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EDITORIAL

Liver transplantation and sleeve gastrectomy in the medically complicated obese: New challenges on the horizon

Diego C Reino, Keri E Weigle, Erik P Dutson, Adam S Bodzin, Keri E Lunsford, Ronald W Busuttil

Diego C Reino, Keri E Weigle, Adam S Bodzin, Keri E Lunsford, Ronald W Busuttil, Division of Liver and Pancreas Transplantation, Department of Surgery, University of California Los Angeles, Los Angeles, CA 90095, United States

Erik P Dutson, Division of Minimally Invasive and Bariatric Surgery, Department of Surgery, University of California Los Angeles, Los Angeles, CA 90095, United States

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Correspondence to: Ronald W Busuttil, MD, PhD, FACS, Distinguished Professor and Chair, Division of Liver and Pancreas Transplantation, Department of Surgery, University of California Los Angeles, Pfleger Liver Institute, 757 Westwood Plaza, Suite 8501, Los Angeles, CA 90095, United States. rbusuttil@mednet.ucla.edu
Telephone: +1-310-2678054
Fax: +1-310-2673668

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Abstract

In the last 30 years, operative, technical and medical advances have made liver transplantation (LT) a life-saving therapy that is used worldwide today. Global industrialization has been a contributor to morbid obesity and this has brought about the metabolic syndrome along with many downstream complications of such. Non-alcoholic steatohepatitis (NASH) has become a recognized hepatic manifestation of the metabolic syndrome and NASH cirrhosis is predicted to be the primary indication for LT in the United States by 2025. Several case series and database reviews have begun analyzing the efficacy of weight reduction surgery in the LT recipient. These data have reasonably demonstrated that weight reduction surgery in the LT recipient is a feasible endeavor. However, several questions have been raised regarding the type of weight reduction surgery, timing of surgery in relation to LT, patient and allograft survival and post-LT maintenance of weight loss to name a few. We look forward to a time when weight reduction surgery will work to improve the technical conduct of LT, improve perioperative benchmarks such as blood transfusions, intensive care unit length of stay and help to prevent recurrence of NASH cirrhosis in the medically complicated obese patient. In the meantime, well-designed prospective clinical trials that focus on the issues highlighted will help guide us in the care of these complicated patients who will soon account for the majority of the patients in our clinics.

Key words: Non-alcoholic steatohepatitis cirrhosis; Liver transplantation; Sleeve gastrectomy; Roux-en-Y gastric bypass; Weight reduction surgery

Core tip: Non-alcoholic steatohepatitis (NASH) has become a recognized hepatic manifestation of the metabolic syndrome and NASH cirrhosis is predicted to be the primary indication for liver transplant (LT) in the United States by 2025. Previous reviews have shown that weight reduction surgery is a feasible endeavor in the liver failure patient. However, our review of the available literature highlights the need for a prospective clinical trial that will focus on the efficacy of sleeve gastrectomy in relation to LT perioperative outcomes, patient and allograft survival and prevention of NASH recurrence in the post-transplant setting.

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TEXT

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver injury that is marked by triglyceride accumulation in hepatocytes. The severity of liver injury ranges from benign steatosis that may be found incidentally on ultrasound or cross sectional imaging to nonalcoholic steatohepatitis (NASH), which is characterized by neutrophil infiltration into portal triads. NASH cirrhosis marks the final stage within the spectrum of NAFLD and this has become a leading indication for liver transplant (LT) in the United States[1]. In 1980, Ludwig *et al*[2] first described NASH as a clinical entity when they analyzed the liver biopsies of twenty patients with no history of alcohol abuse and found that the histologic profile was indicative of an inflammatory process as evidenced by hepatic steatosis, lobular hepatitis, focal necrosis with inflammatory infiltrates and Mallory bodies. A common variable for this group of patients was that they had manifestations of metabolic syndrome as most of the patients were female, obese, hypertensive, with diabetes mellitus and hyperlipidemia[2]. This observation has led many to believe that NASH is the hepatic manifestation of the metabolic syndrome.

