Bariatric Surgery and NASH: A Feasible Option

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18.1 Background

In 1992, the National Institutes of Health (NIH) issued the eligibility criteria for bariatric surgery [1], which are currently endorsed by the majority of scientific societies [2, 3]. The NIH criteria include a body mass index (BMI) ≥ 40 kg/m^2 or a BMI between 35 and 40 kg/m^2 in individuals with high-risk comorbidities, such as decompensated type 2 diabetes or cardiovascular risk factors.

The joint statement of second Diabetes Surgery Summit (DSS-II), an international consensus conference, however, suggests that gastrointestinal "surgery should also be considered for patients with T2D and BMI 30.0–34.9 kg/m^2 [4] if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications." Adjustments on BMI should also be made in relation to the ethnicity and body fat distribution.

Non-alcoholic steatohepatitis (NASH) can be plenty considered as a high-risk comorbidity of obesity.

Indeed, both non-alcoholic fatty liver disease (NAFLD) and NASH are regarded as the liver manifestation of the metabolic syndrome, which is a cluster of clinical and metabolic parameters including obesity, insulin resistance, hyperlipidemia, and hypertension [5].

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Obesity is the most common risk factor for NAFLD with more than 95% of the patients undergoing bariatric subjects being affected by NAFLD [6]. Instead, data on the prevalence of NASH in subject who underwent bariatric surgery are hectic, with some authors reporting a prevalence of 35% [7], others of 45% [8], and yet others of only 7% [9].

Regarding bariatric surgery to treat NAFLD, the EASL–EASD–EASO Clinical Practice Guidelines for the management of NAFLD [10] state with evidence B that "by improving obesity and diabetes, bariatric (metabolic) surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis."

The American Association for the Study of Liver Diseases in its recent practice guidelines [11] outline that "foregut bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH," but that "it is premature to consider foregut bariatric surgery as an established option to specifically treat NASH."

18.2 Types of Bariatric Operations

18.2.1 Intragastric Balloon

Endoscopic bariatric therapies fill in the invasiveness and efficacy gaps in the spectrum of options currently available for the management of overweight and obesity. Intragastric balloons (IGBs) (Fig. 18.1) have been demonstrated to be effective therapeutic options for the treatment of obesity and obesity-related metabolic conditions, holding a low rate of adverse events [12, 13]. IGBs can be either resorbable

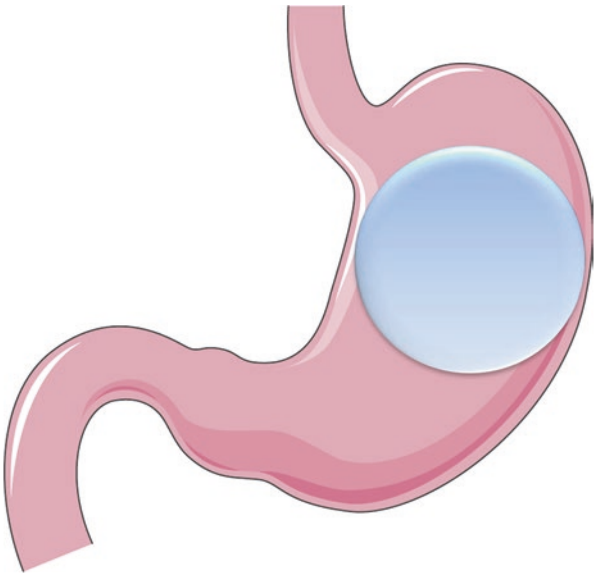

Fig. 18.1 Intragastric balloon occupying part of the stomach. The majority of the balloons are positioned via endoscopy while a new device can be swallowed as a small capsule connected to a tubing system and is then inflated with normal saline once it has reached the stomach

or non-resorbable. Non-resorbable IGB placement and removal requires sedation and upper endoscopy and mainly include the following: BioEnterics (BIB, Inamed Corporation, Arklow, County Wicklow, Ireland and Bioenterics Corporation, carpentry, California, USA) and Orbera (Apollo Endosurgery, Austin, TX, United States, now Allergan). On the other hand, Elipse Balloon System (Allurion Technologies, Natick, MA, USA) is a novel IGB device that requires neither endoscopy nor sedation for placement or removal. In fact, it can be swallowed as a small capsule connected to a tubing system and is then inflated with normal saline once it has reached the stomach. An abdominal X-ray is performed to confirm the correct balloon positioning. After about 16 weeks, the balloon is designed to spontaneously deflate and is eliminated through the gastrointestinal tract.

