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Chapter

Non-alcoholic Fatty Liver Disease and Surgery

Monjur Ahmed

Abstract

There is an epidemic of nonalcoholic fatty liver disease (NAFLD) paralleling the epidemic of obesity and metabolic syndrome. NAFLD is the most common cause of abnormal liver function test and chronic liver disease in the Western world. NAFLD can progress to nonalcoholic steatohepatitis, cirrhosis of the liver, and hepatocellular carcinoma. Most patients with NAFLD die from cardiovascular disease and malignancy. Medical therapy for NAFLD is not very effective at the present time. Treatment of NAFLD starts with weight loss. Bariatric surgery is able to cause significant and sustained weight loss. There are different models of bariatric surgery. Commonly performed ones are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and laparoscopic adjustable gastric banding (LAGB). They can improve steatosis, steatohepatitis, and fibrosis in non-cirrhotic and compensated cirrhotic patients. Each of them has benefits and risks. The bariatric surgical procedures need to be individualized according to the patient's condition.

Keywords: nonalcoholic fatty liver disease, bariatric surgery, role of surgery in NAFLD, liver transplantation and NAFLD

1. Introduction

There is a tremendous rise in the prevalence of nonalcoholic fatty liver disease (NAFLD) throughout the world [1]. About 20% of the world population suffer from NAFLD [2]. NAFLD is the most common cause of chronic liver disease in the developed countries. In the United States, it is the second most common indication of liver transplantation. It affects all age groups and ethnicities [3]. The epidemic of NAFLD parallels the epidemic of obesity and metabolic syndrome in the world. In fact, most (80%) of the patients suffering from NAFLD are overweight [4], and 85% of morbidly obese individuals with body mass index (BMI) >40 have NAFLD [5]. As the disease is related to insulin resistance, 70% of non-insulin-dependent diabetic patients suffer from NAFLD [6]. The disease starts with benign reversible macrovesicular steatosis affecting more than 5% of the hepatocytes. Then it progresses to nonalcoholic steatohepatitis (NASH), steatofibrosis, cirrhosis of the liver, liver failure, and hepatocellular carcinoma [7]. Weight loss, pharmacological intervention, and bariatric surgery are the three main modes of therapy of NAFLD. Weight loss by diet, exercise, and lifestyle modification is the first-line treatment of NAFLD. There are few pharmacologic agents available for the treatment of NAFLD. But as it is difficult to lose weight and maintain targeted body weight by lifestyle modifications, and pharmacological interventions are not

that successful, there is a potential role of bariatric surgery in the treatment of NAFLD. In this chapter, we will be discussing the indications and types of bariatric surgery as well as their benefits and risks.

At the present time, bariatric surgery is indicated only for morbidly obese individuals. The American Society for Metabolic and Bariatric Surgery (ASMBS) recommends bariatric surgery for individuals who have BMI of ≥40 or ≥35 plus at least one or more obesity-related complications (type II diabetes mellitus, hypertension, hyperlipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, gastrointestinal disorders, osteoarthritis, heart disease) and have failed to achieve targeted weight loss despite diet and exercise [8]. The American Association for the Study of Liver Diseases (AASLD) recommends to consider bariatric surgery in otherwise obese individuals with NALFD or NASH.

Bariatric surgery is able to achieve severe (40–71%) weight loss and improve insulin resistance and obesity-related metabolic complications [9]. There are many studies showing the benefits of weight loss in NAFLD following bariatric surgery. But at the present time, there is no large randomized control trial evaluating the effects of bariatric surgery in NAFLD.

Bariatric surgical procedures are classified into three broad categories on the basis of their mechanism of action [10]:

1. Restrictive procedures: The size of the stomach is surgically reduced, and as a result, the food intake is diminished. These procedures include sleeve gastrectomy, laparoscopic adjustable gastric banding (LAGB), and vertical band gastroplasty (not done anymore because of high complication rate and difficulty in maintaining weight loss). In sleeve gastrectomy (**Figure 1**), the gastric fundus and greater curvature of the stomach are resected vertically (>80% of the stomach is removed) making the stomach tubular (like a banana) with less capacity (initial filling volume of <100 ml) and less stretchy with rapid gastric emptying. Feeling of hunger is reduced because of resection of fundus containing ghrelinergic cells [11]. In LAGB (**Figure 2**), an adjustable and inflatable silicone band is placed around the upper stomach dividing the stomach into two compartments: a proximal small gastric pouch (20–30 ml volume) and

