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The Role of Bariatric Surgery in Fatty Liver

Anja Geerts and Sander Lefere

Abstract

Non-alcoholic fatty liver disease (NAFLD) is a crucial health problem with a prevalence that is increasing concurrently with the obesity epidemic on a global scale. Steatosis, nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), cirrhosis, and advanced fibrosis constitute the disease spectrum covered by NAFLD. NASH-related cirrhosis and HCC is currently the second most common indication for liver transplantation. Although lifestyle modifications, especially weight loss, effectively reduces the liver injury in NASH, adherence in the clinical setting is low. Potential treatments for NASH are still under investigation in phase 2–3 studies. Bariatric surgery can improve metabolic components and cause great weight loss. Therefore, bariatric surgery may reverse the pathological liver changes in NAFLD and NASH patients. However, complications such as liver failure after bariatric surgery can occur. This chapter will give an overview of the benefits and pitfalls of bariatric surgery in patients with NAFLD, liver transplant candidates and post-liver transplant patients.

Keywords: bariatric surgery, NAFLD, NASH, liver transplant, liver failure

1. Introduction

Over the last decades, there has been a drastic increase in obesity prevalence. Health statistics reports of 2018 showed that 40% of the total adult population of the United States were obese (BMI (body mass index) $> 30 \text{ kg/m}^2$).

The obesity epidemic has led to a dramatic rise in the obesity-related liver disease non-alcoholic fatty liver disease (NAFLD). NAFLD currently affects one quarter of the global population [1]. Steatosis or fatty liver, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) make up the spectrum of conditions that NAFLD represents. The frequency of liver transplantation undertaken in patients with cirrhosis and HCC due to NASH has been increasing worldwide [2]. NAFLD has also been found to be associated with several health conditions like cardiovascular diseases which affect organs outside the liver and constitute the major cause of deaths in patients with NAFLD.

Lifestyle modification is the cornerstone of NAFLD therapy. As a matter of fact, reduced intake of calories combined with increased activity can make this achievable. The main driver of NAFLD improvement is the amount of actual weight loss, while the type of diet seems to be less important. Respective of how one achieves weight loss, the highest rates of steatohepatitis resolution (90%) as well as improvement of fibrosis (45%) can only be induced by $>10\%$ weight loss. A weight loss of $>5\%$ improves steatosis in about 64% and weight loss of $>7\%$ can resolve

steatohepatitis in 72% [3]. Regrettably, the necessary weight loss goal of >7% to 10% is achieved only by a minority of the patients.

Currently, a vast array of drugs are being tested for NASH, and some of them are already in the third phase, but until now, there is no pharmacological therapy for NASH [4]. In our current understanding, any pharmacological treatment that is indicative for NASH should be prescribed only to patients with NASH and advanced liver fibrosis. The recommendations above result from data which show that fibrosis is the strongest prognostic predictor, with a decline in survival from fibrosis stage 2 onwards [5].

The use of bariatric surgery as a therapy for obesity is increasingly common, and evidence that also supports its therapeutic use for metabolic disturbances (so called “metabolic surgery”) is increasing [6]. In addition, bariatric surgery is a promising therapeutic alternative for NAFLD as risk factors such as diabetes, inflammation, insulin resistance, and dyslipidemia that contribute to NAFLD pathogenesis can be reversed by it, and it is also effective for achieving long-term weight loss in patients [7].

According to current reimbursement guidelines, it is only administered to obese patients who are 18 years or over with a BMI > 40 kg/m² or BMI > 35 kg/m² with related co-morbidities such as diabetes mellitus, uncontrolled arterial high blood pressure and OSAS despite triple therapy. Consequently, NASH is not one of the co-morbidities regarded as an indication for bariatric surgery.

In this chapter, we will first elucidate the benefit of bariatric surgery in the field of NAFLD. Secondly, the possible role of bariatric surgery will be discussed in patients who are candidates for liver transplantation. Special consideration will also be given to patients who develop recurrent or de novo NASH after liver transplantation. Finally, we outline the possible pitfalls with the risk of liver failure after bariatric surgery.