Early complications mainly comprise epigastric pain and nausea that develop in a majority of patients (70–90%) several hours after IGB insertion; such symptoms, however, usually regress 7 days from IGB placement. Early endoscopic IGB removal due to digestive intolerance is reported in 2.43%.

Late complications have been inconsistently described by various authors and include gastroesophageal reflux disease (GERD) esophagitis (1–11%), gastroduodenal ulcers (0.4%), gastric perforation (0.21%), hypokalemia (6–8%), and kidney failure (1–4%).

Deflation or rupture of the IGB is a potentially threatening complication, with rates ranging from 19 to 27% in earlier studies, to 0–4% in later ones. This can cause migration down to the ileo-cecal valve causing intestinal obstruction. Bowel obstruction may require surgical, endoscopic, or combined IGB removal and is described in 0.17% of cases [13, 14].

18.2.2 Adjustable Gastric Banding

Adjustable gastric banding (AGB) (Fig. 18.2) is a solely restrictive bariatric surgical procedure, involving an inflatable silicone band, placed around the proximal stomach, and connected to a tubing-port system placed subcutaneously. The gastric portion located just above the band forms a pouch with a capacity of approximately 10–20 mL. The AGB can be subsequently inflated through the tubing-port system. The small gastric pouch is quickly replenished with food and slows down the bolus passage, leading to early satiety.

In 2011, the Food and Drug Administration (FDA) revised its indications by expanding the approved BMI category to 30–40 kg/m^2 [15]. As a simple, rapid, and reversible operation, AGB gained widespread popularity between 2003 and 2008, followed by a steep decline after this period [16].

Long-term outcome studies have revealed a rather variably elevated rate of late complications (1.1–60%) and reoperations (0.92–60%). The major long-term complications after AGB include persistent nausea and vomiting, dysphagia, GERD, port-site infection, tubing system malfunction, and gastric pouch dilatation, with the most severe adverse events consisting of band slippage, erosion, and migration.

Fig. 18.2 Adjustable gastric banding (AGB) involves an inflatable silicone band, placed around the proximal stomach and connected to a tubing-port system placed subcutaneously. The gastric portion located just above the band forms a pouch with a capacity of approximately 10–20 mL. The AGB can be subsequently inflated through the tubing-port system to reduce the gastric volume thus inducing satiety

18.2.3 Sleeve Gastrectomy

Sleeve gastrectomy (SG) (Fig. 18.3) entails the longitudinal resection of the stomach along its greater curvature, carefully performing a complete excision of the gastric fundus, part of the body and antrum, yet maintaining a portion of the latter and the pylorus itself. The tube-shaped gastric sleeve maintains a capacity of approximately 60–150 mL.

SG was initially considered the first step of a more complex procedure (i.e., biliopancreatic diversion with duodenal switch). Nonetheless, with time this operation proved to generate superimposable weight loss and comorbidity resolution rates to that of other long-lived bariatric surgical procedures (namely RYGB) [17]. This allowed SG to become the most commonly performed bariatric operation worldwide [18].

Major complications after SG include staple-line bleeding, gastric leak, stricture, GERD, and nutrient deficiency. Early and late complications were documented to be 0.7–5.8% and 1.2–10.8%, respectively. Reoperation rates range from 1 to 34% and also include those revisional bariatric procedures due to weight regain or severe GERD non-responsive to medical treatment [19].

18.2.4 Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) (Fig. 18.4) has been for long time the most popular bariatric-metabolic procedure worldwide and has been superseded only in recent years by SG.

