Review Article

Endoscopic Bariatric and Metabolic Therapies for Liver Disease: Mechanisms, Benefits, and Associated Risks

Mengting Ren, Xinxin Zhou, Lu Lv and Feng Ji*

Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Abstract

Nonalcoholic fatty liver disease (NAFLD), including advanced-stage nonalcoholic steatohepatitis (NASH), is currently the most common chronic liver disease worldwide and is projected to become the leading indication for liver transplantation (LT). However, there are no effective pharmacological therapies for NAFLD. Endoscopic bariatric and metabolic therapies (EBMTs) are less invasive procedures for the treatment of obesity and its metabolic comorbidities. Several recent studies have demonstrated the beneficial effects of EBMTs on NAFLD/NASH. In this review, we summarize the major EBMTs and their mechanisms of action. We further discuss the current evidence on the efficacy and safety of EBMTs in people with NAFLD/NASH and obese cirrhotic LT candidates. The potential utility of EBMTs in reducing liver volume and perioperative complications in bariatric surgery candidates is also discussed. Moreover, we review the development of liver abscesses as a common serious adverse event in duodenal-jejunal bypass liner implantation.

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Introduction

The global prevalence of obesity has increased over the past few decades, reaching epidemic proportions.[1,2] Obesity is associated with several comorbidities, such as cardiovascular disease, type 2 diabetes mellitus (T2DM), metabolic syndrome, and certain cancers.[3,4] The health ramifications of obesity and its comorbidities and the associated medical expenses have imposed a considerable public health burden in both developed and developing countries.[5,6]

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease characterized by excessive accumulation of lipids in hepatocytes, and is considered as the hepatic manifestation of metabolic syndrome.[7] Given the increasing prevalence of obesity, NAFLD is currently the most common liver disease, affecting an estimated 25% of the general population and 30–90% of obese patients.[8–10] NAFLD encompasses a spectrum of conditions ranging from simple steatosis or nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), which may lead to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[7] Approximately 41% of NASH patients experience progression to fibrosis, and the annual incidence of HCC in people with NASH is 5.29 per 1,000 person–years.[9] In fact, NASH is currently the leading cause of liver transplantation (LT) in women in the US and the second leading cause in men; therefore, obesity management represents a significant challenge for LT candidates.[11]
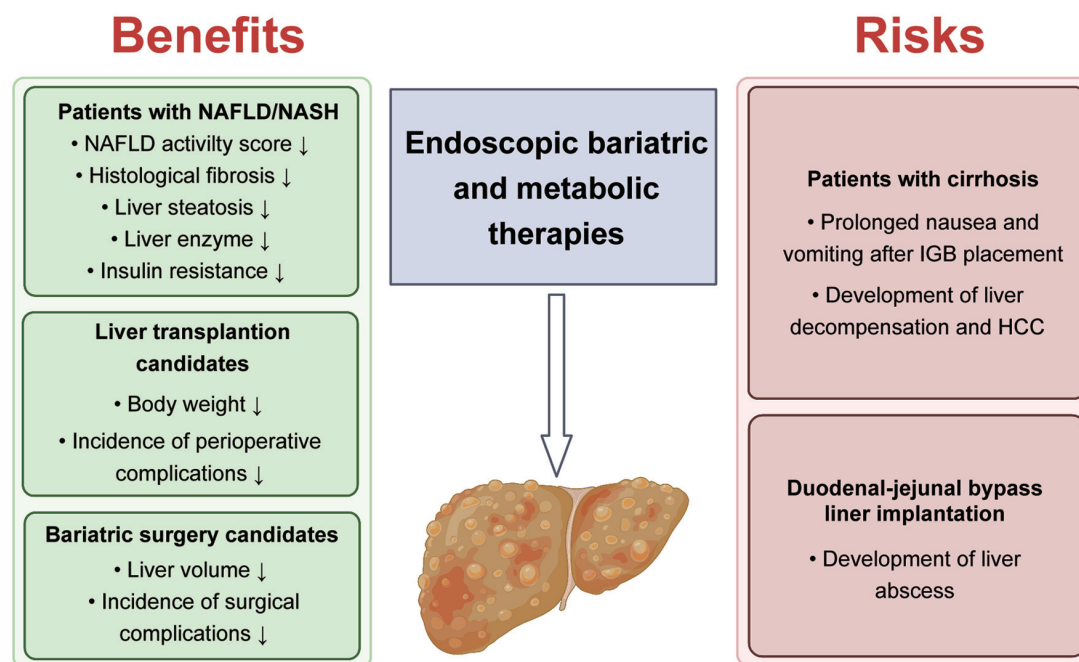
Although the global burden of NAFLD has been established, the optimal therapy for this disease remains investigational. Lifestyle modification is the cornerstone of NAFLD treatment, as there is currently no approved pharmacotherapy for NAFLD;[12] however, maintaining a long-term healthy lifestyle is challenging for people with NAFLD.[13] Currently ongoing clinical trials of several anti-NASH drugs such as saroglitazar, resmetirom, and cenicriviroc, have shown some benefits.[12,14] Bariatric surgery, the current most effective treatment for achieving long-term weight loss,[15] has been reported to improve liver histological characteristics and metabolic parameters in people with NASH.[16,17] However, the safety of bariatric surgery for those with this disease, especially those with cirrhosis, is not well established. In addition, the potential complications of bariatric surgery and the high cost are barriers to its wider use.[18]

