“Weighing the risk”: Obesity and outcomes following liver transplantation

Trevor W Reichman, George Therapondos, Maria-Stella Serrano, John Seal, Rachel Evers-Meltzer, Humberto Bohorquez, Ari Cohen, Ian Carmody, Emily Ahmed, David Bruce, George E Loss

Abstract

Obesity is on the rise worldwide. As a result, unprece-
INTRODUCTION

Obesity or the excessive accumulation of body fat contributes to a host of chronic health problems. Obesity is defined by a body mass index greater than 30 whereas severe obesity, morbid obesity and super obesity are defined by a body mass index (BMI) ≥ 35, 40, and 50, respectively\[^{1}\]. Obesity rates have continued to soar throughout the world as populations continue to adopt a more “Western” type of lifestyle. A diet of highly processed, refined foods, fat, and red meats has also been linked to increase rates of cardiovascular disease and cancer. Based on recent statistics, it is estimated that greater then 2.1 billion people in the world are either overweight or obese\[^{2}\]. In the United States, there are approximately 30 million people who are overweight equaling greater than 30% of the population\[^{2}\].

Obesity is associated with the clinical condition known as the metabolic syndrome that includes hypertension, hyperlipidemia, hyperglycemia, and increased abdominal fat deposition\[^{3}\]. In addition to obesity, insulin resistance has also been found to be associated with the metabolic syndrome\[^{4}\]. Individuals with a diagnosis of metabolic syndrome are at increased risk for cardiovascular events, stroke, diabetes, and chronic liver disease.

The natural course of chronic liver disease is progression to cirrhosis and end stage liver disease (ESLD) if the inciting factor(s) is not controlled. ESLD leads to portal hypertension and a host of other complications including gastrointestinal bleeding, encephalopathy, jaundice, ascites, malnutrition, and hepatocellular cancer (HCC). Although there are multiple causes of chronic liver disease and cirrhosis (e.g., viral hepatitis, autoimmune hepatitis, cholestatic liver diseases, excessive alcohol consumption), the most common cause of chronic liver disease in the United States is now non-alcoholic fatty liver disease (NAFLD) or its more aggressive form, non-alcoholic steatohepatitis (NASH)\[^{5}\].

Obesity and its associated complications is thought to have a significant impact on post-operative outcomes and survival after surgical procedures. The allocation of health resources and the expense associated with caring for obese patients continues to be controversial especially in light of the current changing health care landscape. Nowhere is this more true than in the field of liver transplantation in which there is not only an obligation to provide cost effective care but also the responsibility of allocating a scarce resource.

NAFLD, NASH, and obesity

NAFLD is thought to be the hepatic manifestation of the metabolic syndrome. NAFLD encompasses a spectrum of clinicopathological disease ranging from hepatic steatosis (in the absence of significant alcohol consumption) to the more aggressive form NASH in which fatty deposition and necroinflammation are present. Pathologically, NASH is characterized by macrovesicular steatosis, ballooning degeneration with or without Mallory bodies, and lobular or portal inflammation, with or without fibrosis\[^{6}\]. The majority of patients with NAFLD have a benign course and many have stable fatty liver disease. NASH is thought to result from a two-hit insult in which accumulation of fat is the first step but an additional stressor is necessary in order to lead to progressive liver damage and NASH\[^{7}\]. Interestingly, there also appears to be a genetic predisposition to developing NAFLD and NASH\[^{8}\]. In addition, there are racial differences observed in the prevalence of NAFLD in the United States with the highest prevalence found in Hispanics, followed by Caucasians, and then African-Americans\[^{9-14}\].

It is estimated that greater than 25% of patients with NASH will develop progressive fibrosis over time with approximately 10%-20% of patients eventually developing advanced fibrosis or cirrhosis\[^{12}\]. Clinical risk factors for progression of fibrosis include insulin resistance and hypertension\[^{13}\]. NASH likely accounts for a large portion of cases that were previously labeled as cryptogenic cirrhosis especially those cases of cirrhosis that occur in the setting of obesity, diabetes, and cardiovascular disease. Further support for the link between NASH and cryptogenic cirrhosis comes from the fact that patients transplanted for cryptogenic cirrhosis have a high prevalence of NAFLD and NASH in their post transplant grafts\[^{14}\].

