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FATTY LIVER DISEASE (Z YOUNOSSI, SECTION EDITOR)

Surgical Issues in NASH: Bariatric Surgery and Liver Transplantation

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Abstract

Purpose of Review The rising prevalence of obesity in general and non-alcoholic steatohepatitis (NASH) specifically as an indication for liver transplantation has occurred in parallel with an increase in the consideration and performance of bariatric surgery before and after liver transplantation. We review the impact and relative merits of bariatric surgery before, during, and after liver transplantation.

Recent Findings The sleeve gastrectomy approach has several practical advantages over other forms of weight loss surgery and has been shown to improve metabolic parameters. Bariatric surgical procedures inevitably affect immunosuppression pharmacokinetics, with the least impact being observed following sleeve gastrectomy. In the non-transplant setting, bariatric surgery has been shown to be an effective therapy for histological features of NASH.

Summary When compared to lifestyle changes alone, bariatric surgery performed during or after liver transplantation results in sustained weight loss and improved metabolic parameters associated with liver disease, cardiovascular risk, and overall mortality. Further studies are needed to confirm which surgical procedures, timing, and NASH patients will receive most benefit.

Keywords NASH · Bariatric surgery · Histology · Liver transplantation

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the USA with an estimated prevalence of 30% [1]. It encompasses a spectrum of diseases ranging from simple hepatic steatosis to steatosis with hepatocyte inflammation and ballooning (non-alcoholic steatohepatitis or NASH). The incidence of NAFLD has increased by a factor of 5 since 1997, with the most exponential increase in younger adults aged 18–39 years old [2]. Up to 30% of patients with NAFLD will eventually develop NASH, with 15–25% of NASH patients developing advanced cirrhosis [3]. Untreated, NASH may lead to advanced fibrosis and cirrhosis and ultimately hepatic complications including portal hypertension, hepatocellular cancer (HCC), and the need for liver transplantation [4–6].

Obesity is the most common risk factor for NAFLD with up to 75% of patients that are overweight and 90–95% of patients with morbid obesity affected by NAFLD [7, 8]. Additionally, there is a high prevalence of NAFLD in patients with type 2 diabetes mellitus (T2DM), with some studies citing up to 33–66% with T2DM having concomitant NAFLD [9, 10]. T2DM and obesity are the two most important risk factors for the development of advanced fibrosis and cirrhosis in patients with NAFLD [11]. Additionally, the severity of fibrosis progression is related to the degree of insulin resistance, T2DM, and central obesity with 5–20% fibrosis progression in 10 years [12, 13].

Metabolic syndrome (that includes three of the following: hypertension, insulin resistance, central obesity, elevated serum triglycerides (TG), and low high-density lipoprotein (HDL) cholesterol) [14] is also a risk factor for NAFLD, with prevalence rates ranging from 36 to 63% [15–17].

The presence of metabolic syndrome also increases the risk of severe fibrosis by an odds ratio of 3.5 (95% confidence interval (CI) 1.1–11.2) [18]. Some conditions also have emerging associations with NAFLD and include hypothyroidism, obstructive sleep apnea, hypopituitarism, and hypogonadism [19].

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Patients with NAFLD are at risk for both liver- and non-liver-related events. One study that prospectively studied 458 NAFLD patients with F3 and F4 fibrosis found that those with F3 fibrosis had an increased risk of major vascular events and non-hepatic malignancies (9 and 10% respectively) while those with F4 cirrhosis were at increased risk of hepatic decompensation and the development of HCC [20]. NAFLD is an independent risk factor for death with increasing mortality with increased metabolic comorbidities and associated with cardiovascular events, especially in those without metabolic comorbidities [2]. Additionally, it has been associated with the development of chronic kidney disease and even increased risk of colon cancers [21, 22].

Given the increase in obesity and NAFLD, there has been a significant increase in liver transplantation (LT) for NASH since 2001 from 1.2 to 9.7% in 2009. By 2025, it is expected that 25 million Americans will be diagnosed with NASH with 20% progressing to cirrhosis making NASH the leading new indication for LT, surpassing hepatitis C (which is highly treatable now with effective direct-acting antiviral therapies) [23, 24]. However, given the comorbidities associated with NAFLD as discussed, unique challenges arise in the management of these patients pre-, peri-, and post-LT. Additionally, some of these patients may benefit from bariatric surgical procedures at the time of LT.

Although multiple medical therapies are in clinical trial development for the treatment of NASH and NAFLD, currently, there are no FDA-approved drug therapies for the treatment of NAFLD and NASH. Diet, exercise, and risk factor modification remain the cornerstone of treatment. There have been studies that have shown that weight loss of at least 3–5% of body weight can improve steatosis with 7–10% body weight reduction needed to reverse steatohepatitis and fibrosis [25, 26•]. However, long-term sustained weight loss is difficult to achieve in clinical practice, with only about 3–6% of subjects achieving this goal [27, 28]. Additionally, preliminary data also do suggest that aggressive risk factor modification may have an added benefit to the treatment of NAFLD [29–31]. Any intervention done to treat NAFLD should also improve comorbid risk factors, especially truncal obesity and insulin resistance [13].

Because sustained weight loss with diet and exercise alone is often difficult to achieve, many have turned to bariatric surgery as an option. We will review the current literature on the various types of bariatric surgery and its long-term efficacy and also discuss the emerging role of bariatric endoscopy in the treatment of NAFLD. In addition, we will review the role of LT in NAFLD and its unique challenges that need to be addressed in the care of these patients.

Bariatric Surgery

Although weight loss through hypocaloric diet and exercise can reverse the hepatic changes seen in NAFLD and NASH including early-stage fibrosis [26•], sustained weight loss is difficult to achieve through diet and exercise alone [32]. Because of this, bariatric surgery has emerged as an option that is increasingly utilized over the last several decades with achieved weight loss to be three times greater than that seen with behavior modification or pharmaceutical therapy over a 10-year period [33]. Introduced first in the 1950s, surgical techniques, volumes, and outcomes have evolved and improved since this time. Indications for bariatric surgery according to the National Institutes of Health include a BMI greater than 40 kg/m^2 or in those with a BMI greater than 35 kg/m^2 with other high-risk comorbidities including diabetes, hyperlipidemia, OSA, and cardiovascular disease [34].