RYGB involves the formation of a gastric pouch of approximately 30 mL which is anastomosed to the jejunum which is transected approximately 50–75 cm distal to

Fig. 18.3 Sleeve gastrectomy (SG) entails the longitudinal resection of the stomach along its greater curvature, carefully performing a complete excision of the gastric fundus, part of the body and antrum, yet maintaining a portion of the latter and the pylorus itself. The tube-shaped gastric sleeve maintains a capacity of approximately 60–150 mL

the ligament of Treitz (alimentary limb). The excluded gastric remnant in continuity with the duodenum and proximal jejunum represents the biliopancreatic limb, which is then connected to the alimentary channel through a jejuno-jejunostomy, 100–150 cm distal to the gastro-jejunostomy.

Early complications are stated to range from 4.8 to 9.4%, while late complications between 14.8 and 20.2% of cases. Reoperations are necessary in 2.5–38% of patients. Complications comprise anastomotic leaks, anastomotic strictures, marginal ulcers, internal hernia, dumping syndrome, and micronutrient deficiencies [19].

18.2.5 Biliopancreatic Diversion with Duodenal Switch

Initially projected by Scopinaro in 1979 [20], the biliopancreatic diversion (BPD) (Fig. 18.5) was consequently modified with the intention of reducing symptoms related to the "postgastrectomy syndrome" (i.e., nausea, vomiting, dumping syndrome, marginal ulcers). The duodenal switch (DS) adaptation of BPD was

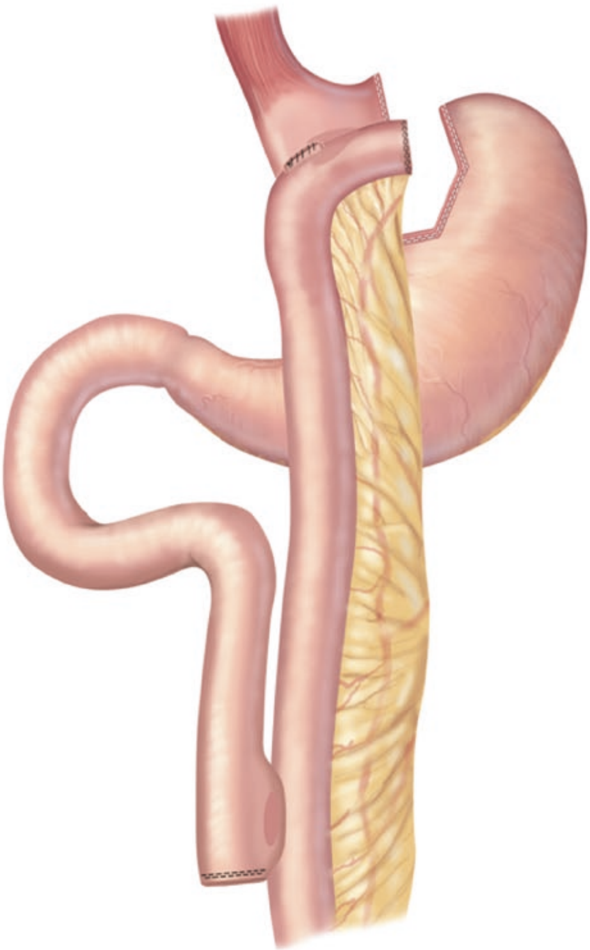

Fig. 18.4 Roux-en-Y gastric bypass (RYGB) involves the formation of a gastric pouch of approximately 30 mL which is anastomosed to the jejunum which is transected approximately 50–75 cm distal to the ligament of Treitz (alimentary limb). The excluded gastric remnant in continuity with the duodenum and proximal jejunum represents the biliopancreatic limb, which is then connected to the alimentary channel through a jejuno-jejunostomy, 100–150 cm distal to the gastro-jejunostomy. (With the kind permission of the New England Journal of Medicine (N Engl J Med 2012; 366:1577–1585))

described by Hess and Marceau [21, 22] aiming at the conservation of the pylorus which in turn contributes to reducing the risk of anastomotic marginal ulcers and dumping syndrome.