The incidence of NAFLD in Western countries is estimated to be between 20%-30%\[^{15}\]. Currently in the United States, NAFLD and NASH are the leading causes of chronic liver disease and NAFLD is estimated to effect approximately 30% of the general United States population and up to 90% of people with morbid obesity. NASH is thought to affect about 5%-13% of the general population, and studies have shown the presence of NASH in 31% of patients with a clinical diagnosis of NAFLD on ultrasound\[^{9}\].

NASH in pediatric patients

The obesity epidemic has not spared the pediatric population in the world. Typically thought of as a disease of adulthood, obesity rates and the incidence of NAFLD and NASH have skyrocketed in the pediatric population. Like adults, NAFLD now is the most common cause of chronic liver disease in children and adolescents\[^{16}\]. An autopsy study found that 9.6% of the American population aged 2-19 years old have NAFLD, and the percentage increased to 38% among those who were obese\[^{17}\]. NAFLD appears to be more prevalent in the older adolescents as compared to younger children and is also more common in boys (ratio of 2:1)\[^{18}\]. NAFLD is more prevalent in the Mexican communities and also in children from Asian-Indian and Asian-American descent\[^{19,20}\]. Rates in Asian patients are thought to potentially be due to increased rates of insulin resistance.
and visceral adiposity. The long-term outcomes of pediatric NAFLD are not well known and are actively being investigated. A recent study, however, suggests that biopsies from adolescents with NAFLD have significantly higher incidence of NASH, hepatocyte injury scores and fibrosis when compared to a similar group of adults. The authors concluded that adolescents with severe obesity have more advanced liver damage and more severe systemic inflammation than adults suggesting differences in NAFLD etiologies and more aggressive disease progression in the young obese population.

The data on NAFLD/NASH progression and the need for liver transplantation are scant. However, in one study, 66 children with NAFLD were followed for up to 20 years and 2 of these children underwent liver transplantation for decompensated cirrhosis. In both of these children, NAFLD recurred in the allograft with one case progressing to cirrhosis requiring retransplantation. Further studies are needed to identify those children that are at higher risk for progression of NAFLD to NASH and ultimately might require liver transplantation.

**Obesity and HCC**

One of the major indications for liver transplantation is HCC, especially when the tumor is multifocal or when it occurs in the setting of chronic liver disease. Obesity has been identified in several studies as a clear risk factor for the development of HCC. In the case of NAFLD, it is estimated that HCC occurs in up to 27% of patients with cirrhosis, but even patients without NASH are at risk for developing HCC. The etiology of HCC in NAFLD and NASH is thought to be related to chronic inflammation and repeated injury to hepatocytes from the accumulation of fat in the liver. Interestingly, recurrence-free survival in patients with HCC in the setting of NASH appear to be significantly better than in the setting of hepatitis C virus (HCV) for both resection and liver transplantation.

**OUTCOMES FOLLOWING LIVER TRANSPLANTATION IN OBESE INDIVIDUALS**

Early reports of liver transplantation in obese recipients demonstrated mixed outcomes perhaps because of small sample sizes. Studies have also included heterogeneous groups of recipients; some focus simply on obese patients (BMI ≥ 30) whereas other studies differentiate between obese patients and morbidly obese patients (BMI ≥ 40). Initial single center reports showed equivalent short term survival rates for obese and severely obese patients with some centers also documenting higher complication rates (especially wound infections) and higher health care costs for transplantation. More recently, there have been several single center and multicenter studies that have focused on pre-operative and long outcomes following liver transplantation.

