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Obesity and liver transplantation

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Abstract

The percentage of overweight and obese patients (OPs) waiting for a liver transplant continues to increase. Despite the significant advances occurred in bariatric medicine, obesity is still considered a relative contraindication to liver transplantation (LT). The main aim of this review is to appraise the literature on the outcomes of OPs undergoing LT, treatments that might reduce their weight before, during or after surgery, and discuss some of the controversies and limitations of the current knowledge with the intent of highlighting areas where future research is needed.

Key words: Liver transplantation; Bariatric surgery; Obesity; End-stage liver disease; Weight-loss; Access to transplantation

Core tip: The prevalence of obesity in the general population has doubled and the number of obese patients (OPs) affected by end-stage liver disease has increased with the same pace. There is conflicting data on the outcomes of OPs undergoing liver transplantation (LT) and the main aim of this review is to appraise the literature on the outcomes of OPs undergoing LT, treatments that might reduce their weight before, during or after surgery, and discuss some of the controversies and limitations of the current knowledge with the intent of highlighting areas where future research is needed.

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INTRODUCTION

The incidence and prevalence of obesity, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have increased worldwide. In 2010, 35.7% of the adults living in the United States were affected by obesity and the estimated prevalence of NAFLD and NASH were 30% and 12% respectively[1,2].

In the last decade, the indication for liver transplantation (LT) for NASH has risen from 1.2% to 9.7%, and is currently the third most common cause of liver failure and might become the leading indication for LT by 2025[3].

Since the percentage of obese patients (OPs) with end-stage-liver-disease (ESLD) continues to rise, familiarity with the evolving field of bariatric medicine is necessary for transplant specialists. The main objectives of this paper is to review the most recent literature on the treatment options, to discuss some of the implications that obesity has for LT recipients, and finally, to explore current controversies and possible directions for future research.

DEFINITION OF OBESITY

Obesity is defined by the World Health Organization[4] as the presence of excessive body fat that poses health risks, and body mass index (BMI) is the most common metric used by normalizing a person's weight to her/his height. Individuals with a BMI equal or greater than 30 kg/m^2 are defined as obese and individuals with a BMI equal or greater than 40 kg/m^2 are categorized as morbidly obese.

NON-SURGICAL THERAPIES IN CIRRHOTIC PATIENTS

Dieting, physical activity, behavioral therapy, and pharmacotherapy are acceptable but poorly effective options for the treatment of obesity. The Food and Drug Administration has approved orlistat, lorcaserin, and phentermine-topiramate for weight loss but not for cirrhotic patients[5]. Orlistat (Xenical®) acts by blocking gastric and pancreatic lipases and inhibits triglycerides absorption. Locaserin HCl (Belviq®) suppresses the appetite and promotes satiety by acting as an agonist for serotonin receptors in the hypothalamus. Finally, phentermine-topiramate (Qsymia®) decreases appetite by a catecholamine effect in the central nervous system[6].

Medically supervised weight-loss (MSWL) has a low success rate[6-9] as patients fail to maintain their desired weight[10]. Additionally, possible interactions between immunosuppressive medications and drugs used to reduce BMI are unknown[11] and further research is needed before weight-loss medications can be recommended either before or after LT.

BARIATRIC SURGERY

In recent years, the introduction of minimally invasive techniques has considerably reduced the perioperative morbidity and mortality of patients undergoing bariatric surgery (BS)[12]. The Metabolic and BS Accreditation and Quality Improvement Program have created national standards for bariatric programs similarly to what UNOS has done for transplant centers[13] with the subsequent fall of perioperative mortality to 1%[14]. Because of its safety and long-term effectiveness, BS has become the most frequent therapy for non-cirrhotic OPs[15].

BS can be categorized into three main classes: restrictive, mostly restrictive and malabsorptive (Figure 1). Although most of the BS have overlapping effects, restrictive surgeries primarily work by reducing the gastric capacity while malabsorptive surgeries prevent absorption of nutrients.