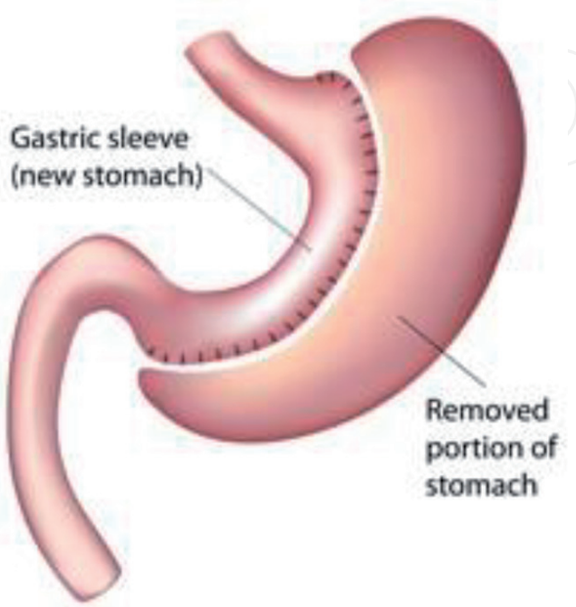

Figure 1.
Sleeve gastrectomy.

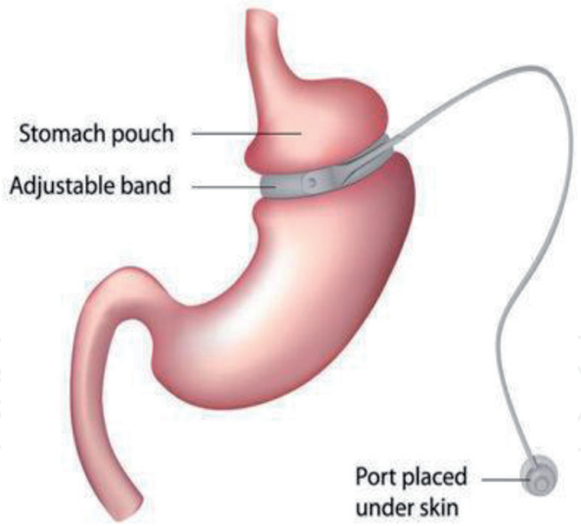

Figure 2.
LAGB.

a distal larger residual stomach. The size of the opening between the gastric pouch and the residual stomach can be adjusted as the band is connected to a subcutaneous infusion port [12].

2. Malabsorptive procedures: A long segment of the small intestine is bypassed, and as a result, the digestive juices digest the food in the distal part of the small intestine, and malabsorption of food occurs. These procedures include biliopancreatic diversion with duodenal switch (**Figure 3**) and biliopancreatic diversion (**Figure 4**).

In biliopancreatic diversion (BPD) with duodenal switch (DS), the stomach size is first reduced by doing a partial sleeve gastrectomy and preserving the pylorus. Then the first part of the duodenum is divided distal to the pylorus. The distal

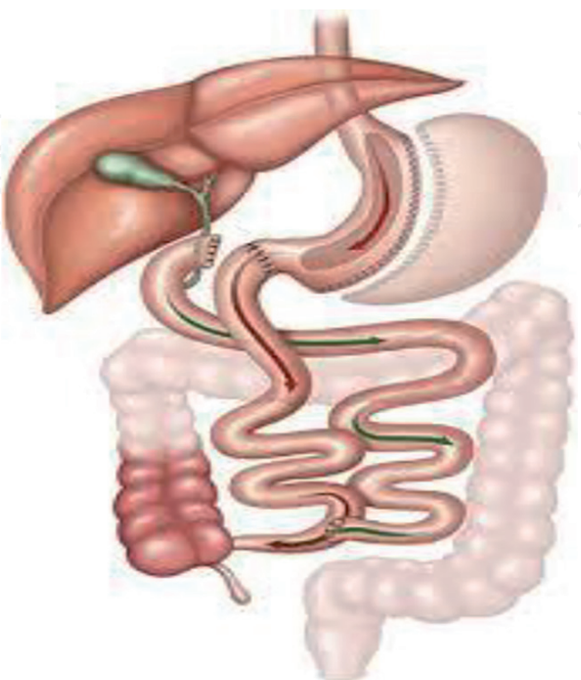

Figure 3.
BPD with duodenal switch.