In recent years, endoscopic bariatric and metabolic therapies (EBMTs) have emerged as safe and effective procedures for the treatment of obesity and its comorbidities, with lower associated costs and risk of complications than bariatric surgery.[19–21] The major EBMTs currently available include intragastric balloons (IGBs), endoscopic sleeve gastroplasty (ESG), primary obesity surgery endoluminal (POSE), aspiration therapy, duodenal-jejunal bypass liner (DJBL), duodenal mucosal resurfacing (DMR), and incisionless magnetic anastomosis system.[22] Several observational studies suggest that EBMTs can improve liver steatosis, fi-

Benefits

Patients with NAFLD/NASH
- NAFLD activilty score ↓
- Histological fibrosis ↓
- Liver steatosis ↓
- Liver enzyme ↓
- Insulin resistance ↓

Liver transplantion candidates
- Body weight ↓
- Incidence of perioperative complications ↓

Bariatric surgery candidates
- Liver volume ↓
- Incidence of surgical complications ↓

Endoscopic bariatric and metabolic therapies

Risks

Patients with cirrhosis
- Prolonged nausea and vomiting after IGB placement
- Development of liver decompensation and HCC

Duodenal-jejunal bypass liner implantation
- Development of liver abscess

Fig. 1. Benefits and associated risks of endoscopic bariatric and metabolic therapies for liver disease. HCC, hepatocellular carcinoma; IGB, intragastric balloon; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

brosis, NAFLD activity score (NAS), and metabolic parameters in people with NAFLD/NASH.[23–25] Among obese LT candidates, EBMTs have been reported to induce significant short-term weight loss, thus reducing the incidence of obesity-related complications.[26] Moreover, EBMTs were shown to significantly reduce liver volume in bariatric surgery candidates, leading to a clearer field of vision for surgeons and reductions in the rate of perioperative complications.[27]

In this article, we review the weight loss and metabolic benefits of EBMTs and their underlying mechanisms of action. We also review the evidence pertaining to the efficacy and safety of EBMTs in people with NAFLD/NASH and those with obesity and cirrhosis awaiting LT. Moreover, we discuss the potential role of EBMTs in reducing liver volume and surgical complications in those undergoing bariatric surgery. The current understanding of liver abscesses as a common serious adverse event (SAE) of DJBL implantation is also summarized. Figure 1 illustrates the benefits and associated risks of EBMTs for liver disease.

Weight loss and metabolic benefits of EBMTs

IGBs

IGBs are the most well established EBMTs for class I and II obesity (body mass index [BMI] of 30 to <40 kg/m²) worldwide, two of which, the Orbera Intragastric Balloon System (previously known as the BioEnterics Intragastric Balloon or BIB; Apollo Endosurgery, Austin, TX, USA) and the Obalon Balloon System (Obalon Therapeutics, Carlsbad, CA, USA) are currently approved by the US Food and Drug Administration (FDA). The Orbera fluid-filled IGBs are endoscopically placed and then removed endoscopally after 6 months of treatment. In a multicenter post-FDA regulatory approval study conducted in a real-world setting, Orbera IGBs achieved a mean total body weight loss (TBWL) of 11.8% at 6 months.[28] The Obalon Balloon System consists of three 250 mL nitrogen-filled balloons that are placed by swallowing and removed after 6 months by endoscopy. A double-blind, randomized, sham-controlled trial investigated the efficacy and safety of Obalon IGBs for weight loss. On completion of treatment at 6 months, the mean TBWL achieved was 7.1±5.0% in the treatment and 3.6±5.1% in the control group.[29] In addition to weight loss, IGB treatment also confers metabolic benefits, with significant improvements in lipid profile, blood sugar, and blood pressure measurements after 6 months of IGB therapy.[28]