2. Types of bariatric surgery

A variety of procedures for bariatric surgery have been developed over the last decades. The 2 most frequently performed types of bariatric surgery are Roux-en-Y gastric bypass (RYGB) and Sleeve gastrectomy (SG). There has been a progressive decline in the use of the adjustable gastric banding procedure after sleeve gastrectomy was developed. Biliopancreatic diversion with duodenal switch (BPD-DS) is the procedure of choice for severe morbidly obese patients. Very low mortality and morbidity rates are associated with almost all bariatric operations performed laparoscopically [8]. In the USA and countries around the world, the currently most performed bariatric procedure is sleeve gastrectomy. The increase in popularity of the SG could be due to its relative technical simplicity, as there are no concerns for late complications such as internal herniation, ulcerations on anastomosis and no malabsorption of iron, calcium and vitamins. Malabsorptive surgery as jejunoileal bypass, biliopancreatic diversion (BDP), biliopancreatic diversion with duodenal switch (BDP-DS), and distal gastric bypass (D-GBP) can lead to large weight loss, yet can cause severe long-term complications.

Figure 1 shows the different types of surgery. The RYGB procedure consists of two components. First, a small gastric pouch of ~30 cm³ in volume is constructed, secondly the small intestine is divided ~30–50 cm distal to the ligament of Treitz. The distal end of the small intestine that has been divided also known as the Roux limb is connected to the gastric pouch that was newly fabricated. The Roux limb ranges from 75–150 cm in length. SG is formed from a tubular gastric pouch (sleeve) that remains after ~80% of the lateral part of the stomach has

