robust, no significant complications, follow up only 5 months, no comparison group
Nesher et al	Not stated	LT and simultaneous SG (n=3)	SG	Simultaneous	Normal allograft function, robust weight loss at 13 months. No comparison group.

Lin et al	2007-2011	SG post LT (n=8)	SG	Post-transplant	30- day complications include 3 re-ops. Weight loss robust, allograft function normal, improved metabolic parameters
Osseis et al	2008-2015	SG post LT (N=6)	SG	Post-transplant	Surgical outcomes, liver and kidney function tests, outcomes of obesity related complications, excess weight loss
Tsamalaidze et al	2010-2016	SG after LT (n=12) and SG with no previous transplant (n=36)	SG	Post-transplant	Case-control noted similar ost-operative events, long term weight loss, comorbidity resolution. Slightly longer hospital stay in those with prior LT

Elli et al	2008-2014	Post solid organ transplant recipients undergoing sleeve gastrectomy and non-transplant patients undergoing sleeve gastrectomy -Kidney transplant (n=6) -Liver transplant (n=2) -Pancreas transplant (n=2)	SG	Post-transplant	Percentage excess weight loss, perioperative and post-operative complications
Khoraki et al	2008-2014	Post solid organ transplant patients undergoing SG Liver (n= 5) Also heart and kidney patients reported (total 10)	SG	Post-transplant	Robust weight loss, resolution or improvement of obesity related co morbidities, normal allograft function. Splenectomy required in LT recipient due to bleeding, with subsequent PV thrombosis and need for TIPS
Al-Nowaylati et al	2001-2009	Patient who underwent open RYGB after OLT (n=7)	RYGB	Post-transplant	Robust weight loss, improved glycemic control and Dyslipidemia control. One death and one reversal due to complications related to surgery

10 FIGURES

FIGURE 1. The Survival Benefit of Kidney Transplantation in Obese Patients. The figure shows the multivariate adjusted hazard ratio for death in recipients of a living donor (LD; a), standard criteria deceased donor (SCD; b), and expanded criteria deceased donor (ECD; c) grouped by BMI compared to patients of the same BMI who had been on dialysis for equal lengths of time but had not yet received a kidney transplant (reference group denoted in blue with as relative risk of 1.0 in each figure). Reproduced from original publication Gill JS et al. *Am J Transplant*. 2013;13(8):2083-90. Reproduced with permission from Wiley Publishing Co.

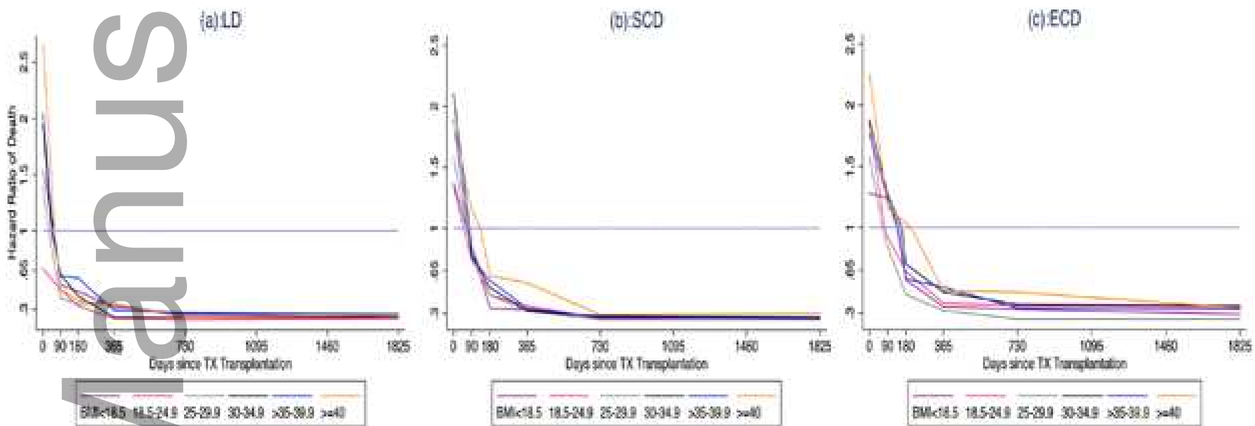

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FIGURE 2A. Short-term outcomes in recipients of kidney transplant after undergoing laparoscopic sleeve gastrectomy (LSG) compared to controls (recipients of kidney transplants with similar BMI who did not undergo LSG). Abbrev. MI: myocardial infarction, CVA: cerebrovascular accident, TIA: transient ischemic attack. Reproduced from original publication Kim Y et al. *Am J Transplant.* 2018;18(2):410-416.