Endoscopic gastroplasty

Endoscopic gastroplasty is a promising bariatric endoluminal procedure that aims to reduce gastric volume and gastric motility. Two devices are currently approved by the FDA for this procedure, the OverStitch Endoscopic Suturing System (Apollo Endosurgery) for ESG and the incisionless operating platform (USGI Medical, San Clemente, CA, USA) for POSE. ESG was found to achieve worse long-term weight loss outcomes than laparoscopic sleeve gastrectomy and laparoscopic greater curvature plication in obese people (TBWL at 2 years: 18.5%, 28.3%, and 26.9%, respectively).[30] However, patients receiving ESG had significantly shorter hospital stays (1 day vs. 3 days for both laparoscopic procedures) and lower complication rates (0.5% vs. 4.9% in laparoscopic sleeve gastrectomy and 8.3% in laparoscopic greater curvature plication). Regarding the safety and efficacy of POSE for weight loss, a meta-analysis of seven studies with 613 people who received POSE had a pooled TBWL of 13.45% (95% confidence interval [CI]: 8.93–17.97) at 3–6 months and 12.68% (95% CI: 8.13–17.23) at 12–15 months.[31]

Aspiration therapy

Aspiration therapy utilizes an FDA-approved device called As-

Table 1. The characteristics and mechanisms of action of endoscopic bariatric and metabolic therapies

Type of EBMT	Characteristic	Mechanism of action
Intragastric balloons	Orbera Intragastric Balloon System (Apollo Endosurgery): fluid-filled, endoscopically placed and removed through endoscopy. Obalon Balloon System (Obalon Therapeutics): gas-filled, placed by swallowing and removed via endoscopy	Gastric volume ↓; Gastric emptying ↓; Gastric accommodation ↓; Gut hormone: ghrelin, PYY −; Circulating sirtuin 1↑
Endoscopic sleeve gastroplasty	OverStitch Endoscopic Suturing System (Apollo Endosurgery): full thickness suturing along the greater curvature of the stomach, leaving the fundus intact	Gastric volume ↓; Gastric emptying ↓; Gut hormone: ghrelin? ↓, GLP-1 −, PYY −
Primary obesity surgery endoluminal	Incisionless operating platform (USGI Medical): plications are created first near the fundus and then in the distal gastric body	Gastric volume ↓; Gastric emptying ↓; Gut hormone: ghrelin ↑, PYY ↑
Aspiration therapy	AspireAssist (Aspire Bariatrics): endoscopic placed gastrostomy tube	Calorie absorption ↓; Water consumption ↑
Duodena-jejunal bypass liner	Endobarrier (GI Dynamics): a 60-cm impermeable sleeve placed via endoscopy to prevent nutrient absorption in the duodenum and proximal jejunum	Intestinal malabsorption; Foregut hypothesis; Gastric emptying ↓; Gut hormone: GLP-1 ↑, PYY ↑, ghrelin ↑, GIP ↓, CCK ↓; Postprandial unconjugated bile acid responses ↑;Gut microbiota: typical small intestinal bacteria ↑
Duodenal mucosal resurfacing	Hydrothermal ablation of the duodenal mucosa using a minimally invasive balloon catheter	Intestinal malabsorption; Foregut hypothesis

CCK, cholecystokinin; EBMTs, endoscopic bariatric and metabolic therapies; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY.