**Outcomes of Obese Patients: Peri-operative Morbidity and Length of Stay**

Liver transplant recipients have a significant survival advantage as compared to patients that continue on the waiting list regardless of their BMI at the time of transplant. Greater peri-operative morbidity and increased post-operative length of stay appears to be a fairly consistent but not absolute finding in the obese and/or morbidly obese patients in the studies examined (Table 1). In the studies that document a higher morbidity in obese patients, wound related and infectious complications appear to predominate. In one study, obese patients surprisingly did not require prolonged ventilatory support as compared to non-obese patients.

The differences seen in peri-operative morbidity amongst the different studies can potentially be explained by the heterogeneity amongst the obese and morbidly obese patients in that co-morbid conditions were not taken into consideration. Several studies attempted to take into account these co-morbid conditions. One group examined obesity along with the presence of coronary artery disease, and hypertension and calculated patients’ risk of post-operative events. The presence of obesity and diabetes appeared to be the strongest predictors of post-operative events. The presence of cardiovascular risk factors however did not alter the peri-operative risk. Similarly, Nair et al. examined the combination of several pre-operative risk factors that included obesity and diabetes to create a risk score and tested its ability to predict post-operative outcomes. Compared to the prior study, they found no difference in pre-operative morbidity and length of stay between the low risk and high-risk groups. Neither study found that these conditions affected short-term survival.

Cardiovascular events are a significant cause of morbidity in the post liver transplant patients, which maybe related to the higher prevalence of risk factors associated with the metabolic syndrome such as hypertension and hyperlipidemia in these patients. A similar small study also found an increased risk of cardiovascular events in post liver transplant patients although this did not seem to correlate with obesity as the normal weight cohort had a similar rate of cardiovascular events. A more recent, larger study using the OPTN database attempted to identify predictors of early cardiovascular events. A total of 1576 deaths in the first 30 d post transplant were identified out of 54697 liver transplant recipients of which 42.1% were secondary to cardiovascular events. Surprising, obesity and complications of the metabolic syndrome were not found to be independent predictors of early cardiovascular mortality. Several other recipient factors were found to be significant predictors including pre-operative hospitalization, intensive care unit and ventilator status, and the presence of portal vein thrombosis. Interestingly, Ayala et al. also found that obesity was a risk factor for pre-transplant portal vein thrombosis.
Long-term outcomes

The long-term outcomes of patients with obesity and morbid obesity have yet to be fully determined. One would assume that persistence of obesity and the metabolic syndrome post transplant would clearly put these patients at higher risk for developing serious cardiovascular disease including myocardial infarction and stroke. In 2002, Nair et al. published a review of the UNOS database from 1988 to 1996 comparing outcomes following liver transplant for patients that were obese, severely obese, and morbidly obese. A total of 18172 patients were examined and the authors found an increased risk of primary non-function and an increased risk of mortality at 30 d, 1 year, 2 years, and 5 years in the morbidly obese group. The severely obese group also had an increased risk of mortality at 5 years. All obese patients (BMI > 30) had an increased risk of death from cardiovascular events. This led to the recommendation by the American Association for the Study of Liver Disease that morbid obesity was a contraindication to liver transplant. Similarly, in 2003, Rustgi et al. published their analysis of the UNOS database from 1992 to 2000 examining a total of 26920 patients. In this study, patients with BMI ≥ 35 were found to be at increased risk of post-transplant death.

Conversely, a more recent publication examining the SRTR database from 2004 to 2011 identified 38194 recipients of which 8196 were considered obese. Unlike the review by Nair et al., they found no risk of increase mortality across the different categories of obese patients as compared to the control group. In fact, the authors found a protective affect of overweight male recipients but not female recipients with BMIs ranging between 25 and 35. Another center also recently examined a very similar cohort of patients (SRTR database from 2007-2011) and also confirmed no difference in short-term outcomes. They, however, noted increased resource utilization by patient with BMIs ≥ 40 with more patients disabled in the pre-operative setting and longer post-operative hospital stays.