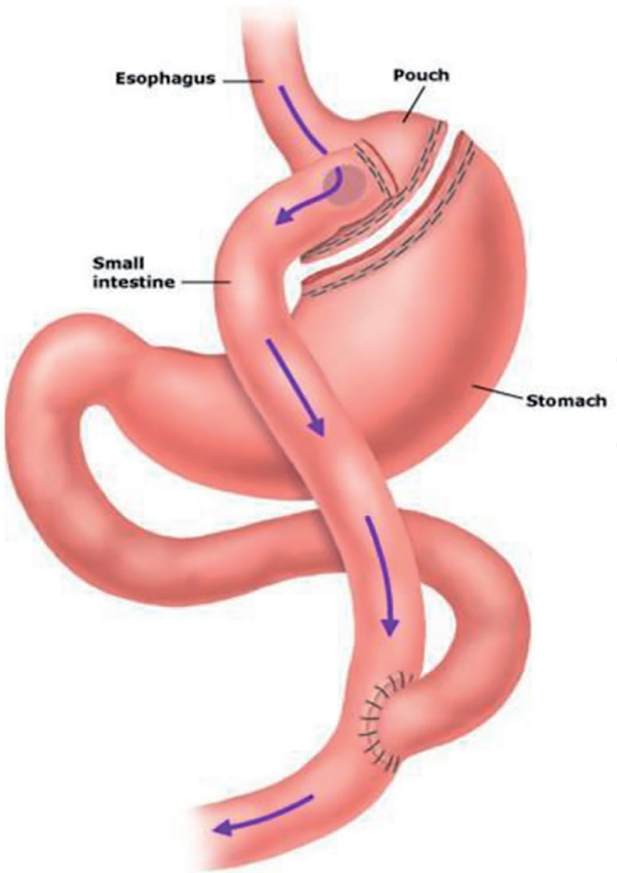

Figure 4.
Biliopancreatic diversion (BPD).

end of the duodenum is closed. The jejunum is then divided 250 cm proximal to the ileocecal valve. The distal end of the jejunum is then anastomosed to the proximal end of the duodenum creating a duodenojejunostomy (duodenal switch). The proximal end of the jejunum is then attached to the ileum 100 cm proximal to the ileocecal valve. As a result, there is restriction of food intake due to gastric sleeve, and most of the small intestine is bypassed leading to malabsorption of nutrients. The biliary pancreatic limb carries biliary and pancreatic secretions into the distal part of the ileum (biliary pancreatic diversion).

In biliopancreatic diversion (BPD), the lower and middle third of the stomach is resected leaving a small gastric pouch. The upper end of the duodenum is closed. The distal jejunum is divided. The distal end of the jejunum is then anastomosed to the gastric pouch. The proximal end of the jejunum is then anastomosed to the distal ileum forming a short common channel in which biliary and pancreatic juices mix with food prior to proceeding into the colon [13].

3. Hybrid procedures: There is combination of restriction of food intake and malabsorption of food. The typical example is Roux-en-Y gastric bypass (RYGB). This procedure divides the upper part of the stomach to create a small gastric pouch with a capacity of 20–30 ml (**Figure 5**). The proximal jejunum is divided 50 cm beyond the ligament of Treitz. The distal jejunal end is then connected to the gastric pouch. The proximal jejunal end of the small bowel is sutured to the jejunum (75–150 cm from the gastric pouch) to form the so-called Roux-en-Y reconstruction. The small gastric pouch (restrictive component) causes early satiety and helps in decreasing food intake. The Roux or alimentary limb (typically 75–150 cm long) extends from the gastric pouch to the