The hypothesis surrounding the mechanism in which bariatric surgery induces weight loss is evolving. Previously, surgery was thought to be related to either a restrictive or malabsorptive process [35]. Restrictive surgeries reduce stomach size and consequently limit meal size and caloric intake and adjustable gastric banding (AGB) and vertical sleeve gastrectomy (SG). Malabsorptive surgery involves rearranging intestinal anatomy and bypassing variable intestinal lengths to minimize the absorptive surface, for example, jejunoileal bypass representing the most extreme form of malabsorptive surgery (and is no longer performed given its significant morbidity and mortality from severe weight loss, electrolyte disturbances, and rarely hepatic failure) [13]. Combinations of restrictive and malabsorptive procedures include Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BDP). However, increasingly, it is thought that bariatric surgery induces physiological changes in gut peptide levels (increases in gut peptides such as GLP-1, PYY, CCK, and amylin, and decrease in ghrelin in the case for RYGB) and circulating bile acids [35]. Surgery also changes intestinal morphology and the microbiome and alters gastrointestinal signals to the brain and other tissue (such as the pancreas and liver) from a metabolic and neuronal perspective that results in weight loss [35].

Currently, RYGB and SG are the two most commonly performed surgeries in the USA, with SG rates on the rise since 2011 (18% in 2011 to 59% in 2017) [36]. In RYGB, suturing of the proximal stomach creates a small gastric pouch and connects to the mid-jejunum. The remaining distal stomach and proximal intestine remain but are bypassed without a digestive or nutritional role [35]. In SG, the stomach is resected along the greater curvature with about 80% being removed but with unchanged intestinal anatomy. Weight loss and resolution of metabolic parameters with SG and RYGB appear comparable [37].

Other surgical techniques include AGB where a 30-cc gastric pouch is created by placing a band around the upper stomach just below the gastroesophageal junction. A subcutaneous port linked to the band allows for the injection of saline, thereby modifying the degree of gastric constriction [38]. Given that the AGB is minimally invasive and allows for adjustability after surgery makes the gastric band an attractive option for some.

However, its use has sharply declined from 35% in 2011 to 2.8% in 2017 because it produces less weight loss than other bariatric procedures with higher reoperation rates than RYGB [36, 37]. BPD with duodenal switch entails a SG with similar intestinal routing as in RYGP but the intestinal limb is bypassed to a greater extent with creation of an ileoduodenostomy [13]. Although this procedure produces more weight loss than RYGB, it also causes greater macro- and micronutrient deficiencies and can often lead to malnutrition and currently accounts for less than 1% of current bariatric procedures [36].

Effects of Bariatric Surgery on Mortality, Cardiovascular Disease, and Malignancy

There are established short- and long-term benefits in patients with medically complicated obesity who undergo bariatric surgery with durability of weight loss and remission and prevention in comorbid disease, including T2DM, hypertension, dyslipidemia, cardiovascular disease, and malignancy risk even up to 12 years post-surgery [33, 39, 40, 41••, 42–44]. The effects of bariatric surgery in the non-transplant setting are well established. In the Swedish Obese Subjects (SOS) study, patients that underwent bariatric surgery achieved greater maximal weight loss in 1–2 years post-surgery with the greatest loss of 32% achieved in those undergoing RYGB with sustained weight loss after 10 years [33]. Additionally, overall mortality was decreased in those undergoing weight loss surgery with the 0.71 hazard ratio (HR, $p = 0.01$) after adjusting for sex, age, and other risk factors with myocardial infarction and cancer being the most common causes of death [33]. Bariatric surgery also reduced the number of cardiovascular deaths in addition to the total first-time cardiovascular events (including myocardial infarction or stroke) [40].

Cancer incidence after bariatric surgery has also been found to be lower compared to matched controls. In a study looking at 6781 morbidly obese patients matched for age and sex, patients who underwent bariatric surgery had a 76% decrease in overall cancer incidence, especially that of breast cancer (reduced by 82%) [45]. Similar studies have reported decreases in overall cancer mortality of 60% at 7 years and 46% at 12.5 years and a 24% decrease in overall cancer incidence [46]. This effect is especially seen in females with hormone-related tumors [47]. These effects of bariatric surgery on cardiovascular and cancer mortality are especially important given that patients with NAFLD are at greatest risk of death from these causes.

Effects of Bariatric Surgery on NAFLD and NASH

In addition to improved mortality and cardiovascular risk, bariatric surgery also provides promising changes in those with NAFLD and NASH [13]. The decrease in adiposity seen after bariatric surgery is important given that adiposity is associated with insulin resistance, which in turn is associated with hepatic steatosis [48]. About 25% of patients undergoing bariatric surgery have NASH with incident cirrhosis found in about 1–2% of patients [13]. The initial experiences of bariatric surgery resulting in large amounts of weight loss with jejunoileal bypass, BPD, and RYGB with extended Roux limbs resulted in severe hepatic dysfunction with steatohepatitis and cholestasis, and even deadly hepatic failure [13, 49, 50]. Since that time, however, outcomes have improved.

Earlier smaller studies in patients undergoing AGB [51–53] and RYGB [54–58] showed promising effects on NAFLD and metabolic parameter improvements. A 2015 meta-analysis looked at the effects of bariatric surgery on several NAFLD histological features and found improvement in steatosis (50.2%), fibrosis (11.9%), ballooning (67.7%), and lobular inflammation (50.7%) in 16 studies in addition to liver enzymes including ALT, AST, alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) [59].

A study conducted from 1994 through 2013 in France prospectively studied 109 morbidly obese patients undergoing bariatric surgery [60••]. Sixty-four percent underwent gastric bypass, 30% underwent gastric bands, 5.5% underwent sleeve gastrectomies, and 1 patient (0.9%) underwent biliointestinal bypass. NASH resolved in 85% of patients (95% CI 76–92%) with improvements in BMI, ALT, GGT, and insulin resistance index values at 1 year. Notably, compared to previous studies, fibrosis also decreased in 34% of patients (95% CI 24–45%). Those undergoing gastric banding had less weight loss and more persistent NASH than those undergoing RYGB (BMI change 6.4 vs 14.0; persistent NASH 30.4 vs 7.6% respectively).