Several single center studies have also documented long term outcomes. One of the largest series examined 1325 patients from Leeds, United Kingdom and the authors report no significant difference in graft and patient survival up to 10 years post transplant. Another large single center study found an increased rate of the metabolic syndrome in their post transplant patients with BMIs ≥ 38; however, this did not correlate with poor 3 years outcomes. A smaller study from Ireland also found no difference in long-term survival between their obese patients and non-obese patients. Conversely, a study that examined outcomes over an extended period of time, dividing patients into different eras, found a consistent improvement in outcomes over time. However, in all eras, survival of the morbidly obese patients was worse, and morbid obesity was an independent predictor of death. Interestingly, the risk of morbid obesity appeared to be exacerbated in the MELD era in this study with the poorest long-term survival seen in morbidly obese patients with MELD 22. A Danish group also had similar poor outcomes for their obese group. Another single center study which examined long term outcomes (≥ 5 years) noticed a significant decline in both graft and patient survival at 5 years despite similar outcomes at 3 years.

Studies that do demonstrate poor long-term out-
comes associated with obesity have been criticized by the fact that they do not take into account malnutrition, low albumin levels and ascites. In one study, conventional BMI appears to be able to be mitigated by conversion to modified BMI that takes into account low albumin levels and fluid accumulation. When converted to a modified BMI (calculated by multiplying the serum albumin by the BMI), there was no difference in long-term survival of the different groups\[59,68\]. Similarly, Leonard et al\[64\] found that when correcting BMI for ascites, up to 20% of patients moved to a lower BMI category. Furthermore, the corrected BMI was not a predictor of poor long-term outcomes.

The inconsistency in results reported from different centers would suggest that patient selection plays a critical role in the outcomes of obese patients after transplant. The more recent trend in better outcomes may reflect better patient selection and improved care in the more recent era. However, more long-term data looking at 5 years and beyond are needed in order to adequately characterize the long-term risk to obese and morbidly obese patients.

**Recurrent disease in obese patients following liver transplantation**

The risk of recurrent NAFLD in post transplant patients has been documented and ranges between 25%–60%\[55-58\]. In one study, 39% of recipients transplanted for NAFLD had either recurrent NAFLD or NASH with the strongest independent predictors of recurrence being high pre transplant and post transplant BMIs. The presence of recurrent disease, however, did not appear to affect overall survival at least in the short term\[56\]. Similarly, patients transplanted for cryptogenic cirrhosis (of which several of the patients were believed to have NASH) have also been shown to develop NAFLD or NASH in the post transplant setting\[59\]. A more recent study examined the prevalence of post liver transplant NAFLD in patients transplanted for non-NAFLD related liver disease and found steatosis in 40% of patients\[60\]. BMI pre- and post-transplant appeared to correlate with the risk of developing post transplant steatohepatitis. Commonly used immunosuppressive medications such as steroids and calcineurin inhibitors could be potential factors contributing to insulin resistance/hyperglycemia, hyperlipidemia, and hypertension. In fact, exposure to a high total dosage of glucocorticoids has been associated with the development of NASH\[61\].

The association between chronic HCV infection and post transplant diabetes is well known. HCV appears to be partially responsible for inducing insulin resistance and diabetes mellitus. Unfortunately, the presence of diabetes mellitus portends a bad outcome with patients suffering from an accelerated progression to fibrosis leading to poor graft and patient survival\[62\].

Obesity also appears to affect recurrence of HCC. In a study by Mathur et al\[63\], the authors demonstrate a doubling in recurrence rates of HCC in both overweight and obese patients as compared to a lean group of patients following liver transplant. Similarly, patients with a BMI > 25 had more accelerated time to recurrence.