pireAssist (Aspire Bariatrics, King of Prussia, PA, USA) that allows postprandial drainage of approximately 30% of the ingested calories through an endoscopic placed gastrostomy tube.[32] Several studies have demonstrated the efficacy and safety of the device.[32–35] In a meta-analysis of five studies with a combined study population of 431 obese people conducted by the Association for Bariatric Endoscopy and the American Society for Gastrointestinal Endoscopy, patients receiving AspireAssist had a pooled TBWL of 16.6% (95% CI: 12.8–20.4) at 1 year. A significant weight loss was maintained at 2, 3, and 4 years of follow-up.[36] AspireAssist was also reported to have beneficial effects on obesity-related co-morbidities. According to a meta-analysis of five studies with a combined study population of 590 obese patients, after treatment with AspireAssist for 1 year, systolic blood pressure decreased by 7.8 (95% CI: 4.9–10.7) mmHg, diastolic blood pressure decreased by 5.1 (95% CI: 3.2–7.0) mmHg, triglycerides by 15.8 (95% CI: 7.6–24.0) mg/dL, hemoglobin A1c (HbA1c) by 1.3 (95% CI: 0.8–1.8) %, alanine aminotransferase (ALT) by 7.5 (95% CI: 5.2–9.8) U/L, and aspartate transaminase (AST) by 2.7 (95% CI: 1.3–4.1) U/L.[37]

DJBL

The DJBL (Endobarrier, GI Dynamics, Lexington, MA, USA), also known as a duodenal-jejunal bypass sleeve, is a 60 cm impermeable sleeve placed via endoscopy to prevent nutrient absorption in the duodenum and proximal jejunum. Several studies have demonstrated the efficacy of DJBL in achieving weight loss and glycemic control. A meta-analysis of 14 studies enrolling 388 obese people with T2DM found that DJBL improved HbA1c by 1.3 (95% CI: 1.0–1.6)% and homeostasis model assessment of insulin resistance (HOMA-IR) by 4.6 (95% CI: 2.9–6.3).[38] Moreover, the mean weight loss was 11.3 kg (95% CI: 10.3–12.2), corresponding to an average BMI reduction of 4.1 kg/m^2 (95% CI: 3.4–4.9), TBWL of 18.9% (95% CI: 7.2–30.6), and excess weight loss (EWL) of 36.9% (95% CI: 29.2–44.6). Improved liver parameters and metabolic parameters[39] and reduced cardiovascular risks[40]

were also observed after the removal of DJBL.

DMR

DMR is a type of EBMT that involves hydrothermal ablation of the duodenal mucosa using a minimally invasive balloon catheter. The procedure aims to reduce the effects of anti-incretins in the proximal small bowel, thus regulating blood glucose levels. A recent meta-analysis of four studies enrolling 127 patients explored the effects of DMR in patients with T2DM.[41] The results showed that pooled HbA1c decreased by 0.94% (95% CI: 0.68–21.21, $p<0.001$). However, there was no significant change in body weight, with a mean difference of 1.84 (95% CI: 2.09–5.78) kg, $p=0.360$.[41]

Mechanisms of action of EBMTs

Gastric EBMTs

The primary mechanism of restrictive gastric EBMTs, including space-occupying devices (e.g., IGBs) and endoscopic gastroplasty (e.g., ESG and POSE), is to limit the intake of calories by reducing gastric volume and thereby achieving satiety. However, a recent meta-analysis found no significant correlation between IGB filling volume and TBWL on meta-regression analysis,[42] indicating that additional mechanisms may also be at play (Table 1).

IGB implantation may alter gastric motility. IGB implantation was found to significantly delay gastric emptying,[43–45] which returned to normal level after IGB removal.[43] Furthermore, the gastric emptying time was positively correlated with weight loss.[43,45] In addition, IGB placement altered gastric accommodation, and changed the distribution of food, resulting in distention of the antrum and relaxation of the fundus.[46]

Changes in gut hormones following IGBs implantation are currently debated. Ghrelin is an orexigenic hormone pro-

duced mainly by the stomach. Samson *et al*.[47,48] found an increase in ghrelin level with IGB *in situ* that returned to baseline after IGB removal. In contrast, plasma ghrelin levels were reported to decrease[44] and remain stable[49] in two other independent studies. Levels of postprandial peptide YY (PYY), an appetite-suppressing hormone, remained stable after IGB implantation.[47] Levels of circulating sirtuin 1, a deacetylase that regulates metabolism and controls several physiological processes,[50] increased after IGB insertion.[51]