The first stage of the surgical procedure involves a SG which is then transected about 2 cm below the pylorus. The ileum is transected 250 cm cephalad to the ileo-cecal valve, and a duodenal-ileal anastomosis is created (alimentary limb). The biliopancreatic limb is anastomosed to the alimentary limb by an ileo-ileal anastomosis, 100 cm from the ileo-cecal valve, to form the common limb. This procedure comprises restrictive features to a greater malabsorptive component due to the short length of the alimentary tract, resulting in an elevated degree of nutrient malabsorption compared to other bariatric procedures. BPD-DS is also performed as a two-stage operation in order to reduce perioperative risk in super-obese patients (i.e., BMI >50 kg/m^2).

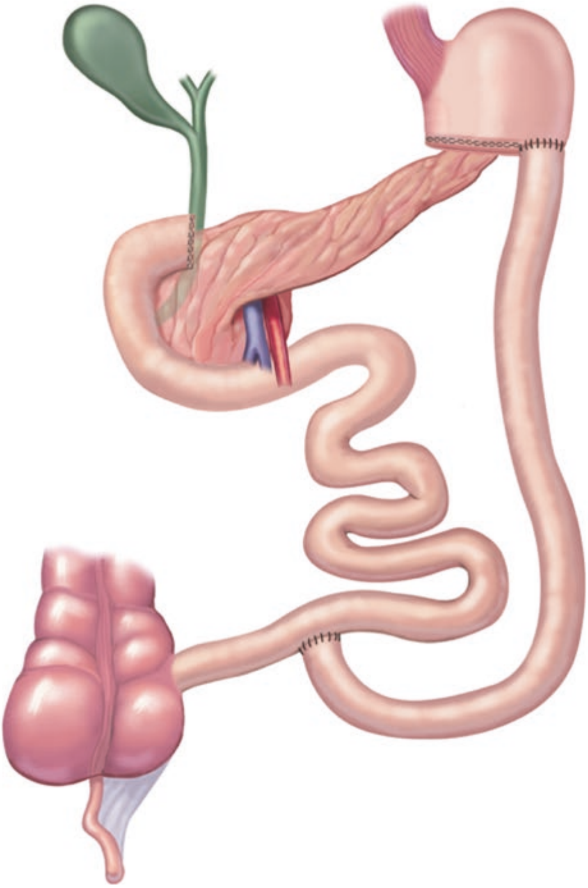

Fig. 18.5 Classic biliopancreatic diversion (BPD) consists of an about 60% distal gastric resection with stapled closure of the duodenal stump. The residual volume of the stomach is about 300 mL. The small bowel is transected at 2.5 m from the ileo-cecal valve, and its distal end is anastomosed to the remaining stomach. The proximal end of the ileum, comprising the remaining small bowel carrying the biliopancreatic juice and excluded from food transit, is anastomosed in an end-to-side fashion to the bowel 50 cm proximal to the ileo-caecal valve. Consequently, the total length of absorbing bowel is brought to 250 cm, the final 50 cm of which, the so-called common channel, represents the site where ingested food and biliopancreatic juices mix. (With the kind permission of the New England Journal of Medicine (N Engl J Med 2012; 366:1577–1585))

Early and late complications have been reported in 5.5–7.6 and 3.5–25.6%, respectively, while rate of reoperations is between 1.9 and 11.5%. BPD-DS complications include GERD, anastomotic or gastric leak, anastomotic stricture, internal hernia, severe malnutrition, nutrient deficiencies, increased bowel movements, and malodorous stools [19, 23, 24].

A modification of BPD-DS, the single-anastomosis duodeno-ileal switch (SADIS), has recently been introduced and is receiving growing attention. It has demonstrated promising weight loss and comorbidity resolution rates. However, it is still at an early stage and no definitive conclusion can be made regarding its safety and effectiveness.

18.3 Bariatric Surgery and NASH: Clinical Trials

No data are reported in the literature regarding the effect of bariatric surgery on NASH in comparison to lifestyle modifications in randomized-controlled trials (RCT), rather the majority of the available information derive from small cohort studies.

Recently, the results of an RCT with primary outcome the weight loss deriving from RYGB or SG was analysed for NAFLD histological changes [9]. Liver biopsies were obtained during surgery in the whole cohort consisting of 66 subjects and liver function test performed at 1, 6, and 12 months after surgery; however, no histological data were obtained after surgery. About half of the subjects had histological diagnosis of NASH. At 1 year, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (γGT) were all significantly reduced. Circulating levels of albumin and INR were reduced after RYGB but not after SG, which may have implied some liver damage.