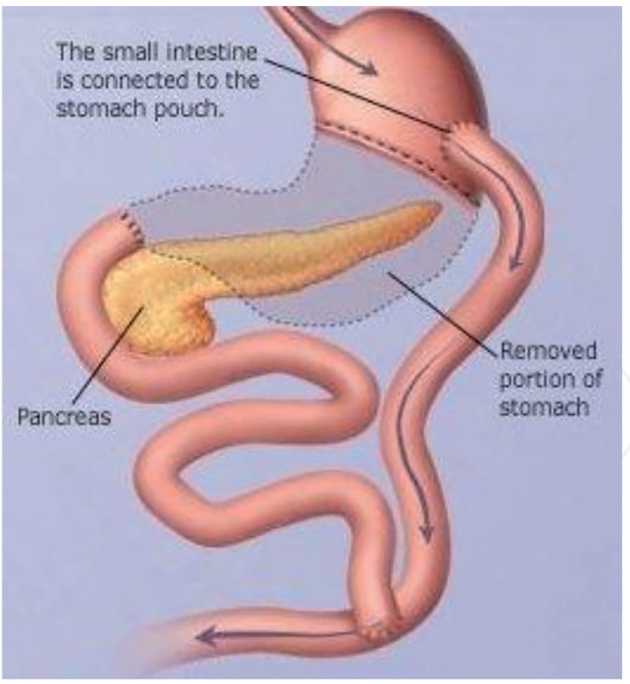

Figure 5.
RYGB.

jejunojejunostomy site and carries ingested food. The proximal biliopancreatic limb (30–60 cm long) containing excluded stomach, duodenum, and proximal jejunum transfers biliary and pancreatic secretions to the jejunojejunostomy site. Most of the digestion and absorption occur in the common channel which extends from the jejunojejunostomy site to the ileocecal valve.

A schematic diagram of different bariatric surgeries is shown below.

2. Benefits and risks of bariatric surgery on NAFLD

Sleeve gastrectomy: Different studies were done to find out the effect of sleeve gastrectomy on NAFLD. Algooneh et al. observed that 56% of total 84 transabdominal ultrasonographically diagnosed NAFLD patients showed complete resolution of hepatic steatosis 3.3 years (average) after isolated sleeve gastrectomy [14]. Karcz et al. found that there was significant reduction (>50%) of transaminases in NASH patients within 6 months of isolated sleeve gastrectomy [15]. Parveen-Raj et al. did a prospective observational trial and found that surgically induced weight loss improved NAFLD histology significantly 6 months after isolated sleeve gastrectomy in morbidly obese patients [16].

LAGB: There have been several studies showing the effects of LAGB on NAFLD. Most of the studies reported improvement of hepatic steatosis, steatohepatitis, and fibrosis, but some studies showed mild increase in fibrosis.

Few LAGB studies with their effects on NAFLD are mentioned in **Table 1**.

Biliopancreatic diversion (BPD) and biliopancreatic diversion with duodenal switch (BPD with DS): Both procedures produce long-term malabsorption and severe weight loss. They are not widely done. Their effects on NAFLD are summarized in two studies in **Table 2**.

In patients with BPD with DS, the transient deterioration of transaminases and steatohepatitis seen in the first 6 months postoperatively was possibly due to rapid weight loss. Transaminases became normalized by 12 months. Then there

Study	Outcome	Sample size	Follow-up
Luyckx et al. [17]	↓ Steatosis ↑ Mild hepatitis	69	27 ± 15 months
Busetto et al. [18]	↓ Steatosis	6	24 weeks
Stratopoulas et al. [19]	↓ Steatosis ↓ Steatohepatitis ↓ Fibrosis	51	17 months
Jaskiewicz et al. [20]	↓ Steatosis ↓ Steatohepatitis	87	41 months
Phillips et al. [21]	↓ Steatosis ↓ Gamma-glutamyl transferase	29	3 months
Dixon et al. [22]	↓ Steatosis ↓ Steatohepatitis ↓ Fibrosis	60	29.5 ± 10 months
Mathurin et al. [23]	↓ Steatosis ↓ Fibrosis	381	60 months

Table 1.
Summary of LAGB studies showing effects on NAFLD.

Study	Type of surgery	Outcome	Sample size	Follow-up
Keshishian et al. [24]	BPD with DS	Transaminases and NASH worsened at 6 months Steatosis and NASH decreased after 6 months	78	36 months
Kral et al. [25]	BPD	Severe fibrosis decreased in 27% and mild fibrosis appeared in 40%: 41 ± 25 months after BPD	104	41 ± 25 months

Table 2.
Summary of effects of BPD and BPD with DS on NAFLD.