**SPECIAL CIRCUMSTANCES**

**Bariatric surgery prior to liver transplantation: Lessons learned from the jejuno-ileal bypass surgery**

There is no question that a prior history of upper abdominal surgery can increase the risk of peri-operative complications at the time of liver transplant. Abdominal scarring and adhesions can increase the complexity of the initial hepatectomy. In addition, vascularization of these adhesions from portal hypertension can result in greater blood loss. Many morbidly obese patients have attempted weight loss surgery prior to transplantation which puts the remnant stomach at risk for devascularization and luminal perforations.

The jejunoileal bypass (JIB) was a bariatric procedure that was performed with high frequency in the 1960 and 1970s. This weight loss procedure consisted of dividing and anastomosing the first 35 centimeters of proximal jejunum to the terminal 10 centimeters of ileum in an end-to-side or end-to-end fashion\[64\]. Although this procedure was effective in causing malabsorption and weight loss, it also carried the complication of chronic liver disease and in some cases acute liver failure\[65\].

There have been several reports that have documented the feasibility of performing liver transplants in patients who had previously undergone a JIB. Although the reports were small series, they documented that transplant was feasible with reasonable patient outcomes. In all cases, reversal of the bypass appears to be critical for the prevention of recurrent disease in most patients\[56,66-67\]. More recently, there have been several reports of patients requiring transplant after a biliopancreatic diversion (Scopinaro procedure or duodenal switch) from massive steatosis and sub-fulminant hepatic failure\[66,69\].

A recent survey of transplant centers in Belgium identified patients that had undergone liver transplant after bariatric surgery. They identified 10 patients listed for liver transplantation with a mean time to wait listing post bariatric surgery of 5 years. The majority of the patients (9 of 10) had undergone biliopancreatic diversion. Of the 10 patients, 7 were transplanted, 2 died waiting for transplant, and one was still waiting at the time of publication. Of the 7 patients transplanted, 4 patients were still alive. One of the 4 patients required retransplantation at 10 mo due to rapid recurrence of liver disease. Although, liver transplantation can salvage patients with post bariatric surgery liver failure, outcomes appear to be poor and bariatric patients should be monitored closely for liver dysfunction following surgery\[69\].

**Bariatric surgery in conjunction with or after liver transplantation**

An attempt at bariatric surgery is appropriate for patients with early stage liver disease\[71\], but is never indicated in patients with advanced stage liver disease or cirrhosis. For many of these patients, continued long-
term obesity post transplant will undoubtedly increase patients’ risk for long term complications associated with the metabolic syndrome. The risk obesity poses to the recurrence of NASH and HCV are also now coming to light. For many post-transplant patients, diet and exercise is rarely enough to incur significant, sustainable weight loss. Bariatric surgery has taken on many different forms (e.g., gastric bypass, sleeve gastrectomy, gastric band) all of which have varying rates of technical complexity, associated complications, and effectiveness in terms of weight loss.

Several groups have documented the safety of performing bariatric surgery on post liver transplant patients either in small studies or case reports. An initial report by Duchini et al[73] documented that roux-en-Y gastric bypass (RYGB) could be safely performed in post liver transplant patients. This study was further supported by larger studies by Al-Nowaylati et al[73] and Tichansky et al[74]. Although RYGB was effective in inducing weight loss, this did not come without risk. Complications post bariatric surgery included dumping, wound infections, and in one severe case, multi-system organ failure and death. One patient required reversal due to intractable malnutrition and gastrojejunal ulcers. Other groups have also shown that a sleeve gastrectomy can be performed safely and is effective in inducing weight loss in the post liver transplant patient[75,76].

Due to the increased technical complexity secondary to adhesions and complications related to long-term immunosuppression, some groups have attempted bariatric surgery at the time of transplant. In an initial report, Campsen et al[77] reported safely performing a gastric band in patients immediately after the new liver was transplanted. In a similar approach, Heimbach et al[78] from the Mayo Clinic reported their initial experience with performing the gastric sleeve at the time of liver transplant. This was chosen over the gastric band due to increased efficacy in inducing weight loss and the fact that there was no need for a foreign body in an immunosuppressed patient. In their initial report of 7 patients that underwent a combined liver transplant-sleeve gastrectomy, all patient attained weight loss and none developed post liver transplant diabetes or hepatic steatosis. However, one patient did have excessive weight loss and one patient leaked from the gastric staple line. There were no graft failures or deaths in the combined groups.