One of the largest prospective studies linking clinical data with liver biopsy at the time of bariatric surgery with 5-year follow-up looked at 381 adult patients with severe obesity [61]. The majority of patients underwent gastric band (56%) with 23% and 21% having biliointestinal bypass and RYGB respectively [61]. Twenty-nine percent of patients had severe steatosis with only 4.1% with advanced fibrosis (F3–F4) at index biopsy. At 5 years following surgery, there were significant decreases in steatosis (37 to 16%), the NAFLD fibrosis score (1.97 to 1), ballooning (0.2 to 0.1), and percentage of patients with probable or definite NASH (27 to 15%) with parallel improvements in insulin resistance [61]. Severe insulin resistance was also most closely associated with persistent steatosis and ballooning. However, there was also a small but statistically significant increase in mean fibrosis score at 5 years, from 0.27 ± 0.55 to 0.36 ± 0.59, $p = 0.001$. Ninety percent of patients with fibrosis worsening increased from F0 to F1. The clinical significance of this finding is unclear given that 5 years only 0.5% had bridging fibrosis (F3) with 96% of patients with F1. Worsening fibrosis after RYGB has been reported in 2 other studies in 2 patients, with both developing perisinusoidal fibrosis [62, 63].

SG is now the most commonly used bariatric surgical procedure, but there are limited data on its effects on NAFLD. A retrospective review looking at 236 patients undergoing SG found overall improved weight loss with decreases in BMI from 45 to 29.7 at 1 year and 31.6 at 3 years. Using liver tests as a surrogate marker for NASH in 87 patients, the study found improvements in AST, ALT, triglyceride levels, and HDL levels at 6 and 12 month follow-ups [64]. Another smaller study compared 14 RYGB and 9 SG and found similar weight loss with both; however, all aspects of the NAFLD activity score improved significantly after RYGB but only steatosis and total score improved after SG [65]. Although fibrosis improved in both groups, greater effects were seen in RYGB.

The BariScan in Germany looked at the effects of SG (n = 59) and RYGB (n = 41) on NAFLD between 2012 and 2015 [66••]. However, liver biopsy was not done in this study and instead NAFLD was assessed using laboratory-based fibrosis scores and transient elastography. Significant improvements were seen across all liver fibrosis scores with improvements in liver stiffness (12.9 ± 10.4 vs 7.1 ± 3.7 kPa, $p < 0.001$) at median follow-up of 12.5 months. Similar to the previous study [65], RYGB showed greater fibrosis improvements than SG after adjusting for baseline liver stiffness.

Bariatric Surgery in Patients with NAFLD Cirrhosis

Few studies have examined reported bariatric surgery outcomes in patients with NAFLD cirrhosis. A 2015 meta-analysis found 122 patients in 11 studies with cirrhosis undergoing bariatric surgery, including BPD (n = 15, 12%), RYGB (n = 51, 42%), SG (n = 41, 34%), and AGB (n = 15, 12%) [67]. All patients had compensated cirrhosis and only 7 (n = 6%) had portal hypertension. The analysis found an overall complication rate of 21% with a 6.5% risk of liver decompensation. The early surgery-related mortality rate was 1.6% and the late surgery-related mortality rate was 2.45% and found only in those undergoing BPD (n = 3/15, 20%) and RYGB (3.9%, n = 2/51) but not in those undergoing VSG or AGB.

A larger study not included in the previous meta-analysis looking at inhospital mortality for patients undergoing surgery between 1998 and 2007 in the USA and found patients with compensated (n = 3888) or decompensated cirrhosis (n = 62) had significant higher mortality rates than those without cirrhosis (n = 670,950; 0.9% and 16.3% vs 0.3%, p = 0.002) with an adjusted odds ratio of mortality of 2.17 (95% CI 1.03–4.55) for compensated patients and 21.2 (95% 5.39–82.9) for decompensated cirrhosis compared to non-cirrhotics [68]. Mortality improved with increasing surgical volumes (> 100 surgeries/year).

This evidence shows that although bariatric surgery can be a safe option in patients with compensated cirrhosis, the risks and benefits of the surgery, type of surgical procedure, and patient selection are of paramount importance [32]. Additionally, pre-operative biopsies may be necessary in those at risk for NAFLD and advanced fibrosis, especially given that normal liver function tests such as ALT may not reliably exclude those with NASH [69].

Given the overall markedly positive evidence, the most recent AASLD guidelines on NAFLD management recommend that although it is premature to consider foregut bariatric surgery a specific option for the treatment of NASH, it can be considered in otherwise eligible obese patients with NAFLD and NASH [32]. NASH alone is currently not an indication for bariatric surgery based on NIH criteria [34] but it may be possible that this will change in the future given the histological and metabolic reversal seen. The optimal surgical procedure remains unclear. Additionally, hepatic function should be closely monitored following surgery given the potential, albeit small risk, for worsening fibrosis [70].

The Emerging Role of Bariatric Endoscopy

Over the past decade, bariatric endoscopy is emerging as a potential treatment option for obesity. Bariatric endoscopy can be used as the initial weight loss before bariatric surgery, as primary treatment for obesity or diabetes, or as a bridge to other interventions such as orthopedic surgery or even LT [71, 72]. Endoscopic therapies may also offer added advantages of reversibility, repeatability, and cost-effectiveness over bariatric surgery but these have to be balanced to the amount of weight loss and procedure durability [72, 73]. Most endoscopic therapies are indicated for patients with a BMI between 30 and 40 kg/m^2 who have failed lifestyle or pharmacological interventions or who do not want to undergo bariatric surgical procedures [72].

Intragastric balloons (IGBs) have been found to be effective at total body weight loss with percent loss ranging from 6.8 to 14% at 6 months [72]. A single-blinded randomized controlled pilot study examined IGBs in 18 patients with NASH who were randomized either to sham or to real IGB placement for 6 months [74]. The IGB group had significantly decreased BMI and NAFLD activity score compared to the sham-treated group. There were no significant differences in median steatosis, inflammation, ballooning, or fibrosis in both groups. Additionally, a recent systematic review of 10 studies with 504 patients found ALT, GGT, and BMI all decreased with IGB therapy (− 10.02 U/l, − 9.82 U/l, and 4.98 kg/m^2 respectively) [75]. There were also improvements in hepatic steatosis from baseline after 6 months as measured by magnetic resonance imaging fat fraction with lower NAS. Although preliminary results are promising, there has been recent question of their long-term safety data as the FDA has reported 12 deaths occurring (7 in the USA) in patients with liquid-filled intragastric balloon systems since 2016 [76]. Further trials regarding the safety and efficacy of IGBs are needed in this area to recommend IGBs for the treatment of NAFLD.