Study	Outcome	Sample size	Follow-up
Mottin et al. [26]	↓ Steatosis	90	12 months
Matter et al. [27]	↓ Steatosis ↓ Fibrosis	90	12 months
Clark et al. [28]	↓ Steatosis ↓ Steatohepatitis ↓ Fibrosis	16	305 ± 131 days
Silverman et al. [29]	↓ Steatosis ↓ Fibrosis	91	18.4 months
Lie et al. [30]	↓ Steatosis ↓ Steatohepatitis ↓ Fibrosis	39	18 months
Barker et al. [31]	↓ Steatosis ↓ Steatohepatitis ↓ Fibrosis	19	21.4 months
Klein et al. [32]	↓ Steatosis	7	12 months

Study	Outcome	Sample size	Follow-up
Furuya et al. [33]	↓ Steatosis ↓ Fibrosis	18	24 months
Weiner et al. [34]	↓ Steatosis ↓ Steatohepatitis ↓ Fibrosis	116	18.6 ± 8.3 months
De Almeida et al. [35]	↓ Steatosis ↓ Steatohepatitis ↓ Fibrosis	16	23.5 ± 8.4 months

Table 3.
Summary of effects of RYGB on NAFLD.

was progressive improvement of steatosis and steatohepatitis up to 3 years. In patients who had BPD, the appearance of mild fibrosis was possibly related to severe diarrhea, hypoalbuminemia, some intake of alcohol, and postmenopausal status.

Roux-en-Y gastric bypass (RYGB): Effects of RYGB have been studied extensively in different studies. Most of the studies showed improvement of steatosis, steatohepatitis, and hepatic fibrosis. Summary of some of the RYGB studies are mentioned in **Table 3**.

3. How does bariatric surgery help NAFLD?

1. By achieving weight loss: Weight loss is the key in the treatment of NAFLD [36]. Seven to ten percent of weight loss by lifestyle modification has been shown to improve hepatic steatosis and steatohepatitis [37]. Significant and sustained weight loss is common after bariatric surgery.

2. By improving insulin resistance: Obesity is associated with insulin resistance, i.e., insulin receptors fail to work. How does this happen? Adipose tissue works as a metabolically active endocrine organ and produces proinflammatory cytokines—TNF-α, IL-1, IL-6, IL-8, IL-18, and C-reactive protein [38]. In obesity, excessive production of these cytokines occurs leading to a proinflammatory state which is associated with insulin resistance. Adiponectin is a fat cell hormone produced in the white adipose tissue. It plays an important role in the regulation of glucose and fat metabolism in insulin-sensitive tissues. It increases fatty acid oxidation and decreases de novo synthesis of fatty acid. In diet-induced obesity, the circulating level of adiponectin is paradoxically decreased [39]. Hypoadiponectinemia in obesity is associated with insulin resistance [40]. In obesity, excessive intraperitoneal fat promotes free fatty acid (FFA) reflux directly into the hepatocytes via the portal vein [41]. FFA metabolites (long-chain acyl-CoAs and diacylglycerol) then transfer cytoplasmic protein kinase Cs to the cell membrane. Subsequently, intracellular portions of insulin receptors are phosphorylated by protein kinase C leading to insulin resistance.

As a result of insulin resistance, lipolysis occurs in the adipose tissue with increased levels of plasma FFA and excessive influx of FFA into the hepatocytes. In the hepatocytes, fatty acid oxidation is inhibited, and de novo synthesis of fatty acid occurs leading to triglyceride synthesis and hepatic steatosis.

Bariatric surgery reduces insulin resistance by decreasing production of proinflammatory cytokines and improving the adiponectin level.

3. By improving dyslipidemia: NAFLD is associated with increased levels of serum triglyceride (TG) and low-density lipoprotein (LDL) and decreased level of high-density lipoprotein (HDL). As they are the main risk factors for the development atherosclerosis and coronary artery disease, cardiovascular disease is the main cause of mortality in NAFLD patients [42]. Bariatric surgery significantly improves the dyslipidemic state, and most of the patients do not need anymore lipid-lowering agents [43].