A prospective study including 109 subjects had 79% of patients' retention at 1 year [25]. This study demonstrated histological resolution of NASH in 85% of the subjects at 1 year after bariatric surgery that consisted in RYGB, bilio-intestinal bypass, or gastric banding. In another prospective study from the same authors [26], 381 liver biopsies were performed at baseline, 267 at 1 year and 215 at 5 years after surgery. The percentage of patients with NASH declined from 27.4 to 14.2% at 5 years. Steatosis and ballooning were drastically reduced at 1 year remaining stable at 5 years; instead, fibrosis worsened at 5 years although more than 95% of the patients had a fibrosis score ≤F1.

Very recently, a meta-analysis [27] including 15 retrospective and 17 prospective cohort studies with 3093 liver biopsies was published. Bariatric surgery determined biopsy-proven resolution of steatosis in 66%, inflammation in 50%, ballooning in 76%, and fibrosis in 40% of subjects. However, in 12% of subjects fibrosis worsened if present or appeared if absent at the baseline.

The effect of bariatric surgery on fibrosis is, however, controversial. In fact, in another study [28] involving 160 subjects with biopsies taken during the operation and between 6 months and 5 years after surgery, NASH was present at baseline in 27% of subjects with morbid obesity, who underwent bariatric surgery. NASH resolved in 90% of the cases. Overall, fibrosis resolved in 53% of the patients and improved in 3%, while grades 2 and 3 resolved in 60%.

A recent meta-analysis including 21 studies and 2374 patients shows that NASH improved in 59% and fibrosis in 30% of the patients [29]. Interestingly, the improvement of histological features was higher with a wedge than with a needle biopsy meaning that the type of biopsy is relevant for a correct diagnosis of NASH.

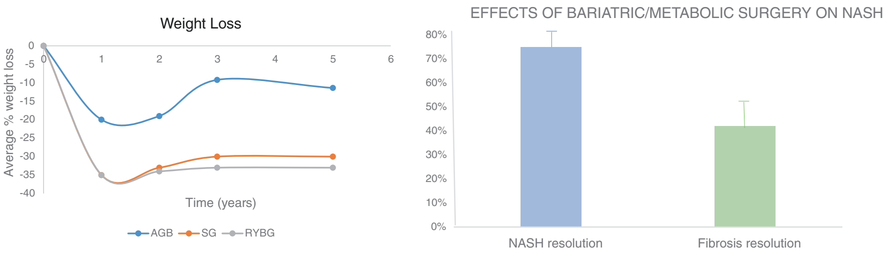

Fig. 18.6 Effects of bariatric/metabolic surgery on percent weight loss and on NASH and fibrosis resolution

At the moment, there are only two ongoing RCTs regarding the treatment of NASH with bariatric surgery. "A randomized controlled study on the effects of Roux-en-Y Gastric Bypass versus Sleeve Gastrectomy on Intensive Lifestyle Modifications on Non-Alcoholic Steato-Hepatitis," acronym BRAVES, on 288 obese subjects with NASH conducted at the Catholic University of Rome, Italy; ClinicalTrials.gov Identifier: NCT03524365.

The other RCT is "Vertical Sleeve Gastrectomy and Lifestyle Modification for the Treatment of Non-Alcoholic Steatohepatitis" conducted at the University of Minnesota—Clinical and Translational Science Institute on 60 participants. ClinicalTrials.gov Identifier: NCT03587831.

Few cases of hepatic failure have been described after biliopancreatic diversion with duodenal switch (BPD-DS) [30].

Figure 18.6 summarizes the effects of bariatric/metabolic surgery on percent weight loss and on NASH and fibrosis resolution.

18.4 Mechanisms of Action of Bariatric Surgery on NASH

Bariatric surgery has been renamed as "metabolic surgery" because some of its metabolic effects are independent of body weight reduction [4]. Metabolic surgery, in fact, dramatically improves insulin resistance just few days after BPD when the body weight was not significantly changed [31].

Metabolic surgery determines also type 2 diabetes remission with a weight-independent mechanism [32–36].