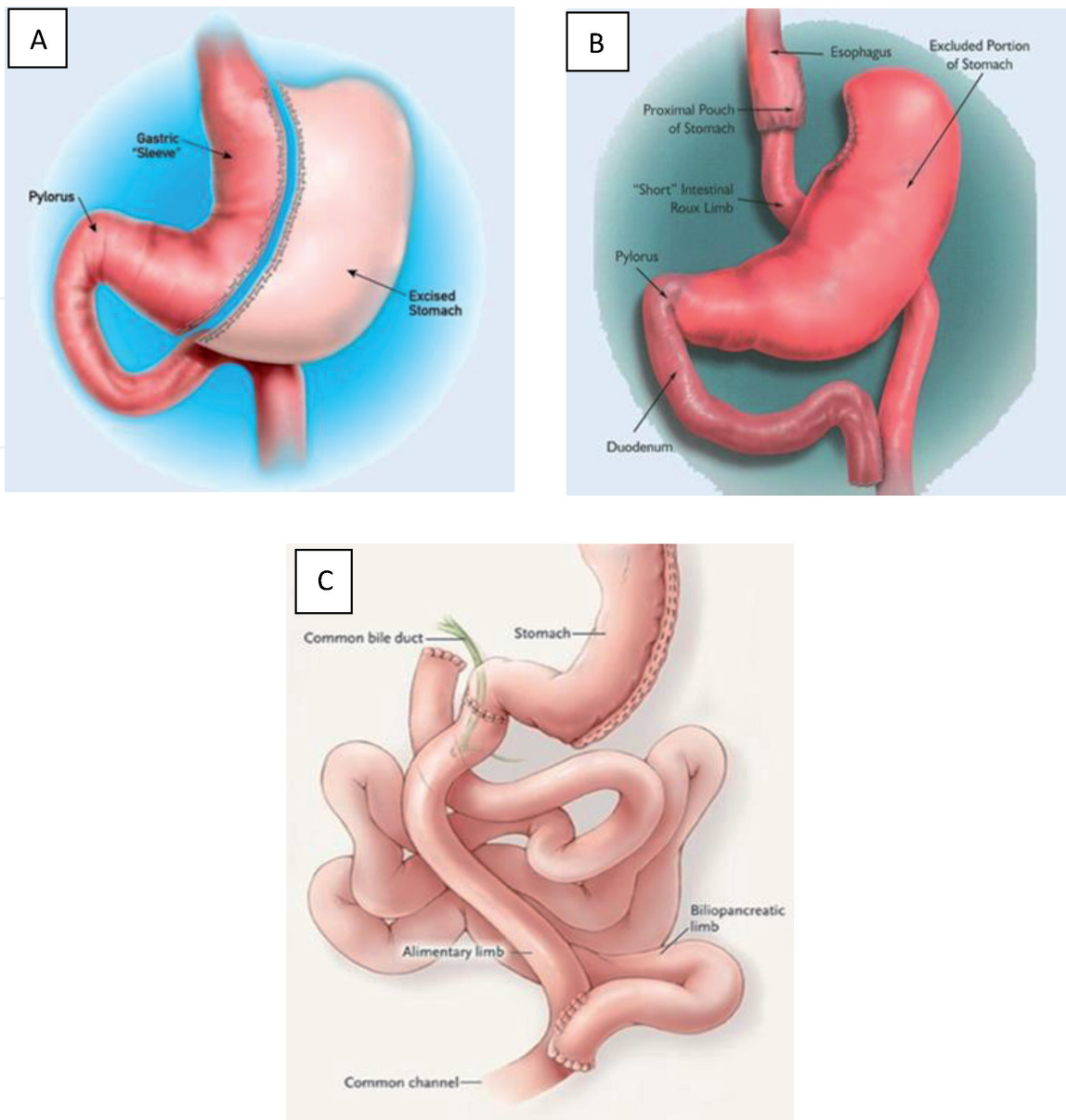


Figure 1.
Bariatric surgery procedures. (A) sleeve gastrectomy, (B) roux-en-Y gastric bypass, (C) biliopancreatic diversion with duodenal switch (reproduced with permission from www.uzgent.be).

been removed. The BPD–DS is a procedure where first a vertical gastrectomy is performed, similar to the SG. Next, a large portion (~50%) of the small intestine is bypassed, which creates malabsorption. The duodenum is divided immediately after the pylorus. At 250 cm proximal to the ileocecal valve, a portion of the distal ileum is divided and anastomosed to the duodenum in a Roux-en-Y configuration after bringing it up. Another anastomosis of the ileoileostomy is performed at 100 cm proximal to the ileocaecal valve to complete the operation [9].

3. Benefits of bariatric surgery in NAFLD patients

Already in 2008, Mathurin et al. published data showing an improvement of steatosis, ballooning and NAS score 5 years after bariatric surgery in NAFLD patients. However they reported a worsening of fibrosis in 19.8% of patients. This initial finding made the use of bariatric surgery questionable in the area of NASH. However, the worsening of fibrosis at 5 years was slight, 95% of the patients had a fibrosis score less than 1 and a lot of patients had no biopsy-proven NASH [10]. The same

group reported recently data of a biopsy-proven cohort of NASH patients with liver samples 1 and 5 years after bariatric surgery [11, 12]. In this long-term prospective trial, NASH resolution was induced by bariatric surgery without fibrosis worsening in 84% of the patients at 5 years. Regression of fibrosis was seen in 70% of the patients, beginning to improve within 1 year and continued throughout 5 year follow-up. Also in patients with baseline fibrosis grade 3, there was an improvement seen in 68%. The non-responders (20%) to bariatric surgery were patients with low weight loss and less improvement in insulin resistance after their surgery. This large trial has demonstrated that there is an understandable benefit to consider bariatric surgery as a treatment option for patients with clinically significant NASH.