Among all the BS procedures, adjustable gastric banding (AGB) (Figure 1A) is the least invasive and it is purely restrictive. An adjustable band is positioned at the upper portion of the stomach and connected to a subcutaneous port that allows health care providers to inflate (or deflate) the band with the final goal of reducing the gastric capacity and patients' appetite.

Sleeve gastrectomy (SG), is a restrictive procedure that involves the removal of the majority (60%-70%) of the greater curvature of the stomach, leaving only a sleeve of functioning stomach (Figure 1B). This procedure reduces the gastric volume and the level of ghrelin secreted by the stomach with subsequent decrease of patients' sensation of hunger. Roux-en-Y gastric bypass (RYGB), a mostly restrictive procedure creates a small gastric pouch (approximately 5% of the original gastric volume) and re-routes 100-150 cm of proximal intestine (Figure 1C). Duodenal switch (DS), also known as biliopancreatic diversion, combines malabsortive and restrictive effects as a partial gastrectomy and extensive re-routing of the small intestine are performed simultaneously (Figure 1D). The common intestinal channel where food can be absorbed is reduced to only 75-150 cm and is currently performed in selected groups of morbidly OPs accounting for only 1% of all BS performed annually in the United States.

BENEFITS OF BS

Pontiroli *et al*[16] performed a systematic review and meta-analysis of eight trials involving 44022 OPs and found that BS reduced their risk of death due to metabolic syndrome (MS) (OR = 0.55; $P < 0.05$). Similar results were reported by Johnson *et al*[17]. Schauer *et al*[18] analyzed 150 patients randomized to BS *vs* best medical therapy for the treatment of type Ⅱ diabetes (T2DM). At 12-mo, the glycemic control was significantly better in patients who underwent BS. After 3-years, the target HbA1c level was achieved in 5% of the medical group *vs* 38% in patients who underwent RYGB and 24% in the SG group. A systematic review and meta-analysis of 6587 patients[19], found that for every five-point drop in BMI, the risk reductions for T2DM, hypertension, and dyslipidemia were 33%, 27%, and 20%, respectively. Similar results were reported in another systematic review of 22092 patients[20] where BS was associated with improvement or complete resolution of T2DM (86% of patients), dyslipidemia (70%), hypertension (78%), and obstructive sleep