Endoscopic sleeve gastroplasty (ESG) decreases the size of the gastric cavity to facilitate weight loss. In a study of 248 patients with baseline BMI 37.8 kg/m^2, ESG was found to achieve weight loss of up to 2 years [77] and also delay gastric emptying, improve insulin resistance, and induce early satiation [78]. Although not specifically looked at for the treatment of NAFLD, 91 patients undergoing ESG from 2013 to 2016 lost 14.4%, 17.6%, and 20.9% of their total body weight at 6, 12, and 24 months respectively with only one adverse event of a perigastric leak [79]. Additionally, at 1 year, there were significant reductions in ALT and metabolic parameters including HgA1c, blood pressure, waist circumference, and serum triglycerides. Given these promising results, future prospective studies looking at the role of ESG in the treatment of NAFLD are warranted.

Liver Transplantation and NAFLD

LT secondary to NASH has become the second most common indication for liver transplant in the USA in 2013 and will likely surpass hepatitis C in the coming years as the leading indication for transplant [23, 80, 81•]. Patients with NASH, however, have risk factors for poor post-operative outcomes including T2DM, obesity, cardiovascular disease, and chronic kidney disease [82]. In addition, NASH patients were significantly older with higher BMIs and lower GFRs [81•]. They also had lower MELD scores and were less likely to undergo LT with decreased 90-day survival on the waitlist as compared to patients with hepatitis C or alcoholic liver disease [81•]. A recent meta-analysis of 9 studies on 717 patients with NASH and 3520 patients without undergoing LT found similar 1-, 3-, and 5-year survival rates but also found that patients with NASH had a greater mortality from cardiovascular complications (OR 1.65, 95% CI 1.01–2.70, $p = 0.05$) or sepsis (OR 1.71; 95% CI, 1.17–2.50; $p = 0.006$) after transplant [83]. Given these findings and their inherent metabolic profile, there are many considerations that arise in patients with NASH that undergo LT in the pre and post setting.

In addition to the effect of NAFLD on LT recipients, the increasing prevalence of NAFLD in the general population also directly impacts the quality and quantity of the donor liver pool available for LT [84]. Graft steatosis can affect graft function (specifically placing recipients at risk for primary graft non-function or delayed graft function) and subsequent outcomes, with more than 30% macrovesicular steatosis being an independent risk factor for impaired 1-year graft survival [85, 86].

NAFLD, Obesity, and Pre-liver Transplantation

Obesity, more commonly found in patients with NAFLD and NASH, brings unique challenges in LT. First, from a surgical perspective, a higher BMI may make the surgery more technically challenging with increased operative times, increased intensive care unit length of stay, and increased infectious and biliary complications [87]. Additionally, a study looking at 161 patients with compensated cirrhosis found that higher BMI increases the risk of clinical decompensation independent of portal pressure and liver function (15% in those with normal BMI, 31% in overweight, 43% in obese patients, $p = 0.011$) [88]. As a result, NASH patients with higher BMI are at increased risk of clinical decompensation with higher MELD scores while awaiting LT [88, 89]. A previous study looking at the UNOS database from 1988 through 1996 concluded that morbidly obese patients had higher risk of primary graft non-function in addition to immediate and 1-, 2-, and 5-year mortality rates (mostly due to cardiovascular events at 5 years) [90]. However, more recent data indicate that when corrected for ascites, higher BMI had no effect on early or late patient and graft survival [91].

Although there is no universal upper limit BMI cutoff that disqualifies patients from LT and such rules are specific to institutions, some weight loss prior to LT is ideal with benefits in the post-LT as well. Additionally, pre- and post-LT weight and BMI have also been found to be the most important predictors of metabolic syndrome following liver transplantation (Fig. 1) [92]. Bariatric surgery at the time or post-LT is increasingly being utilized in patients with NASH. One study looked at the effectiveness of a multidisciplinary protocol for LT patients with a BMI > 35 including intensive lifestyle counseling and combined LT and SG for patients who failed to lose weight prior to LT [93••]. In the 34 patients who achieved adequate weight loss and underwent LT alone, 62% ($n = 21$) gained weight to BMI > 35 in the post-LT period with 35% ($n = 12$) developing T2DM and overall 3 deaths and 3 graft losses. In the 7 patients who underwent combined LT and SG, mean BMI post-LT was 29 and no posttransplant T2DM was observed (Fig. 2) [93••]. One patient developed a gastric leak and 1 had excess weight loss but allograft and patient survival were excellent. A systematic review of 11 studies with 56 patients undergoing LT and bariatric surgery (2 before, 2 simultaneous, and 7 after LT) found that SG (79%) was the most common procedure followed by RYGB (18%) [94]. There were no post-operative deaths within 30 days with a 1-year mortality rate of 5.3%. These early

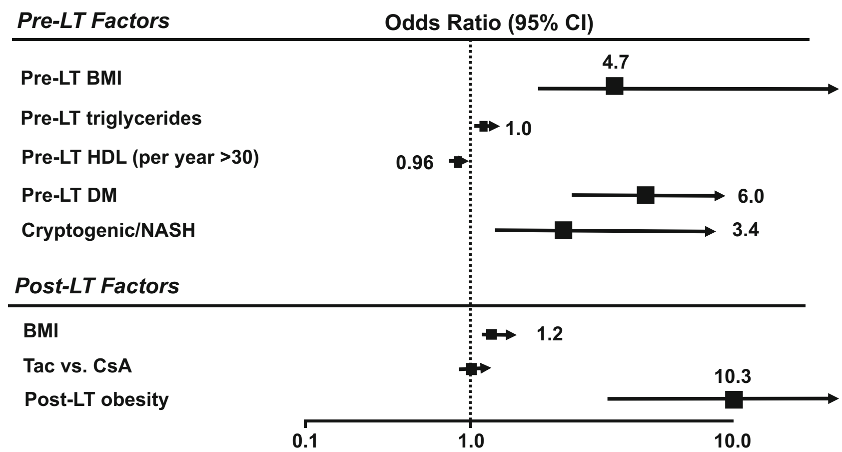

Fig. 1 Predictors of posttransplant metabolic syndrome

results show that SG may be a helpful adjunct to LT in obese patients but future studies are needed to determine optimal timing. There is also likely an evolving role for bariatric endoscopy in this setting.