Lee et al. published in 2019 a systematic review with data of 32 cohort studies comprising 3093 biopsy-confirmed NAFLD patients and the effect of bariatric surgery [13]. The authors looked at complete resolution of the different features of NAFLD instead of improvement. The study results indicated that there was complete resolution of steatosis, inflammation, ballooning and fibrosis in 66%, 50%, 76% and 40%, respectively. A meta-analysis in 2008 of 15 cohort studies showed similar results [14]. By focusing on complete NAFLD resolution, these reviews provide further evidence that bariatric surgery is efficacious and that NAFLD as a comorbidity should prompt evaluation for bariatric surgery in patients with a BMI of 35 to 40 kg/m².

Klebanoff et al. showed that bariatric surgery led to more QALY's for all obese patients and overweight patients regardless of fibrosis stage compared to lifestyle interventions. Their analysis also suggests that for patients in all obesity classes, bariatric surgery, as a therapy, is cost-effective and may even be considered cost-effective therapy for overweight individuals with advanced fibrosis [15]. The majority of the patients in the reported cohorts underwent RYGB, only 5 to 10% underwent Sleeve gastrectomy. A few studies have examined the effect other bariatric surgeries have on NASH. Caiazzo et al. showed that RYGB was associated with significantly greater improvement in the amount of steatosis and NASH at 1 and 5 years after surgery compared to adjustable gastric banding [16].

The use of comparative randomized trials that study the impact of bariatric surgery compared with current medical therapies should be the focus of future clinical studies. Data on new endoscopic bariatric therapies and the effect on NASH are also urgently needed.

4. Bariatric surgery related to liver transplantation

Candidates for transplantation with a BMI > 40 kg/m² have a significantly higher mortality on the waiting list compared with candidates with a BMI > 30 kg/m². The reason is a faster progression of liver deterioration among obese patients versus nonobese [17]. The most frequently used BMI cutoffs in the literature as relative and absolute contra-indication for liver transplantation were 40 and 45, respectively. This is mainly based on the fact that studies reported a higher risk of perioperative complications, mostly wound-related infections, in obese patients. Morbid obesity cannot be considered as an absolute contra-indication for liver transplant despite the presence of associated complications in these patients. This observation leads us to the need to address obesity before and after liver transplantation.

4.1 Bariatric surgery in pre-liver transplant candidates

Treating obesity before transplantation can reduce the risk of decompensation and reduce co-morbidities such as infections and metabolic syndrome in the post-operative period [18, 19].

The first issue to consider is whether bariatric surgery is safe in cirrhotic patients. Data are mostly coming from retrospective incidental findings at the time of bariatric surgery with a prevalence between 0.14% to 1.5% [20, 21]. Younus et al. described a cohort of 26 patients with incidental finding of cirrhosis (proven with biopsy) at the time of bariatric surgery [20]. The type of procedure was mainly RYGB (55%). A higher risk of immediate complications postoperative (38.5% versus 16.7% in non-cirrhotic group) was seen, probably also due to a high BMI in this study (median BMI of 52 kg/m²). No long-term cirrhosis-related complications or increased mortality were noted in this cohort. Jan et al. published a review with pooled data of nine similar studies with a total of 122 cirrhotic patients. The characteristics of the patients were mainly Child Pugh A patients, a few Child Pugh B and 7 patients with portal hypertension. The type of procedure was again predominantly RYGB. There was an overall complication rate of 22.5% with also a 6.5% liver decompensation rate and a late mortality rate of 2.45%. A lower complication rate in cirrhotic patients was seen in the group who underwent SG or gastric banding when compared with malabsorptive bariatric procedures including RYGB [22].

Bariatric surgery can be done in a carefully selected patient group with cirrhosis, especially Child Pugh A patients without significant portal hypertension. It is important to recognize and diagnose cirrhosis, estimate liver function and the presence or absence of portal hypertension pre-operatively. This can help in deciding the type of procedure and anticipating complications. Most of the data currently available indicate that sleeve gastrectomy can be done safely in compensated liver cirrhosis patients [23, 24].