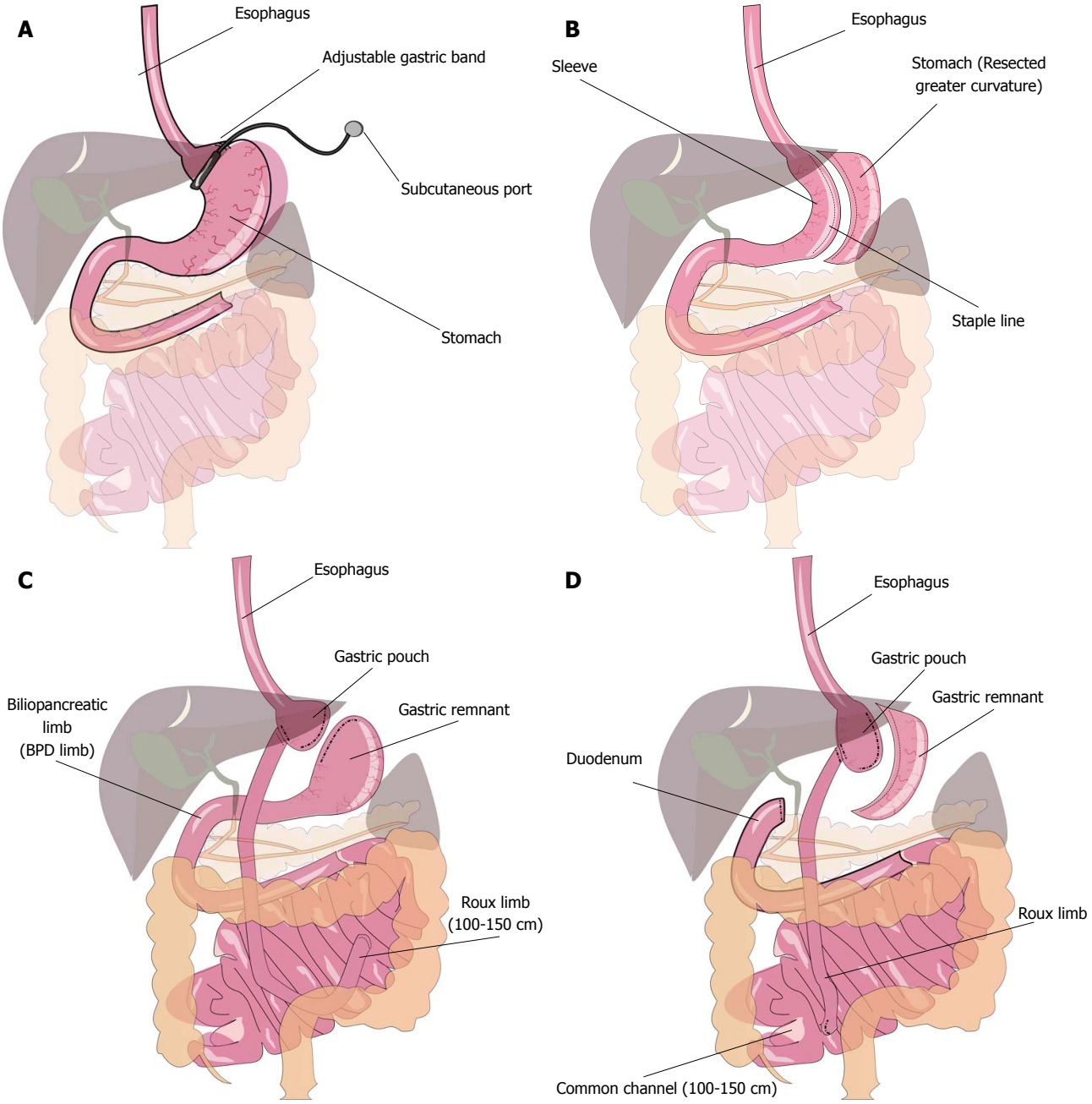

Figure 1 Types of bariatric procedures. A: Adjustable gastric banding; B: Sleeve gastrectomy; C: Roux-en-Y gastric bypass; D: Duodenal switch.

apnea (86%).

OPS WAITING FOR LT: SHOULD THEY UNDERGO BARIATRIC TREATMENT?

Theoretically, OPs with ESLD should benefit from losing weight as it reduces their risk for cardiovascular diseases, T2DM, dyslipidemia, obstructive sleep apnea *etc.* Additionally, OPs on the list for LT might improve their chance of being transplanted as a recent analysis of the United Network for Organ Sharing (UNOS) data[21] has shown that their likelihood of being transplanted was lower in comparison to normal weight individuals. One of the possible explanations is that transplant programs might decline surgery to obese candidates as they are at higher risk for perioperative complications[22] and have lower survival rates in comparison to normal weight patients[3,23]. Although there are some legitimate concerns, declining LT to OPs goes against the principle of fairness, as OPs who undergo LT have a significant survival advantage in comparison to OPs who remain on the waiting list and are not transplanted[24].