The prevalence of adult obesity and the metabolic syndrome has reached epidemic proportions affecting an estimated 34% of the adult population in the United States[3-5]. This has led to a parallel trend in the incidence of NASH cirrhosis as the primary indication for LT from 1.2% in 2001 to 9.7% in 2009, making it the third most common indication in the United States[6]. Agopian *et al*[1] have reported the largest single institution series of patients undergoing LT for NASH cirrhosis over an 18-year period. In this retrospective series, they were able to demonstrate graft and patient survivals at 90 d similar to hepatitis C virus (HCV) as well as a retransplant rate for recurrent NASH cirrhosis of 7%, compared to 8% for HCV[1]. Although the short term data are promising, we have yet to understand the long term graft and patient survival, operative complications, immunosuppression-related morbidity and the financial implications of performing liver transplants on patients with NASH cirrhosis.

Historically, surgical procedures in the obese patient have conferred a higher morbidity and mortality compared to those performed in patients with a lower body mass index (BMI)[7-9]. However, only recently have we begun to examine complications in the obese liver transplant recipient. LaMattina *et al*[10] reviewed their series of 306 obese liver transplant recipients over 11 years and they found that patient and graft survival, blood product transfusion, intensive care unit (ICU) length of stay (LOS), and biliary complications requiring intervention were all higher in the obese patients[10]. Specifically, patient survival at 1, 3 and 5 years for Class Ⅱ obese patients (BMI 35.1-40) was 91%, 78%, and 78%, *vs* 94%, 86% and 83% in the non-obese recipients (P = 0.02)[10]. Following a similar trend, allograft survival for Class Ⅱ obesity was 87%, 76%, and 74%, *vs* 91%, 84% and 80% over the same time period (P = 0.04). Comparing the same two groups, blood transfusion use within the first 48 h was significantly higher in the obese group by 5 units (P = 0.002), ICU LOS was 1.5 d longer (P = 0.04) and the need for biliary interventions *via* endoscopic retrograde cholangiopancreatography or percutaneous approach after LT in Class Ⅱ obesity *vs* non-obese counterparts was also elevated (P = 0.003)[10].

Concerns over outcomes in the obese LT recipient have led to the advent of weight reduction surgery in the liver failure patient. Weight reduction surgery has evolved over the past 15 years and these advances have had a significant impact on the metabolic syndrome in the non-transplant obese patient. Of the weight reduction procedures in practice, the gold standard Roux-en-Y gastric bypass (RYGB) has been associated with the most profound sustained weight loss in long term studies[11]. Similarly, cessation of preoperative insulin and antihypertensive medications have been more closely related to RYGB as compared to restrictive procedures such as gastric banding[12]. Despite improved outcomes with RYGB, early approaches towards combined LT with weight reduction surgery have focused on the use of sleeve gastrectomy (SG) as the weight reduction procedure of choice. RYGB has largely been eliminated from the armamentarium in the LT recipient because of increased complexity with this technique as well as the malabsorption associated with RYGB that may adversely affect early post-transplant immunosuppression levels[13,14]. Combined LT and gastric banding has been previously reported. However, this has largely been abandoned due to concerns for having a foreign body in an immunosuppressed patient[15].

When considering approaches for SG in the LT patient, three approaches can be taken. Pretransplant SG, combined liver transplant and SG (LTSG) or SG in

the post-transplant setting. Heimbach *et al*[15] reported on their experience of combined liver transplantation and gastric sleeve resection (LTSG) for patients who had a BMI greater than 35 kg/m^2 along with a MELD score range of 19-32. Although their series contained a total of 44 patients and only 7 patients who underwent combined LTSG, they had two key findings that were important. First, they were able to demonstrate that noninvasive obesity management programs centered on dietary education are very effective at lowering the mean BMI at the time of enrollment from 40 to a mean BMI at the time of transplant of 33. The seven morbidly obese patients (mean BMI 48) who failed to lose weight from dietary modifications went on to get LTSG. The second critical observation is that at 3 years follow-up, the patients who underwent dietary modification and liver transplant alone achieved the target weight loss pretransplant, but were not able to sustain this weight loss after transplant. This resulted in an increase of the mean pretransplant BMI of 33 to 36 in the post-transplant setting when adjusted for ascites and edema. In contrast, the 7 morbidly obese patients who failed the pretransplant dietary modification program and underwent combined LTSG had a mean BMI of 49 at enrollment, 48 at the time of transplant and after 17 mo follow-up had a mean BMI of 29. Of these 7 patients, one gastric staple line leak occurred in a 60-year-old male who had a MELD of 40 at the time of transplant[15]. Although there were no other complications attributable to SG in this group, this very serious complication raises questions regarding the timing of SG within the spectrum of liver disease. Previous reports of weight reduction surgery in the post-transplant setting have demonstrated acceptable outcomes, but were reported to be technically demanding operations due to the altered surgical field[13,16-18]. Performing this operation in the post-transplant setting may offer an advantage in terms of allograft survival if NASH recurrence could be prevented, however, the surgical and perioperative benefits around the time of transplant are lost by taking this approach. Thus, the greatest advantage of weight reduction surgery can potentially come in the pretransplant setting. The timing of such a procedure is critical and must also take into consideration the effect of SG on the technical aspects of the future liver transplant. Namely, adhesion formation subsequent to SG can potentially impact mobilization of the left lobe of the liver due to dense adhesions between the staple line of the stomach and the left lobe of the liver and may similarly impact porta hepatis dissection.