The risk of 30-day mortality in decompensated cirrhotic patients undergoing bariatric surgery was noted to be 16.7% versus 0.9% in compensated cirrhosis. So, bariatric surgery is absolutely contra-indicated in patients with a decompensated liver disease.

4.2 Bariatric surgery simultaneously with liver transplantation

For patients who are too sick before transplant, a simultaneous bariatric surgery and liver transplantation is another approach to manage obesity in this population. Small series of patients who underwent combined sleeve gastrectomy and liver transplantation has been published from the group of the Mayo Clinic [25]. Death, graft loss, operative complications were similar between the two groups, however post-liver transplantation metabolic outcomes were superior in the group who underwent the combined SG and transplantation. Long-term outcomes were described recently with demonstrating efficacy and maintaining weight loss and favorable metabolic profiles [26]. So far, there are only two other case reports of sleeve gastrectomy and liver transplantation combined that have been reported [27, 28].

The main disadvantage of this approach can be the impact on the nutritional state in the immediate post-operative period. More data and experience is needed before promoting this approach.

4.3 Bariatric surgery after liver transplantation

Long-term weight gain and development of metabolic syndrome are the main concerns post-liver transplantation. Up to 46% of the patients will develop the metabolic syndrome, especially those with a BMI > 30 kg/m² or higher pre-liver transplant BMI. Recently it has been shown that NASH liver transplant recipients have a 10 year graft survival of 61% which is significantly lower than primary sclerosing

cholangitis, auto-immune hepatitis and primary biliary cholangitis recipients (respectively 74%, 71.7% and 71%) [29]. Probably the outcomes of NASH cirrhosis liver transplant recipients are not as good as previously thought and this is due to the development of metabolic risk factors. The bulk of weight gain appears to occur within the first year, with studies reporting a median weight gain of 5 to 10 kg at 12 months after liver transplantation. Recurrent NAFLD/NASH after transplantation is very common, ranging in cohorts from respectively 10 to 100% and 4 to 28%. Risk factors are older age, higher BMI at the time of liver transplantation, presence of diabetes mellitus type 2 pre-liver transplant and dyslipidemia [30–32].

The development of de novo NAFLD is also frequent after liver transplantation. There are reports that described 78% de novo NAFLD and 4% NASH in 2378 liver transplant recipients at 5 year follow-up [33]. A very important finding is the faster progression of fibrosis in patients with de novo NASH after liver transplantation [30–33].

Case reports and series of bariatric surgery in post transplant recipients showed no difference in mortality with the general population [34–36]. Sleeve gastrectomy is the most performed procedure with lack of malabsorption and no interference of immunosuppressive drugs. Optimal timing of bariatric surgery post liver transplantation need to be defined, because delaying too long can cause fibrosis and reduce patient survival.

5. Liver failure as a result of prior bariatric surgery

Decompensated cirrhosis that results from an earlier bariatric surgery, is a clinical condition that is far more demanding. Complications including severely impaired hepatic function are mostly described after jejunoileal bypass (JIB) and biliopancreatic diversion (BPD) procedures. They occurred in up to 10% of the patients. The occurrence of these and other complications resulted in abandonment of JIB surgery. The frequency of hepatic complications after BPD is unclear, but hepatocellular failure has been reported in small series and case reports. In 1992, the first case of chronic end-stage liver disease after BPD was reported [37]. We published a multicenter Belgian Survey on liver transplantation for hepatocellular failure after bariatric surgery. 10 patients who underwent bariatric surgery and developed liver failure afterward were reported in the Belgian survey: 1 after JIB and 9 after BPD. Patients who underwent JIB or BPD subsequently became candidates for liver transplantation, even >20 years after bariatric surgery [38]. Probably, the real incidence of hepatic complications after BPD surgery is underreported in the current literature; so we are still unaware of the real incidence of Scopinaro procedure-induced liver failure. The pathogenesis of post-BPD steatohepatitis remains poorly understood. One important factor implicated in the pathogenesis of liver injury after JIB or BPD was intestinal bacterial overgrowth in the excluded small intestine segment. As we see no liver failure after equivalent intestinal resection, this may explain the role of excluded segment. Bacterial overgrowth leads to mucosal injury and increases gut permeability to especially endotoxins. When these toxins are absorbed via the portal vein to the liver, they can induce hepatocellular damage. Another factor in the pathogenesis of liver failure postbypass surgery is protein and amino acid malnutrition, which can perpetuate or increase lipid accumulation in the liver.