4. By improving the metabolic hormone profile: Gastrointestinal hormones play important roles in the success of weight loss and thus improve manifestations of metabolic syndrome following bariatric surgery. Ghrelin is the hunger hormone (orexigenic) mainly produced in oxyntic glands of gastric fundus [44]. Ghrelin also increases gastrointestinal motility and decreases insulin secretion [45]. In patients with Roux-en-Y gastric bypass, sleeve gastrectomy, and BPD with DS, ghrelin levels are profoundly low, and this may explain loss of hunger sensation and rapid weight loss in these patients [46, 47]. Glucagon-like peptide-1 (GLP-1) is secreted by the L cells in the distal ileum and colon. It promotes glucose-dependent insulin secretion, inhibits glucagon secretion, delays gastric emptying, inhibits gastric acid secretion, and reduces hunger sensation. Peptide tyrosine-tyrosine (PYY) is co-secreted with GLP-1 by the L cells of the distal ileum and colon after ingestion of food. It reduces hunger [48], delays gastric emptying, and decreases gastric acid secretion [49]. Serum levels of GLP-1 and PYY are high in post-RYGB patients because of rapid delivery of nutrients to the distal gut. As a result, the post-RYGB patients experience early satiety, their blood glucose and triglyceride levels decrease, and HDL level increases. The metabolic improvement can be seen as early as 2 days after surgery and do not correlate with the degree of weight loss. Many patients' diabetes mellitus, hypertension, and dyslipidemia either disappear or get under control. The improvement of components of metabolic syndrome has positive effects on NAFLD.

4. Bariatric surgery and cirrhosis of the liver

Bariatric surgery carries an increased risk of morbidity and mortality in patients with cirrhosis of the liver due to NAFLD. Risk assessment should be done by evaluating the severity of liver disease and presence of hepatic reserve. The Child-Turcotte-Pugh (CTP) score and the Model for End-Stage Liver Disease (MELD) score can predict postoperative mortality. The presence of portal hypertension (HVPG >10 mm Hg) indicates worse outcome. Clinically patients may have gastroesophageal varices, ascites, and splenomegaly with thrombocytopenia [50]. Transjugular intrahepatic portosystemic shunt (TIPS) placement is an option for these patients to reduce postoperative complications [51]. There has been no randomized clinical trial of doing bariatric surgery on cirrhotic patients due to NAFLD. Most of the studies were done on unsuspected compensated cirrhotic patients. Brolin et al. published a study in 1998 on unsuspected cirrhotic patients discovered during surgery. Four percent of patients died in the perioperative period, and 8% died late due to liver disease [52]. Mosko et al. reviewed nationwide data collection of patients who had bariatric surgery in the United States between 1998 and 2007 [53]. Non-cirrhotic patients had less mortality and shorter length

of hospital stay in comparison with compensated and decompensated cirrhotic patients (mortality 0.3 vs. 0.9 and 16.3%, respectively, and length of stay 3.2 vs. 4.4 and 6.7 days, respectively). The study also found that high-volume centers (performing >100 surgeries per year) had lower mortality rate (0.2 vs. 0.7%; $p < 0.0001$) than low volume centers (performing <50 surgeries per year). Shimizu et al. did a study on 22 Child's A and 1 Child's B cirrhotic patients who underwent laparoscopic RYGB, laparoscopic sleeve gastrectomy, and LAGB between 2004 and 2011. No patient had decompensation of liver disease after surgery [54]. Pestana et al. did a retrospective review on 14 Child's A cirrhotic patients (4 with portal hypertension and 10 without portal hypertension) who had bariatric surgeries (sleeve gastrectomy and gastric bypass) between 2009 and 2011. Significant weight loss with improvement of hepatic steatosis, diabetes mellitus, hypertension, and dyslipidemia occurred. None of them had peri- or postoperative surgical complications or bleeding [55].

From the above studies, it is apparent that bariatric surgeries can be safely performed in high-volume centers with acceptable morbidity and mortality in carefully selected compensated cirrhotic patients. The next question comes: What type of bariatric surgery is suitable for cirrhotic patients? Currently, three types of bariatric surgery are most commonly done. These include laparoscopic RYGB, laparoscopic sleeve gastrectomy, and LAGB. Each type has its own pros and cons which are mentioned in **Table 4**.