Previous reports based on nationwide admission data, diagnosis and procedure codes have analyzed outcomes for patients who underwent bariatric surgery while having a concomitant diagnosis of compensated *vs* decompensated liver disease or no liver disease at all. Although this data is inherently limited, the expected finding was that patients with decompensated liver disease who underwent bariatric surgery had a higher mortality rate (16.3%) as compared to those patients with compensated (0.9%) or no liver disease at all (0.3%) (P = 0.0002)[19]. By stratifying these groups of patients and focusing on those patients with compensated liver disease, we can potentially identify patients who can tolerate SG prior to LT without progressing to decompensated liver failure. This is a significant barrier that will require increased awareness in order for primary care physicians and hepatologists to identify patients with metabolic syndrome who are at the highest risk of developing NASH cirrhosis.

Weingarten *et al*[20] retrospectively analyzed their prospectively collected data on 340 patients who underwent laparoscopic bariatric operations with morbid obesity as the primary indication for surgery and no known history of liver disease. Liver biopsies were performed intraoperatively and revealed that 44% of the patients had mild NASH with no or minimal fibrosis and 14% had advanced NASH with at least stage 2 fibrosis at the time of their bariatric surgery[20]. The complication rate did not differ significantly across NASH categories when comparing hospital length of stay, 30 d postoperative deaths, or liver failure[20]. This is a critical observation because it implies that we have inherently been operating on patients with advanced, but compensated liver disease who can already be identified as patients who may not recover from their burden of liver disease if left untreated. More importantly, they were able to tolerate a major bariatric operation without any overt decompensation of their newly diagnosed liver disease, as would be expected with this overall minimal degree of liver injury. However, the important observation is that these subsets of patients who have NASH with low grade fibrosis, or perhaps even Child's A cirrhotic patients without any overt evidence of portal hypertension, may be the most appropriate patients who should be considered for SG prior to LT. Although we currently do not have any empiric evidence to support this hypothesis, these observations can be used as preliminary data to help identify the optimal timing for SG in the pretransplant period, while maintaining a low risk for overt decompensation of their liver disease.

CONCLUSION

The future of liver transplant will see a paradigm shift where HCV cirrhosis will become a secondary indication for LT. The advent of direct acting antivirals has changed the playing field when it comes to the treatment of HCV cirrhosis. We can anticipate that NASH cirrhosis will supersede all other indications for LT in the near future if we consider the projection that 25 million Americans will develop NASH by 2025, with 20% progressing to cirrhosis and/or hepatocellular carcinoma that may require LT[3-5]. Our review of the literature summarizes the initial experience with weight reduction surgery in the setting of chronic liver disease and it suggests that we can safely perform SG prior to, in combination with, and in the post-transplant setting. Conventional wisdom would suggest that most centers would consider

patients who have no more than Child's A cirrhosis and a BMI of 35 kg/m^2 for SG in the pretransplant setting. With respect to combined SG and liver transplant in the same setting, we propose that this should be reserved for lower risk patients with low MELD scores or patients who have MELD exceptions and have retained physiologic reserve at the time of transplant. Ultimately, the approach to the timing of SG will likely be center and region specific as centers with very high acuity due to organ constraints may not be able to offer combined SG/liver transplant to their patients as other centers or regions can. Thus, the centers/regions with higher average MELD scores at transplant may be forced to offer this service to their patients in the pretransplant setting, assuming that NASH is the indication for liver transplant and that their liver disease remains compensated. Considering the scope of the problem at hand, a prospective clinical trial that focuses on the timing of SG, long term patient and allograft survival, operative complications, financial implications and NASH recurrence after LT will help guide the future of both of these successful operations.

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