Mahawar et al. confirmed that the length of the biliopancreatic limb (BPL) matters [39]. A long BPL (100–150 cm) results in better weight loss, intensifies the antidiabetic effect in RYGB compared with a shorter BPL of 50–75 cm. The increased risk of insufficiency of protein with successive malnutrition constitute

the drawback of using a long BPL with a shorter alimentary limb length (TALL). Recent data suggests that at least 350–400 cm of TALL must remain [40, 41].

Although liver transplantation and intestinal anatomy restoration have been regarded as the standard therapy for liver failure that results from BDP or JIB surgery, the use of these measures has been reported to be unsuccessful in some cases [42, 43]. We reported a case of refractory subacute steatohepatitis after BPD [43]. There may be a significant improvement when surgery is used to achieve a gastric bypass-like anatomy, however, its feasibility is directly related to the severity of liver decompensation as well as effects of nutritional correction. Correction of vitamin depletion, malnutrition and aggressive nutrition is warranted and might already significantly improve the patient's condition. In case of incipient deterioration, early referral to a liver transplant center is necessary.

The exact magnitude of liver failure after RYGB, which is not associated with much malabsorption, has not yet been fully established. There are some case reports. Mahawar et al. found 10 reports of liver failure after RYGB in the entire surgical literature [39]. In view of the fact that RYGB is the most common performed bariatric procedure worldwide, potentially millions have been carried out, this means that only a minuscule proportion of patients undergoing this operation would suffer from liver failure.

4 out of the 10 reports were seen in cirrhotic patients, 2 had extended limb RYGB, 1 distal RYGB, 2 had early or late complication. Extended limb or distal versions of RYGB can behave like biliopancreatic diversion with higher potential for malabsorption. These versions of RYGB may hence be more likely to predispose to liver failure.

High risk groups of patients undergoing RYGB, such as patients with incidental finding of cirrhosis, extended limb or distal versions of RYGB, complications of surgery and alcohol abuse, should be followed up carefully with routine lifelong monitoring of liver function tests.

6. Conclusions

Bariatric surgery provides effective treatment for obesity and metabolic complications. Lifestyle modification with weight loss is currently the most important treatment in NAFLD patients, but this is hard to achieve in clinical practice. Recent reports showed that bariatric surgery could resolve NASH in 84% of the patients without worsening of fibrosis. These findings support the notion that bariatric surgery is an effective treatment for NASH patients. Bariatric surgery, especially sleeve gastrectomy, also seems to be feasible in compensated cirrhotic patients. Special attention should be paid to recurrent and de novo NAFLD after liver transplantation. It is worthy of note that, on a case-by-case basis and prior to liver transplantation, the feasibility of bariatric surgery as well as interventions and how they are timed and sequenced should be discussed in a broad multidisciplinary discussion.

Liver decompensation or failure hardly occurs in patients undergoing RYGB without pre-existing cirrhosis. Potentially fatal liver complications are described with severe malabsorptive bariatric procedures such as biliopancreatic diversion or distal versions of RYGB. Closely monitoring of liver function is recommended in this high risk group and early referral for surgical conversion is necessary.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Anja Geerts* and Sander Lefere
Hepatology Research Unit, Department of Internal Medicine and Pediatrics, Liver
Research Center Ghent, Ghent University, Ghent, Belgium

*Address all correspondence to: anja.geerts@uzgent.be

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