Living donor liver transplantation
Adult-to-adult living donor liver transplantation (LDLT) has been shown to have outcomes equivalent to deceased donor liver transplantation especially in regions where organ donation is scarce. Death on the waiting list which can be as high as 20% at some United States centers. It is well documented that there is a significant survival advantage to patients transplanted with living donors as compared to those patients that wait on the deceased donor list when compared from time of listing by preventing[79]. In other parts of the world where deceased donation is non-existent, LDLT is the only option for patients with ESLD. Appropriate size matching of the liver graft from the living donor with the recipient is essential for success with most programs using a cutoff graft weight to recipient weight ratio (GRWR) of 0.8. Successful LDLT has been performed with lower GRWR[80] and there is a resurgence of left lobe grafts in the Western world[81].

Appropriate matching of donors with obese recipients can be especially challenging in the setting of LDLT especially when using the common cutoff of 0.8 for the GRWR. Whether this ratio is appropriate in the setting of obesity has yet to be determined. There are no studies that examine the morbidly obese population, and studies examining LDLT in the setting of obesity are scarce. The largest study by Gunay et al[82] examined 380 patients who underwent LDLT of which 74 were considered obese (BMI ≥ 30). No patients were morbidly obese (BMI > 40). Although the obese patients had a harder time finding suitable living donors, the complication rate, graft survival, and patient survival were all similar when comparing the obese recipients to either the overweight or normal weight recipients[82]. A smaller study of 7 patients with NASH of which 6 of the patients were obese also demonstrated that LDLT was feasible, but again these patients appeared to have a more difficult time identifying suitable donors[83]. Further studies are needed to address long-term outcomes of LDLT and also to further investigate the applicability of a GRWR of ≤ 0.8 in the setting of morbid obesity.

OUR EXPERIENCE WITH MORBID OBESITY AND LIVER TRANSPLANTATION AT OCHSNER MEDICAL CENTER

Over the last few years, Ochsner medical center has grown to become one of the largest liver transplant programs in the United States performing 196 liver transplants in 2014. Due to its geographic location in the South Eastern corridor of the United States, the program has a vast experience with liver transplantation of the morbidly obese patient. In our experience, it is important to make sure that the morbidly obese patients are properly cleared from a cardiopulmonary perspective as many of them can have occult coronary disease and/or pulmonary hypertension. From a technical perspective, line placement and exposure during transplant can be challenging and we have moved to using a Thompson retractor with special bariatric blades to aid in exposure.

A chart review of primary liver or combined liver-kidney transplants was performed between September 2005 and December 2008 of which 255 adult transplants were identified. A comparison of morbidly obese patients (n = 34) vs a control group (n = 221) of non-morbidly obese patients was performed and several characteristics including 30 d and 1 year graft and patient survival, length of stay, and 30 d re-operation rate were recorded. Based on our data, morbidly obese patients had longer...
CONCLUSION

There are multiple indications for liver transplantation in the obese patient, but NAFLD is the most common. Obese patients appear to be at higher risk for perioperative complications and length of stay post-transplant is longer which potentially can increase the global healthcare cost to managing these patients. However, this does not appear to impact both short and long term outcomes following transplant. The impact of obesity and the metabolic syndrome on long-term outcomes remains to be determined but these patients are at risk for recurrent steatohepatitis. Weight reduction post transplant is likely to be effective in avoiding complications of post transplant diabetes and steatosis. Weight loss surgery appears to be advantageous at the time of transplant since it avoids the need for an additional surgery and also avoids the potential for increased complications due to abdominal scarring and long-term immunosuppression. Appropriate patient selection is critical for minimizing complications and obtaining optimal short and long-term outcomes.

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