OUTCOMES OF OPS UNDERGOING LT

LaMattina *et al*[25] analyzed the perioperative morbidity of 813 LT patients between 1997 and 2008, and found that OPs had prolonged mean operative time (class Ⅰ obesity: 7.7 h, P = 0.009; class Ⅱ obesity: 7.9 h, P = 0.008;

class Ⅲ obesity: 8.2 h, $P = 0.003$ *vs* normal weight: 7.2 h), ICU stay (Class Ⅱ obesity: 4.1 d *vs* 2.6 d; $P = 0.04$), increased need for transfusions (class Ⅰ obesity: 15 units, $P = 0.005$; class Ⅱ obesity: 16 units, $P = 0.005$; class Ⅲ obesity: 15 units, $P = 0.08$ *vs* normal weight: 11 units), higher incidence of infections (HR 7.21, CI: 1.6-32.4, $P = 0.01$), biliary complications requiring intervention (Class Ⅱ obesity: HR 2.04, CI: 1.27-3.3, $P = 0.003$) and, more importantly, decreased patient (Class Ⅱ obesity: HR 1.82, CI: 1.09-3.01, $P = 0.02$) and graft survivals (Class Ⅱ obesity: HR 1.62, CI: 1.02-2.65, $P = 0.04$). In another study of 73538 LT recipients the overall survival was significantly lower in BMI less than 18.5 and higher than 40, compared to a control group[26]. Death in underweight patients was due to hemorrhagic ($P < 0.002$) and cerebrovascular ($P < 0.04$) complications, while infectious complications and cancer were the most common causes of demise in severely obese group ($P = 0.02$)[26]. Nair *et al*[22] analyzed the UNOS database on 18172 LT patients transplanted between 1988 and 1996 and found that primary graft dysfunction, perioperative mortality at 1, 2, and 5-years were significantly higher in the morbidly obese group due to cardiovascular adverse events. Similar outcomes were reported in 1325 obese LT recipients[27] from the United Kingdom where they had increased morbidity due to infectious complications, longer ICU and hospital stay in comparison to normal weight patients.

However, other studies suggested that higher BMI should not be considered an absolute contraindication to LT[24,28]. In 230 LT patients stratified into a lean group (BMI 20-26 kg/m^2) and an obese group (BMI > 38 kg/m^2), no significant differences were found except that at 3-year follow-up, the obese group had a higher risk of developing MS (46% in obese *vs* 21% in lean patients, OR 4.76; CI: 1.66-13.7, $P < 0.001$). Similar results were noted in a retrospective study of 25647 LT waitlist patients. In comparison to being on waitlist, all subgroups of BMI had survival advantage ($P < 0.0001$) with LT. Similar outcomes were noted by Conzen *et al*[23] in a single-center study of 785 patients. Three-year patient and graft survival were similar in all groups of BMI, while 5-year patient (51.3% *vs* 78.8%; $P < 0.01$) and graft (49% *vs* 75.8%; $P < 0.02$) survival were significantly reduced in morbidly obese *vs* non-OPs.

POSSIBLE ADVANTAGES OF BS FOR OPS REQUIRING A LIVER TRANSPLANT

The potential benefits of BS for patients in need of a LT have never been studied by randomized trials. Theoretically, weight-loss interventions would reduce their risk of suboptimal outcomes and may prevent the development of MS and recurrent NASH after LT. On the other hand, perioperative morbidity and mortality risks might be too high to justify any surgery to reduce their BMI.

THE PROS AND CONS OF DIFFERENT BARIATRIC SURGERIES

AGB is a relatively simple procedure that does not require the rerouting of the gastrointestinal tract and maintains the endoluminal access to the biliary system for endoscopic treatment of biliary complications that can occur after LT. AGB has no risks of anastomotic dehiscence and it is reversible (Table 1). The main drawback of AGB is the presence of a foreign body that could become infected and cause long-term complications from slippage, prolapse, port-site infection and erosion into the stomach with potential serious consequences in immunocompromised patients. Other potential issues with AGB are that the band is positioned near the gastroesophageal junction where varices from chronic portal hypertension develop, and the band could prevent access to the supraceliac aorta for arterial reconstructions during LT if necessary.