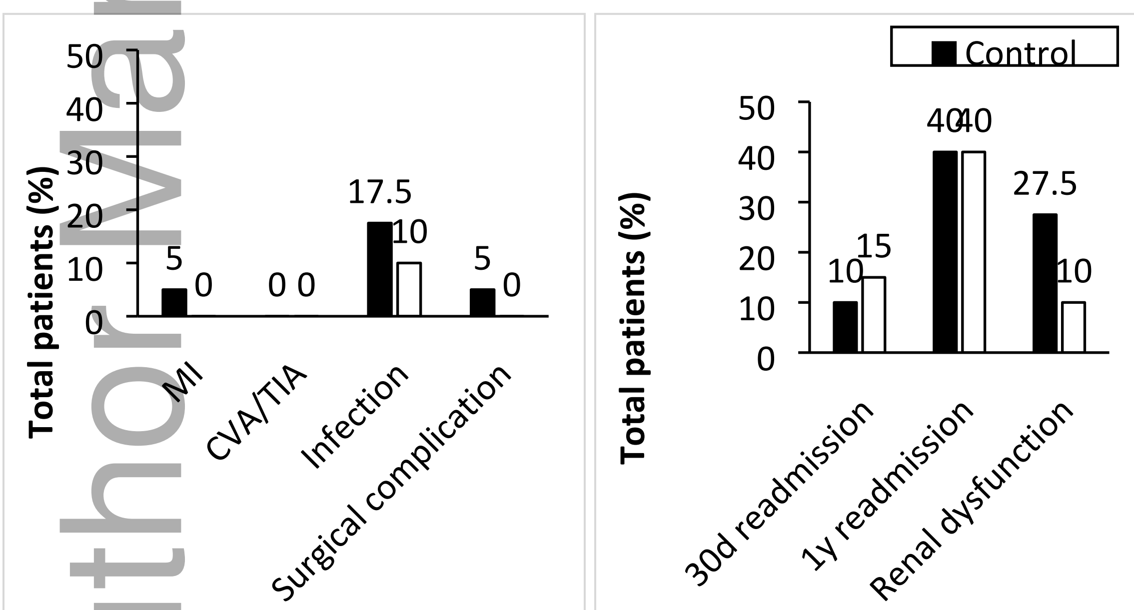
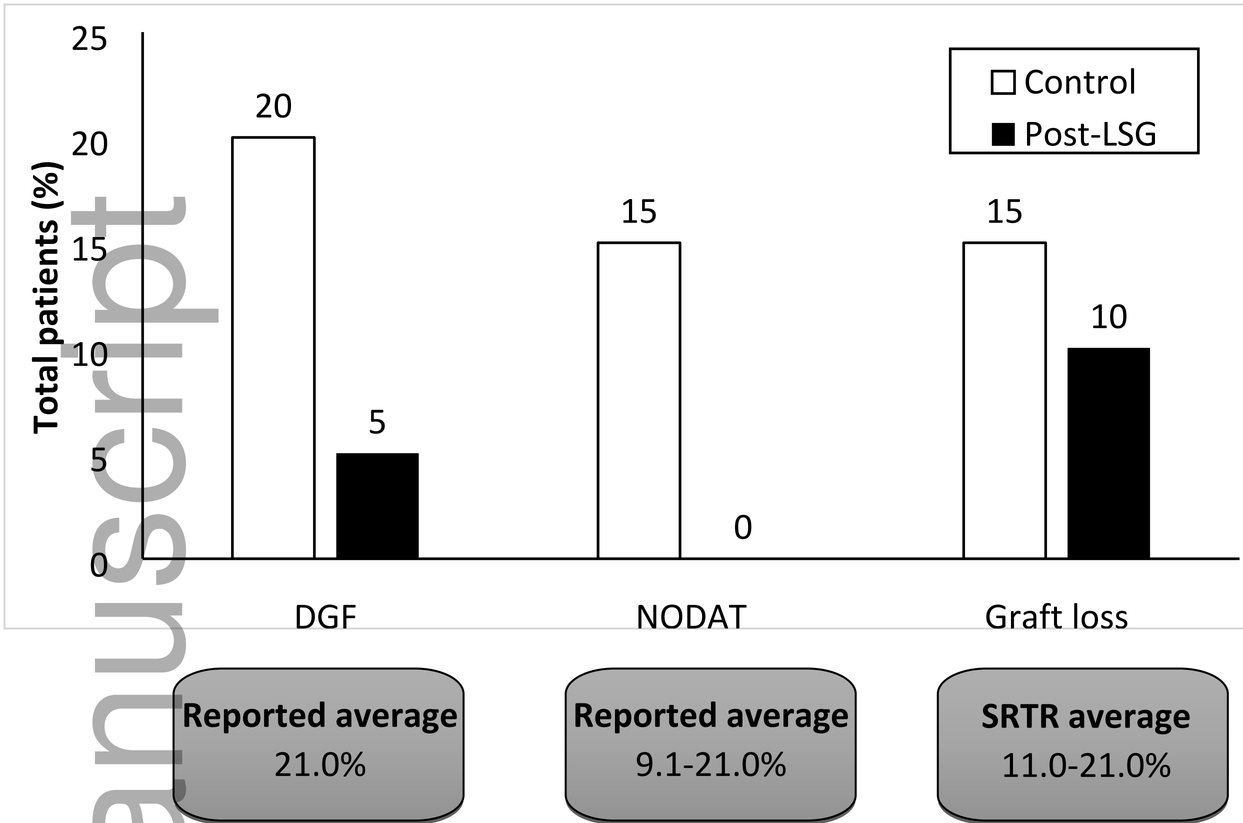