Bariatric surgery alters drug metabolism and this is important given the need for immunosuppression in the post-LT period. The effects of bariatric surgery on the pharmacokinetics of common immunosuppression agents vary greatly between SG and RYGB. The overall effect of RYGB is of decreased absorption and slower metabolism. Drug exposure, as measured by area under the curve (AUC), is reduced by 40–50% for tacrolimus, mycophenolate, and mTOR inhibitors in RYGB. The relative effects of sleeve gastrectomy vs RYGP are summarized in Table 1 [97].

Another key consideration in the pre-operative LT assessment is cardiovascular risk, given its higher prevalence in patients with NASH [98]. The risk for peri-operative cardiovascular mortality is higher in patients with NASH cirrhosis compared to alcohol (OR 4.12, 95% CI 1.91–8.90) even after controlling for risk factors including age, sex, BMI, smoking, history of CAD, or metabolic syndrome [99]. It is currently unclear whether patients with NASH should be more intensively screened during their LT assessment, especially given that dobutamine stress echocardiography has been shown to have poor predictive value for coronary artery disease in NASH compared to patients with alcohol cirrhosis [100], but careful attention should be paid to identifying cardiovascular disease prior to LT [32].

NAFLD and Post-liver Transplantation

Several studies have shown excellent patient and graft survival outcomes in patients with NASH cirrhosis undergoing LT [23, 83]. Patients with severe obesity (BMI > 35) and pretransplant hemodialysis have worse outcomes with decreased graft and overall survival [24]. In addition to cardiovascular risk previously mentioned, patients with NASH are also at increased risk for renal impairment both pre- and post-LT with one study showing 31% of patients developed stage 3b chronic kidney disease within 2 years compared to 8% of non-NASH patients independent of BMI, T2DM, and tacrolimus levels [101]. Additionally, the frequency of simultaneous liver-kidney transplantation is also disproportionally

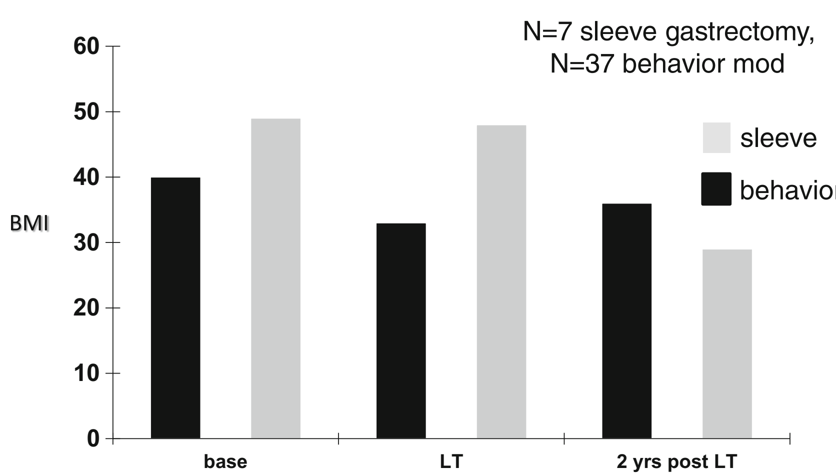

Fig. 2 Impact of simultaneous sleeve gastrectomy

Table 1 Metabolic effects of immunosuppression

Outcome	Corticosteroids	Tacrolimus	Cyclosporine	mTORi
Obesity	+	↔	↔	↓
New-onset DM	+++	+	+	↔
Dyslipidemia	+	+	++	+++
Hypertension	+	++	++	↔

Sources: [95–96]

increasing in NASH cirrhosis compared to other etiologies with poorer outcomes [102].

It is important to remember that the agents for immunosuppression following liver transplantation have very specific and diverse effects on key aspects of the metabolic syndrome (Table 2) that occur independent of weight and BMI [95, 96, 103–105]. These medications also put patients at risk for recurrent NASH in the transplant setting. Bariatric surgery and associated weight loss may not fully negate the effects of immunosuppression on aspects of the metabolic syndrome.

Recurrent NASH in the allograft is common post-LT but likely an uncommon cause of mortality or graft loss given excellent 5-year graft survival [23]. In 257 patients transplanted for either cryptogenic or NASH cirrhosis, 8% developed hepatic steatosis at 1 year with up to 33% at 10 years (compared to 3 and 10% respectively for those transplanted for other indications) [95]. NASH developed in 5% of this cohort but overall survival was not affected. Similar results have been seen in previous studies and found that NASH with progressive fibrosis is rare (5% of LT recipients at 5 years) [103, 105, 106]. This further underscores the importance of maintaining patients on the lowest effective doses of calcineurin inhibitors and rapamycin inhibitors.

Table 2 Impact of gastric sleeve vs Roux-en-Y gastric bypass on immunosuppression pharmacokinetics

- Tacrolimus and mTORis are primarily absorbed in the duodenum
- Intestinal cytochrome P450 is an important component of tacrolimus and mTORi metabolism
- Mycophenolate is absorbed in the stomach
- Cyclosporine is substantially bile salt dependent for absorption
- MMF absorption is decreased by sleeve gastrectomy. Other agents unaffected by this procedure
- Impact of bariatric surgery on immunosuppression pharmacokinetics is highly variable between patients
- AUC is reduced by 40–50% for tac, MMF, and mTORis in RYGB

Source: [97]

Conclusions

The increasing NAFLD prevalence mirrors the global obesity epidemic and presents challenges in the management of these patients. There is an increasing use of bariatric surgery and an evolving role of bariatric endoscopy in patients with NAFLD pre- and post-LT. Such interventions not only aid in sustained weight loss but also improve metabolic parameters associated with liver disease, cardiovascular risk, and overall mortality. Further studies are needed to confirm which surgical procedures, timing, and NASH patients will receive most benefit. Additionally, as NAFLD will become the leading indication for liver transplantation in the USA in the near future, key challenges arise in the management of these patients pre-, peri-, and post-operatively. Optimal evaluation and management of obesity, metabolic parameters, cardiovascular risk, and chronic kidney disease remain challenges with continued need for refinement.