RYGB and DS are more effective than AGB, but have significantly higher perioperative risks of anastomotic leaks, obstructions, marginal ulcers, malabsorption of immunosuppression medications, loss of endoscopic access to the biliary system and are contraindicated for patients who need a Roux-limb for their biliary reconstruction.

In recent years, SG has been viewed as a good compromise as it has lower perioperative risks in comparison to RYGB or DS[29], maintains direct access to the biliary system, it is unlikely to cause malabsorption of immunosuppression medications[30] and provides a gradual and sustained weight-loss[9,31,32].

TIMING FOR BS

Before transplant

The rationale for performing BS prior to LT would be to optimize patients' medical condition before surgery or to bring patients' BMI within the range considered acceptable by some transplant centers.

However, BS performed before LT might delay transplant surgery due to the time necessary to achieve the desired BMI or to the development of perioperative complications. Another drawback of BS before LT is that recipients undergo two separate operations and two hospitalizations with associated increased financial costs, stress, and pain.

Although no randomized controlled trials have ever been conducted to test whether BS is beneficial for OP requiring LT, case reports and observational studies have described the feasibility of BS either pre-, during or post-LT. Lin *et al*[33] published a retrospective review of all SG performed in liver (20 patients) and kidney transplant candidates (6 patients) between 2006 and 2012. The mean excess weight-loss (EWL) at 1, 3, and 12 mo was 17%, 26%, and 50% respectively without any perioperative death. Six cases (16%) experienced postoperative complications, including superficial wound infections, staple line leak, bleeding requiring

Table 1 Summary of advantages and disadvantages of different categories of bariatric surgeries in the context of liver transplantation

Procedure	Category	Description	(%) Excess weight loss	Pros	Cons
Adjustable gastric banding	Restrictive	Silicone band placed at the upper portion of the stomach	40-50	Minimally invasive, adjustable, reversible, removable, access to biliary tree is maintained	Foreign body placement, relatively longer duration for weight-loss, long-term potential complications of band erosion, pouchitis, pouch enlargement, gastric prolapse, slippage and flipped port, tubing breakage, malfunction of the device, port site infections
Sleeve gastrectomy	Restrictive	Removal of greater part of greater curvature of the stomach	50-60	Maintains gastric function with direct access to biliary tree, has better tolerance of oral/medications intake and absorption	Long staple-line on the stomach with a potential for bleeding and gastroinstestinal leak
Roux-en-Y gastric bypass	Mostly restrictive	Creation of gastric pouch and rerouting of intestine	70	Combined restrictive and malabsorptive procedure, resolution of comorbidities is relatively quicker with higher proportion of weight-loss	Relatively higher significant perioperative complications, intolerance to oral consumption, and absorption of medications, loss of direct access to biliary tree and remnant stomach, can lead to excessive weight-loss, higher likelihood of malnourishment
Duodenal switch	Malabsorptive	Subtotal gastrectomy with a very short common channel	80		

Percentage of excess weight loss = [(preoperative weight - weight at follow-up)/(preoperative weight - ideal body weight)] × 100.

transfusion, transient encephalopathy and renal insufficiency. All these patients became transplantable candidates by meeting institutional BMI requirements at 12 mo and the authors concluded that SG is relatively safe and effective.

Similar conclusions were drawn by Takata *et al*[34] who evaluated the effect of BS in end-stage liver, kidney, and lung disease in 15 OPs who were considered unsuitable for transplantation. Mean EWL at or after 9 mo was 61%, 33%, and 61% respectively. Obesity-associated comorbidities improved in all patients and, except for two individuals (13%) who suffered from perioperative complications, no deaths occurred after surgery. More importantly, 93% of patients became transplant candidates by meeting the institutional requirements on BMI. These authors concluded that laparoscopic RYGB and SG is safe and improves the candidacy for transplantation. With gain in experience in cadaveric LT and BS, feasibility is being evaluated also in living donor LT. Taneja *et al*[35] published a successful outcome of SG in a patient with BMI of 55.6 and NASH undergoing living donor LT.