Forty-five milligrams of Pioglitazone daily for 6 months, a selective agonist for peroxisome proliferator-activated receptor-γ (PPAR-γ), in patients with type 2 diabetes or impaired glucose tolerance determined a significant improvement of histological and metabolic features of NASH, except for fibrosis, in comparison with placebo [37]. However, in another study with 30 mg of Pioglitazone per day fibrosis also improved [38].

In another RCT [39], 247 patients were randomized to one of the three arms: 30 mg of pioglitazone per day, 800 IU of Vitamin E per day, or placebo for 96 weeks. The primary outcome was an improvement in the NAFLD Activity Score (NAS) compared with placebo with a significance of <0.025. Although pioglitazone did not reach the statistical threshold, a significantly greater proportion of patients receiving pioglitazone had complete resolution of NAS as compared with placebo: 47% versus 21% ($p = 0.001$).

A recent meta-analysis shows that pioglitazone therapy significantly reduced advanced fibrosis in liver biopsy either in subjects with diabetes or not [40].

Weight loss is effective to improve NAFLD. A 10% weight loss significantly decreased liver steatosis as assessed by CT scan in the Look Ahead Cohort [41]. Another study showed that 7% weight loss significantly improved steatosis, lobular inflammation, ballooning, and NAS, with minimal changes in fibrosis [42].

Since metabolic surgery is effective not only in reducing insulin resistance but also in determining massive weight loss, it is difficult to dissect the effects of each component on NASH. Interestingly, pioglitazone treatment has clearly demonstrated that histological improvement of NASH can be achieved even with a modest weight gain. Therefore, metabolic surgery could improve histological feature of NASH mainly through its action on insulin resistance.

At this regard, the literature is plenty of evidence that RYGB ameliorates hepatic insulin resistance [43–45] early after surgery, while BPD improves whole-body insulin sensitivity [46–48].

Undoubtedly, the conspicuous weight loss that accompanies metabolic surgery contributes to the improvement of hepatic liver features of NASH.

At 1 year, BPD/DS produces a significantly higher weight loss, of 19 kg on average, than RYGB and 35 kg more than lifestyle modifications. At 3 years, RYGB causes a weight reduction of 16.3 kg more than LAGB [49].

Seventy-two percent of patients who underwent RYGB had >20% weight loss, and 39.7% had >30% weight loss at 10 years compared with 10.8% and 3.9%, respectively, of nonsurgical matches [50]. Patients undergone RYGB lost 9.7% more of their baseline weight than patients who underwent SG; this difference was much higher as compared with LAGB (16.9%).

18.4.1 Microbiota After Bariatric/Metabolic Surgery and Its Effect on NASH

Lachnospiraceae bacterium and *Barnesiella intestinihominis* are two bacterial species which are abundant in stool of mice that developed NAFLD, while *Bacteroides vulgatus* is scarcely represented [51]. When transferred into germ-free mice, the former two species induce NAFLD [51]. *Gammaproteobacteria* and *Prevotella* are abundant in the feces of children with NAFLD as compared with children without NAFLD [52].

The relative abundance of the class *Gammaproteobacteria*, belonging to the phylum *Proteobacteria*, is increased in stool of subjects who underwent bariatric surgery as compared with lean controls [53–55]. Another abundant phylum after bariatric/metabolic surgery and, in particular, RYGB is the Verrucomicrobia, i.e., *Akkermansia muciniphila* [56].

The gut microbiota is modified in NAFLD/NASH as it is modified after bariatric/metabolic surgery; however, there are no prospective studies investigating the changes of gut microbiota after gastrointestinal surgery in comparison with lifestyle modifications that can help to clarify the role of intestinal flora in NAFLD/NASH.

18.5 Conclusions

Metabolic surgery is an effective treatment not only for NAFLD but also for NASH with resolution of the histologic features of NASH in more than 80% of the cases and disappearance of fibrosis in almost 50% of the patients. It is unclear, however, if the effects on NASH are due to weight loss or improvement of insulin resistance or both because all studies are conducted for at least 1 year after surgery when the reduction of weight is massive.

RCTs are needed to quantify with grade 1 evidence the efficacy and safety of metabolic surgery on NASH.

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