Compliance with Ethical Standards

Conflict of Interest Michael Charlton and Sonali Paul each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the united states: impact of ethnicity. Hepatology (Baltimore, Md). 2004;40:1387–95.
2. Allen AM, Therneau TM, Larson JJ, Coward A, Somers VK, Kamath PS. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. Hepatology (Baltimore, Md). 2018;67:1726–36.
3. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology (Baltimore, Md). 2010;52:79–104.
4. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology (Baltimore, Md). 2006;43:S99–S112.
5. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology (Baltimore, Md). 2010;51:1972–8.
6. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology (Baltimore, Md). 2010;51:1820–32.

7. Neuschwander-Tetri B. Fatty liver and nonalcoholic steatohepatitis. In: Friedman LSKE, editor. Handbook of liver disease. 3rd ed. Amsterdam: Elsevier Health Sciences; 2012. p. 106–14.
8. Sasaki A, Nitta H, Otsuka K, Umemura A, Baba S, Obuchi T, et al. Bariatric surgery and non-alcoholic fatty liver disease: current and potential future treatments. Front Endocrinol. 2014;5:164.
9. Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int. 2009;29:113–9.
10. Prashanth M, Ganesh HK, Vima MV, John M, Bandgar T, Joshi SR, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. J Assoc Physicians India. 2009;57:205–10.
11. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology (Baltimore, Md). 2002;35:367–72.
12. Fassio E, Alvarez E, Dominguez N, Landeira G, Longo C. Natural history of nonalcoholic steatohepatitis: a longitudinal study of repeat liver biopsies. Hepatology (Baltimore, Md). 2004;40:820–6.
13. Pillai AA, Rinella ME. Non-alcoholic fatty liver disease: is bariatric surgery the answer? Clin Liver Dis. 2009;13:689–710.
14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. Crit Pathw Cardiol. 2005;4:198–203.
15. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care. 2007;30:1212–8.
16. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. Dig Dis (Basel, Switzerland). 2010;28:155–61.
17. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology (Baltimore, Md). 2016;64:73–84.
18. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology (Baltimore, Md). 2003;37:917–23.
19. VanWagner LB, Rinella ME. Extrahepatic manifestations of non-alcoholic fatty liver disease. Curr Hepatol Rep. 2016;15:75–85.
20. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease. Gastroenterology. 2018;155:443–57.
21. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66:1138–53.
22. Yang YJ, Bang CS, Shin SP, Baik GH. Clinical impact of non-alcoholic fatty liver disease on the occurrence of colorectal neoplasm: propensity score matching analysis. PLoS One. 2017;12:e0182014.
23. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011;141:1249–53.
24. Agopian VG, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, et al. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. Ann Surg. 2012;256:624–33.
25. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia. 2012;55:885–904.
26.• Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;149:367–378 e365 quiz e314–365. **One of several reports showing that weight loss improves features of nonalcoholic fatty liver disease.**
27. Glass LM, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, et al. Total body weight loss of >/= 10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. Dig Dis Sci. 2015;60:1024–30.
28. Kleiner DE, Makhlouf HR. Histology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in adults and children. Clin Liver Dis. 2016;20:293–312.
29. Boettcher E, Csako G, Pucino F, Wesley R, Loomba R. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2012;35:66–75.
30. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med. 2017;177:633–40.
31. Kargiotis K, Athyros VG, Giouleme O, Katsiki N, Katsiki E, Anagnostis P, et al. Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome. World J Gastroenterol. 2015;21:7860–8.
32. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the american association for the study of liver diseases. Hepatology (Baltimore, Md). 2018;67:328–57.
33. Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357:741–52.
34. NIH conference. Gastrointestinal surgery for severe obesity. Consensus development conference panel. Ann Intern Med. 1991;115:956–61.
35. Hutch CR, Sandoval DA. Physiological and molecular responses to bariatric surgery: markers or mechanisms underlying t2dm resolution? Ann N Y Acad Sci. 2017;1391:5–19.
36. Surgery. ASfMaB: https://asmbsorg/resources/estimate-of-bariatric-surgery-numbers. https://asmbs.org/resources/estimate-of-bariatic-surgery-numbers. Accessed 18 July 2018.
37. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. JAMA Surg. 2014;149:275–87.
38. Elder KA, Wolfe BM. Bariatric surgery: a review of procedures and outcomes. Gastroenterology. 2007;132:2253–71.
39. Pontiroli AE, Morabito A. Long-term prevention of mortality in morbid obesity through bariatric surgery. A systematic review and meta-analysis of trials performed with gastric banding and gastric bypass. Ann Surg. 2011;253:484–7.
40. Sjostrom L, Peltonen M, Jacobson P, Sjostrom CD, Karason K, Wedel H, et al. Bariatric surgery and long-term cardiovascular events. Jama. 2012;307:56–65.
41.•• Adams TD, Davidson LE, Litwin SE, Kim J, Kolotkin RL, Nanjee MN, et al. Weight and metabolic outcomes 12 years after gastric bypass. N Engl J Med. 2017;377:1143–55. **Large study with several years of following showing the long-term durability of weight loss and prevention of diabetes, hypertension, and dyslipidemia in those undergoing bariatric surgery.**

42. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology (Baltimore, Md). 2007;45:846–54.
43. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366:1577–85.
44. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366: 1567–76.
45. Christou NV, Lieberman M, Sampalis F, Sampalis JS. Bariatric surgery reduces cancer risk in morbidly obese patients. Surg Obes Relat Dis. 2008;4:691–5.
46. Adams TD, Stroup AM, Gress RE, Adams KF, Calle EE, Smith SC, et al. Cancer incidence and mortality after gastric bypass surgery. Obesity (Silver Spring, Md). 2009;17:796–802.
47. Ashrafian H, Ahmed K, Rowland SP, Patel VM, Gooderham NJ, Holmes E, et al. Metabolic surgery and cancer: protective effects of bariatric procedures. Cancer. 2011;117:1788–99.
48. Younossi ZM, Loomba R, Rinella ME, Bugianesi E, Marchesini G, Neuschwander-Tetri BA, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology (Baltimore, Md). 2018;68:361–71.
49. Grimm IS, Schindler W, Haluszka O. Steatohepatitis and fatal hepatic failure after biliopancreatic diversion. Am J Gastroenterol. 1992;87:775–9.
50. Cotler SJ, Vitello JM, Guzman G, Testa G, Benedetti E, Layden TJ. Hepatic decompensation after gastric bypass surgery for severe obesity. Dig Dis Sci. 2004;49:1563–8.
51. Dixon JB, Bhathal PS, Hughes NR, O'Brien PE. Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. Hepatology (Baltimore, Md). 2004;39:1647–54.
52. Dixon JB, Bhathal PS, O'Brien PE. Weight loss and non-alcoholic fatty liver disease: falls in gamma-glutamyl transferase concentrations are associated with histologic improvement. Obes Surg. 2006;16:1278–86.
53. Stratopoulos C, Papakonstantinou A, Terzis I, Spiliadi C, Dimitriades G, Komesidou V, et al. Changes in liver histology accompanying massive weight loss after gastroplasty for morbid obesity. Obes Surg. 2005;15:1154–60.
54. Furuya CK Jr, de Oliveira CP, de Mello ES, Faintuch J, Raskovski A, Matsuda M, et al. Effects of bariatric surgery on nonalcoholic fatty liver disease: preliminary findings after 2 years. J Gastroenterol Hepatol. 2007;22:510–4.
55. Clark JM, Alkhuraishi AR, Solga SF, Alli P, Diehl AM, Magnuson TH. Roux-en-Y gastric bypass improves liver histology in patients with non-alcoholic fatty liver disease. Obes Res. 2005;13:1180–6.
56. de Almeida SR, Rocha PR, Sanches MD, Leite VH, da Silva RA, Diniz MT, et al. Roux-en-y gastric bypass improves the nonalcoholic steatohepatitis (NASH) of morbid obesity. Obes Surg. 2006;16:270–8.
57. Barker KB, Palekar NA, Bowers SP, Goldberg JE, Pulcini JP, Harrison SA. Non-alcoholic steatohepatitis: effect of Roux-en-Y gastric bypass surgery. Am J Gastroenterol. 2006;101:368–73.
58. Mattar SG, Velcu LM, Rabinovitz M, Demetris AJ, Krasinskas AM, Barinas-Mitchell E, et al. Surgically-induced weight loss significantly improves nonalcoholic fatty liver disease and the metabolic syndrome. Ann Surg. 2005;242:610–7 discussion 618–620.
59. Bower G, Toma T, Harling L, Jiao LR, Efthimiou E, Darzi A, et al. Bariatric surgery and non-alcoholic fatty liver disease: a systematic review of liver biochemistry and histology. Obes Surg. 2015;25:2280–9.
60.•• Lassailly G, Caiazzo R, Buob D, Pigeyre M, Verkindt H, Labreuche J, et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology. 2015;149:379–88 quiz e315–376. **One of the earliest studies to report improvement in NASH in patients undergoing bariatric surgery.**
61. Mathurin P, Hollebecque A, Arnalsteen L, Buob D, Leteurtre E, Caiazzo R, et al. Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. Gastroenterology. 2009;137:532–40.
62. Silverman EM, Sapala JA, Appelman HD. Regression of hepatic steatosis in morbidly obese persons after gastric bypass. Am J Clin Pathol. 1995;104:23–31.
63. Csendes A, Smok G, Burgos AM. Histological findings in the liver before and after gastric bypass. Obes Surg. 2006;16:607–11.
64. Karcz WK, Krawczykowski D, Kuesters S, Marjanovic G, Kulemann B, Grobe H, et al. Influence of sleeve gastrectomy on NASH and type 2 diabetes mellitus. J Obes. 2011;2011:765473.
65. Froylich D, Corcelles R, Daigle C, Boules M, Brethauer S, Schauer P. Effect of Roux-en-Y gastric bypass and sleeve gastrectomy on nonalcoholic fatty liver disease: a comparative study. Surg Obes Relat Dis. 2016;12:127–31.
66.• Nickel F, Tapking C, Benner L, Sollors J, Billeter AT, Kenngott HG, et al. Bariatric surgery as an efficient treatment for nonalcoholic fatty liver disease in a prospective study with 1-year follow-up: BariScan study. Obes Surg. 2018;28:1342–50. **Reported improvement in NAFLD after bariatric surgery as measured by non-invasive methods**.
67. Jan A, Narwaria M, Mahawar KK. A systematic review of bariatric surgery in patients with liver cirrhosis. Obes Surg. 2015;25: 1518–26.
68. Mosko JD, Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. Clin Gastroenterol Hepatol. 2011;9:897–901.
69. Kleiner DE, Berk PD, Hsu JY, Courcoulas AP, Flum D, Khandelwal S, et al. Hepatic pathology among patients without known liver disease undergoing bariatric surgery: observations and a perspective from the Longitudinal Assessment of Bariatric Surgery (LABS) study. Semin Liver Dis. 2014;34:98–107.
70. Chavez-Tapia NC, Tellez-Avila FI, Barrientos-Gutierrez T, Mendez-Sanchez N, Lizardi-Cervera J, Uribe M. Bariatric surgery for non-alcoholic steatohepatitis in obese patients. Cochrane Database Syst Rev. 2010:CD007340.
71. Abu Dayyeh BK, Edmundowicz SA, Jonnalagadda S, Kumar N, Larsen M, Sullivan S, et al. Endoscopic bariatric therapies. Gastrointest Endosc. 2015;81:1073–86.
72. Vargas EJ, Rizk M, Bazerbachi F, Abu Dayyeh BK. Medical devices for obesity treatment: endoscopic bariatric therapies. Med Clin N Am. 2018;102:149–63.
73. Abu Dayyeh BK, Kumar N, Edmundowicz SA, Jonnalagadda S, Larsen M, Sullivan S, et al. ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies. Gastrointest Endosc. 2015;82:425–438 e425.
74. Lee YM, Low HC, Lim LG, Dan YY, Aung MO, Cheng CL, et al. Intragastric balloon significantly improves nonalcoholic fatty liver disease activity score in obese patients with nonalcoholic steatohepatitis: a pilot study. Gastrointest Endosc. 2012;76:756–60.
75. Popov VB, Thompson CC, Kumar N, Ciarleglio MM, Deng Y, Laine L. Effect of intragastric balloons on liver enzymes: a systematic review and meta-analysis. Dig Dis Sci. 2016;61:2477–87.
76. Administration. UFaD: Update: potential risks with liquid-filled intragastric balloons—letter to health care providers. https://www.Fda.Gov/medicaldevices/safety/letterstohealthcareproviders/ucm609597.Htm. Last accessed July 1, 2018.