FIGURE 2B. Long-term outcomes in recipients of kidney transplant after undergoing laparoscopic sleeve gastrectomy (LSG) compared to controls (recipients of kidney transplants with similar BMI who did not undergo LSG). Abbrev. DGF: delayed graft function, NODAT: new-onset diabetes after transplantation, SRTR: Scientific Registry of Transplant Recipients. Reproduced from original publication Kim Y et al. *Am J Transplant.* 2018;18(2):410-416.



Total patients (%)
25
20
15
10
5
0
Control
Post-LSG
20
5
15
0
15
10
DGF
NODAT
Graft loss
Reported average
21.0%
Reported average
9.1-21.0%
SRTR average
11.0-21.0%

FIGURE 3. BMI trends for those patients who underwent combined liver transplant plus sleeve gastrectomy (N = 7). Mean follow-up is 17 months. Reproduced from original publication Heimbach JK et al. *Am J Transplant.* 2013;13(2):363-368.

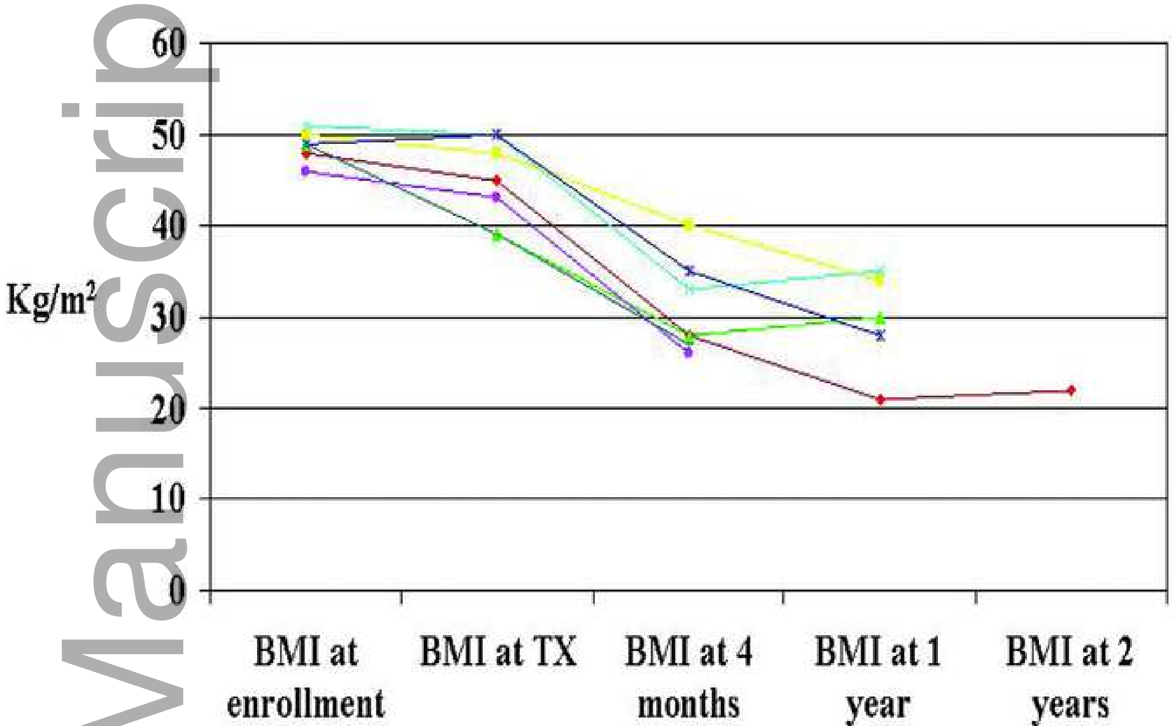


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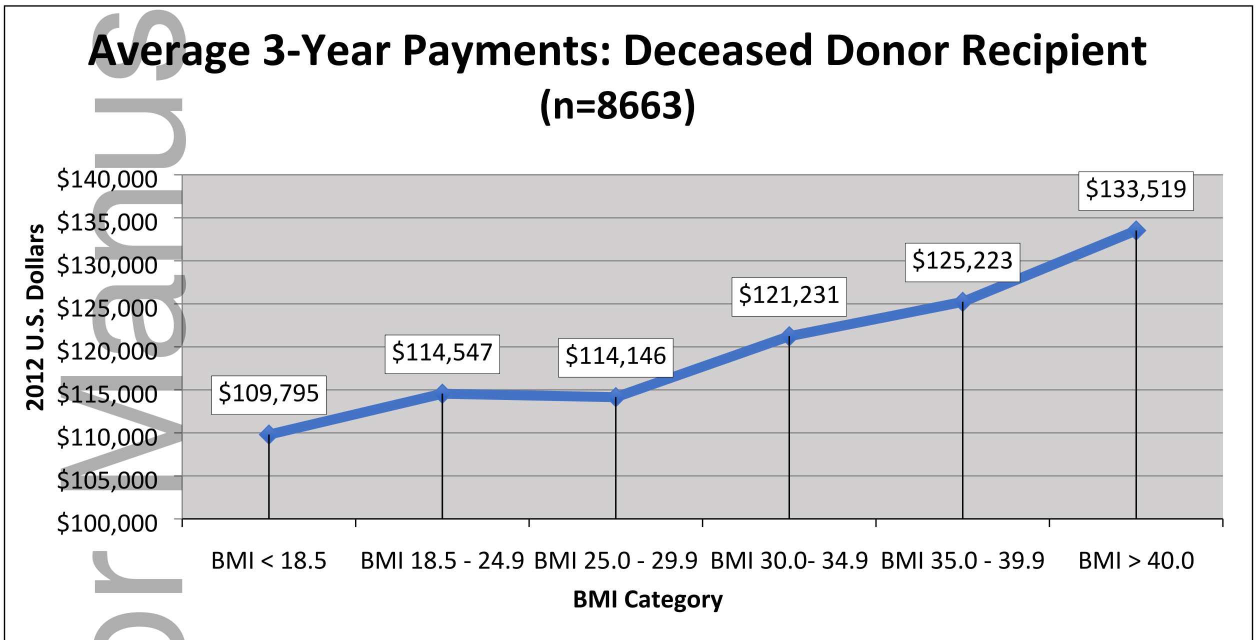
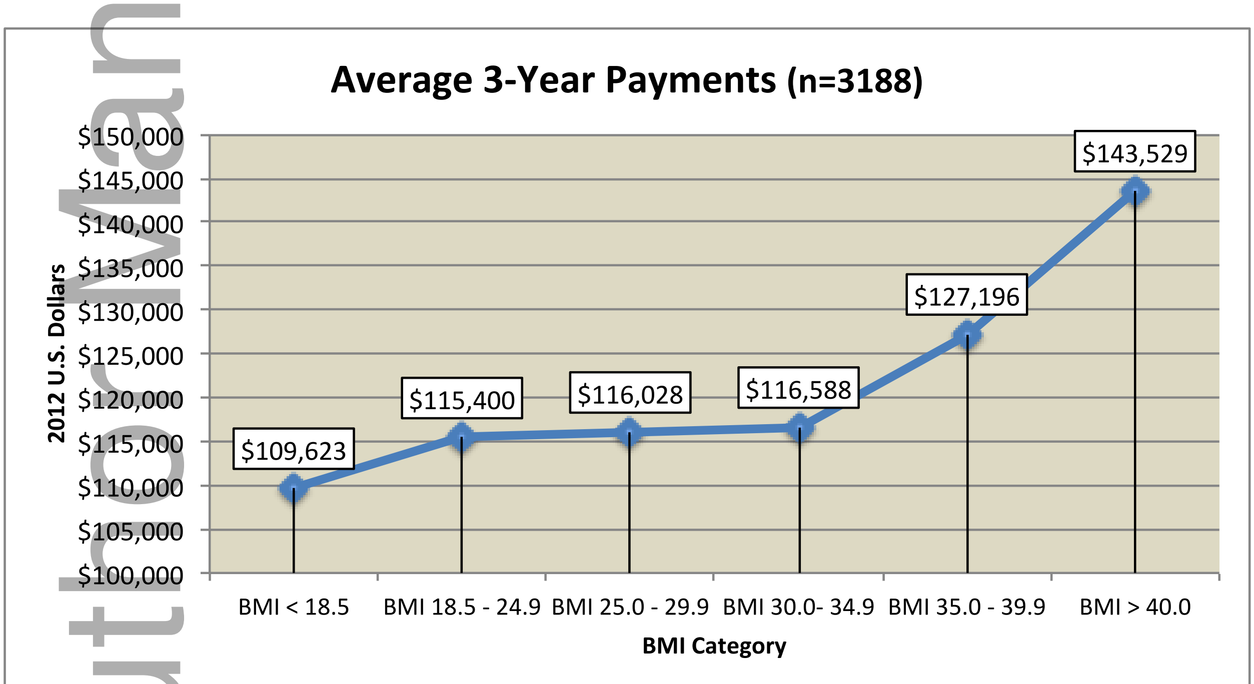
FIGURE 4A. Average accumulated Medicare payments as function of body mass index for select sample of deceased donor recipients who are alive with functioning graphs 3-years post-kidney transplantation. Unpublished data, courtesy of Leah Crow, PharmD, and TS Diwan.