Modality of gastric bypass surgery should be individualized according to patients' comorbidities and pros and cons of each type of surgery. Sleeve gastrectomy is becoming more popular. Although bariatric surgery poses significant risks to patients with cirrhosis due to NAFLD, the considerable benefits of significant

Type of surgery	Pros	Cons
Laparoscopic RYGB	Most significant weight loss out of the three procedures	1. Endoscopic access to the excluded stomach is difficult if there is a need to deal with gastroduodenal bleeding, biliary obstruction, pancreatic mass, or cyst when patients may need laparoscopic gastroduodenoscopy [56] or EUS-guided transgastric access for ERCP and EUS/FNA [57, 58] 2. Malabsorption of micronutrients and vitamin may cause progressive liver dysfunction 3. Alteration of anatomy may complicate future liver transplantation
LAGB	Least invasive procedure out of the three	Foreign device implantation may cause infection, particularly in the presence of ascites Currently contraindicated by the FDA to be placed in cirrhosis of the liver [59]
Laparoscopic sleeve gastrectomy	4. Technically less challenging to the surgeon with short operating time 5. Does not cause malabsorption of micronutrients and vitamins 6. No requirement of foreign device implantation	Risk of significant bleeding in patients with gastric varices

EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine needle aspiration.

Table 4.
Pros and cons of different types of bariatric surgery in cirrhosis of the liver.

weight loss (including decreasing the risk of cardiovascular diseases and malignancy) and candidacy for liver transplantation may overweigh the risks. The AASLD guidelines published in January 2018 do not recommend bariatric surgery to patients with cirrhosis of the liver attributed to NAFLD as the type, safety, and efficacy of bariatric surgery are not yet established in this group of patients [60].

5. Bariatric surgery and orthotopic liver transplantation

Some transplant centers have a strict criteria of not performing orthotopic liver transplantation with BMI > 35. Orthotopic liver transplantation in morbidly obese patients is technically difficult and can be associated with increased bleeding, postoperative complications, morbidity, and mortality [61]. The longevity of morbidly obese transplanted patients is also shortened. Pretransplant bariatric surgery is considered in these patients to reach the BMI goal for liver transplantation. Lin et al. did a retrospective study in pretransplant morbidly obese patients and found that laparoscopic sleeve gastrectomy was safe and successful in causing significant weight loss and improving candidacy for liver transplantation [62]. On the other hand, one third of post-liver transplant patients become obese, and some of them become morbidly obese due to increased appetite, increased calorie intake, sedentary lifestyle, and corticosteroid therapy. A proportion of these patients may develop metabolic syndrome and NAFLD in the transplanted liver. Both RYGB and laparoscopic sleeve gastrectomy have been found to be safe and feasible in post-liver transplant morbidly obese patients [63, 64]. Another small study showed combined liver transplantation and sleeve gastrectomy in morbidly obese patients led to effective weight loss and less metabolic complications. There was no mortality or graft loss in those patients [65]. So bariatric surgery has been found to be safe before, during, and after liver transplantation in selected patients in small studies although there is no consensus about the optimal timing yet.

6. Conclusion

With the epidemic of obesity, there will be steep rise in performing bariatric surgery on NAFLD patients. Multiple cohort studies suggest that bariatric surgeries are extremely effective in lowering significant amount of body weight and in improving the metabolic syndrome and histology of NAFLD. Bariatric surgery helps NAFLD in achieving significant and durable weight loss, decreasing insulin resistance, ameliorating dyslipidemia, and improving metabolic hormone profile. As most of the patients with NAFLD die from cardiovascular diseases and malignancy, bariatric surgery should be considered in otherwise obese individuals with NAFLD. The commonly used bariatric surgeries include laparoscopic RYGB, laparoscopic sleeve gastrectomy, and LAGB. According to cohort studies, bariatric surgeries can be performed safely in patients with compensated Child's A cirrhosis attributed to NAFLD. But at the present time, AASLD does not recommend bariatric surgery in patients with cirrhosis attributed to NAFLD because of the lack of randomized controlled trial. Prospective randomized controlled trials are also needed in morbidly obese patients with end-stage liver disease attributed to NAFLD to find out whether performing simultaneous orthotopic liver transplantation and bariatric surgery are safe and effective.

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