After transplant

The main rationale for performing BS after LT would be to prevent the recurrence of MS and NASH and improve survival by reducing obesity related comorbidities[36]. In a recent publication, Duchini *et al*[37] described two patients who were successfully treated by RYGB for severe graft dysfunction due to recurrent NASH.

However, BS after LT comes with the risk of dealing with severe adhesions, wound complications and anastomotic or staple lines dehiscences due to the use of steroids and/or m-TOR inhibitors. Despite these potential drawbacks, Lin *et al*[38] published a pilot study on the safety and feasibility of SG in nine obese LT recipients with the intent of improving steroid-induced diabetes, steatohepatitis, and MS. Postoperative complications occurred in three patients (33%) who developed mesh infection in a concurrent ventral hernia repair, bile leak requiring drainage and one patient who underwent reoperation for dysphagia. At 6 mo, 55% EWL was achieved without graft rejection and the authors concluded that SG does not adversely affect LT function. On the other hand, some technical challenges associated with BS after LT were reported by Tichansky *et al*[39] who described major adhesions with complete obliteration of the gastrohepatic space during a successful laparoscopic RYGB after LT for a patient with a BMI of 54 kg/m^2.

During LT

Combining BS and LT could theoretically minimize delays, hospital stay and reduce patients' overall pain as the same incision can be used for both operations. However, one of the biggest trade-offs is that the operation for LT will take longer and that patients might suffer from more severe complications due to the increased complexity of the procedure.

Campsen *et al*[40] performed a successful simultaneous LT and AGB and reported that at 6 mo, patients' BMI went from 42 kg/m^2 to 34 kg/m^2 with 45% EWL and resolution of T2DM, hypertension and osteoarthritis. In 2013, Heimbach *et al*[41] published their experience of BS in OPs (BMI $\geqslant$ 35) undergoing LT. OPs with a BMI $\geqslant$ 35 were divided into two groups. Patients who successfully completed MSWL underwent LT (n = 37) alone. Seven patients who failed MSWL underwent simultaneous LT and SG (n = 7). In patients who underwent LT alone, weight-regain (BMI > 35) was noted in 21 of 34 patients (61%), post-transplant diabetes in 12 patients (35%),

steatosis in 7 (20%), graft losses and deaths in 3 (8%). In the group of patients who underwent simultaneous LT and SG (n = 7), all maintained their weight-loss, one had a gastrointestinal leak from the staple-line (14%) and one had excessive weight-loss. Although the majority of patients who did not undergo BS achieved some weight-loss with a non-surgical approach, most regained weight within a mean follow-up of 33 mo. On the other hand, patients treated with combination of SG and LT achieved effective and sustained weight-loss and fewer metabolic complications over a mean follow-up of 17 mo.

CONCLUSION

The obesity epidemic is having a significant impact on the field of transplantation as two-thirds of the adult population in the United States is overweight. Although OPs undergoing LT might experience short and long term-outcomes inferior to patients with normal BMI, their survival with LT is superior to best supportive care. Therefore, their exclusion from LT would violate the idea of fairness and should be challenged. Since medical therapies are relatively ineffective, BS might play a more distinct role in the future of transplantation but there are no well-designed studies on the role of BS in this population. Currently, only low quality evidence (Level 4 and 3b)[42] has shown that BS can be done either prior, during or after LT. However, the number of publications is small, and except for a few case-series, there are no studies that have systematically compared OPs treated with MSWL *vs* BS *vs* no treatment. Similarly, there is lack of data on the best timing of BS (prior to LT, during or after LT) or which type of BS (AGB *vs* RYGB *vs* SG *vs* DS) should be performed.

In summary, the number of OPs requiring LT is rising. To maximize short and long-term outcomes of OPs undergoing LT, prospective studies should be designed to identify if there are benefits from weight-loss treatments and if so, what interventions should be used and when they should be instituted.

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