Mean 3-year Payments	N	Mean	Std. Dev	Std. Error	95% CI for Mean	
					Lower Bound	Upper Bound
BMI < 18.5	196	$109,795	$60,324	$4,309	$101,297	$118,293
BMI 18.5 - 24.9	2758	$114,547	$92,517	$1,762	$111,093	$118,002
BMI 25.0 - 29.9	3014	$114,146	$67,433	$1,228	$111,737	$116,554
BMI 30.0- 34.9	1824	$121,231	$75,451	$1,767	$117,766	$124,696
BMI 35.0 - 39.9	667	$125,223	$75,893	$2,939	$119,453	$130,993
BMI > 40.0	204	$133,519	$78,385	$5,488	$122,698	$144,340
Total	8663	$116,976	$78,704	$846	$115,319	$118,634

FIGURE 4B. Average accumulated Medicare payments as function of body mass index for select sample of living donor recipients who are alive with functioning graphs 3-years post-kidney transplantation. Unpublished data, courtesy of Leah Crow, PharmD, and TS Diwan.



Mean 3-year Payments	N	Mean	Std. Deviation	Std. Error	95% CI for Mean	
					Lower Bound	Upper Bound
BMI < 18.5	94	$109,623	$42,770	$4,411	$100,863	$118,383
BMI 18.5 - 24.9	1127	$115,400	$50,487	$1,504	$112,449	$118,351
BMI 25.0 - 29.9	1072	$116,028	$50,887	$1,554	$112,978	$119,077
BMI 30.0- 34.9	635	$116,588	$49,965	$1,983	$112,694	$120,481
BMI 35.0 - 39.9	194	$127,196	$53,589	$3,847	$119,607	$134,784
BMI > 40.0	66	$143,529	$74,969	$9,228	$125,099	$161,959
Total	3188	$116,977	$51,314	$909	$115,195	$118,759