77. Lopez-Nava G, Sharaiha RZ, Vargas EJ, Bazerbachi F, Manoel GN, Bautista-Castano I, et al. Endoscopic sleeve gastroplasty for obesity: a multicenter study of 248 patients with 24 months follow-up. Obes Surg. 2017;27:2649–55.
78. Abu Dayyeh BK, Acosta A, Camilleri M, Mundi MS, Rajan E, Topazian MD, et al. Endoscopic sleeve gastroplasty alters gastric physiology and induces loss of body weight in obese individuals. Clin Gastroenterol Hepatol. 2017;15:37–43 e31.
79. Sharaiha RZ, Kumta NA, Saumoy M, Desai AP, Sarkisian AM, Benevenuto A, et al. Endoscopic sleeve gastroplasty significantly reduces body mass index and metabolic complications in obese patients. Clin Gastroenterol Hepatol. 2017;15:504–10.
80. Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, et al. Changes in the prevalence of hepatitis c virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology. 2017;152:1090–1099 e1091.
81.• Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148:547–55. **Showed the importance of NAFLD as an increasing and leading indication for liver transplantation.**
82. Mikolasevic I, Filipec-Kanizaj T, Mijic M, Jakopcic I, Milic S, Hrstic I, et al. Nonalcoholic fatty liver disease and liver transplantation - where do we stand? World J Gastroenterol. 2018;24:1491–506.
83. Wang X, Li J, Riaz DR, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12: 394–402 e391.
84. Zezos P, Renner EL. Liver transplantation and non-alcoholic fatty liver disease. World J Gastroenterol. 2014;20:15532–8.
85. de Graaf EL, Kench J, Dilworth P, Shackel NA, Strasser SI, Joseph D, et al. Grade of deceased donor liver macrovesicular steatosis impacts graft and recipient outcomes more than the donor risk index. J Gastroenterol Hepatol. 2012;27:540–6.
86. Spitzer AL, Lao OB, Dick AA, Bakthavatsalam R, Halldorson JB, Yeh MM, et al. The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. Liver Transplant. 2010;16:874–84.
87. LaMattina JC, Foley DP, Fernandez LA, Pirsch JD, Musat AI, D'Alessandro AM, et al. Complications associated with liver transplantation in the obese recipient. Clin Transpl. 2012;26: 910–8.
88. Berzigotti A, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Morillas R, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology (Baltimore, Md). 2011;54:555–61.
89. O'Leary JG, Landaverde C, Jennings L, Goldstein RM, Davis GL. Patients with NASH and cryptogenic cirrhosis are less likely than those with hepatitis c to receive liver transplants. Clin Gastroenterol Hepatol. 2011;9:700–704 e701.
90. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology (Baltimore, Md). 2002;35:105–9.
91. Leonard J, Heimbach JK, Malinchoc M, Watt K, Charlton M. The impact of obesity on long-term outcomes in liver transplant recipients-results of the NIDDK liver transplant database. Am J Transplant Off J Am Soc Transplant Am Soc Transplant Surg. 2008;8:667–72.
92. Laish I, Braun M, Mor E, Sulkes J, Harif Y, Ben Ari Z. Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. Liver Transplant. 2011;17:15–22.
93.•• Heimbach JK, Watt KD, Poterucha JJ, Ziller NF, Cecco SD, Charlton MR, et al. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. Am J Transplant. 2013;13:363–8. **One of the first to report simultaneous bariatric surgery and liver transplantation for patients with NAFLD.**
94. Lazzati A, Iannelli A, Schneck AS, Nelson AC, Katsahian S, Gugenheim J, et al. Bariatric surgery and liver transplantation: a systematic review a new frontier for bariatric surgery. Obes Surg. 2015;25:134–42.
95. Yalamanchili K, Saadeh S, Klintmalm GB, Jennings LW, Davis GL. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease. Liver Transplant. 2010;16:431–9.
96. Seo S, Maganti K, Khehra M, Ramsamooj R, Tsodikov A, Bowlus C, et al. De novo nonalcoholic fatty liver disease after liver transplantation. Liver Transplant. 2007;13:844–7.
97. Rogers CC, Alloway RR, Alexander JW, Cardi M, Trofe J, Vinks AA. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin Transpl. 2008;22:281–91.
98. Lonardo A, Sookoian S, Pirola CJ, Targher G. Non-alcoholic fatty liver disease and risk of cardiovascular disease. Metab Clin Exp. 2016;65:1136–50.
99. Vanwagner LB, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. Hepatology (Baltimore, Md). 2012;56:1741–50.
100. Patel S, Kiefer TL, Ahmed A, Ali ZA, Tremmel JA, Lee DP, et al. Comparison of the frequency of coronary artery disease in alcohol-related versus non-alcohol-related endstage liver disease. Am J Cardiol. 2011;108:1552–5.
101. Houlihan DD, Armstrong MJ, Davidov Y, Hodson J, Nightingale P, Rowe IA, et al. Renal function in patients undergoing transplantation for nonalcoholic steatohepatitis cirrhosis: time to reconsider immunosuppression regimens? Liver Transplant. 2011;17:1292–8.
102. Singal AK, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. Transplantation. 2014;98:216–21.
103. Dureja P, Mellinger J, Agni R, Chang F, Avey G, Lucey M, et al. NAFLD recurrence in liver transplant recipients. Transplantation. 2011;91:684–9.
104. Contos MJ, Cales W, Sterling RK, Luketic VA, Shiffman ML, Mills AS, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. Liver Transplant. 2001;7:363–73.
105. Dumortier J, Giostra E, Belbouab S, Morard I, Guillaud O, Spahr L, et al. Non-alcoholic fatty liver disease in liver transplant recipients: another story of "seed and soil". Am J Gastroenterol. 2010;105:613–20.
106. Maor-Kendler Y, Batts KP, Burgart LJ, Wiesner RH, Krom RA, Rosen CB, et al. Comparative allograft histology after liver transplantation for cryptogenic cirrhosis, alcohol, hepatitis C, and cholestatic liver diseases. Transplantation. 2000;70:292–7.