The ESG procedure appears to lead to decreased ghrelin level without inducing any significant changes in glucagon-like peptide-1 (GLP-1) or PYY levels. It has also been shown to delay gastric emptying and increase satiation.[52] In contrast, POSE may significantly delay gastric emptying and increase ghrelin and PYY levels. Moreover, post-POSE gastric emptying time and the magnitude of change of postprandial PYY levels were both reported to be independent predictors of weight loss after POSE.[53] The primary mechanism of action of AspireAssist is reduced caloric absorption. Moreover, increased water consumption, which increases satiety, also induces weight loss.[32]

Small intestine EBMTs

The main mechanism of action of small intestine EBMTs is intestinal malabsorption. The foregut hypothesis can explain the partial glycemic benefits of DJBL and DMR. Ingested nutrients stimulate the release of an unknown factor from the duodenum and proximal jejunum, contributing to the development of T2DM.[54] As DJBL and DMR bypass the foregut, the release of this putative diabetogenic signal is prevented. Various factors, such as gut hormones, bile acid levels, gastric motility, and intestinal microbiota, may contribute to the weight loss and metabolic benefits of DJBL. Following DJBL implantation, GLP-1 response,[55–57] PYY,[57,58] and postprandial ghrelin[58] all increased, while reduction in the levels of glucose-dependent insulinotropic polypeptide (GIP)[55] and cholecystokinin (CCK)[58] were observed. Moreover, DJBL implantation for 6 months significantly increased postprandial unconjugated bile acid responses and disrupted the bile acid-farnesoid X receptor-fibroblast growth factor 19 axis.[59] DJBL also delays gastric emptying, but the effect is reversed after removal of the device. Moreover, changes in gastric emptying are not associated with weight loss or T2DM control.[60]

Alteration of intestinal microbiota may also play a role in the action of DJBL. De Jonge *et al*.[61] analyzed the fecal microbiota profile of obese T2DM patients who received DJBL implantation at baseline, at 6 months after device placement in situ, and at 6 months after the removal of the device. They found that the abundance of typical small intestinal bacteria such as *Proteobacteria*, *Veillonella*, and *Lactobacillus* spp. increased after 6 months of DJBL treatment, but returned to baseline after removal of the device, though the weight loss remained significant.[61]

EBMTs for the treatment of NAFLD/NASH

In recent years, as the weight loss and metabolic benefits of EBMTs have been widely demonstrated, an increasing number of studies have begun to focus on the potential utility of EMBTs in the treatment of people with NAFLD/NASH. The latest clinical practice guidelines of the Asian Pacific Association for the Study of the Liver on metabolic associated fatty liver disease mention the potential utility of EBMTs for the treatment of this disease.[62] However, most studies evaluated the effects of EBMTs on imaging and serological outcomes in NAFLD; only a few studies reported changes in liver histological characteristics (Table 2).[21,23–25,33,39,63,64–75]

Recently, Jirapinyo *et al*.[76] performed a meta-analysis of 18 studies exploring the potential role of FDA-approved EBMTs for the treatment of NAFLD. They found that FDA-approved EBMTs significantly reduced the liver fibrosis score by a standardized mean difference (SMD) of 0.7 (95% CI: 0.1–1.3, $p=0.02$). There was also significant improvement in ALT (MD −9.0 [95% CI: −11.6 to −6.4] U/L, $p<0.0001$), hepatic steatosis (SMD −1.0 [95% CI: −1.2 to −0.8], $p<0.0001$), and NAS values (MD −2.5 [95% CI: −3.5 to −1.5], $p<0.0001$).[76] However, non-FDA-approved EBMTs were not included in the meta-analysis.

Histological evidence

Liver biopsy is considered the gold standard for the diagnosis of NAFLD/NASH.[77] To date, two studies,[24,63] both focusing on IGBs, reported changes in liver histology in NAFLD/NASH patients following EBMTs. A pilot, randomized, sham-controlled study conducted in Singapore evaluated the efficacy of Orbera IGB in improving biopsy-proven NASH.[63] After 6 months of treatment, the median NAS in the BIB group was 2 (interquartile range [IQR]: 0.75, $n=8$) and was significantly lower than that in the sham group (median NAS, 4 [IQR: 2.25], $p=0.03$).[63] A tendency toward improvement was observed in the liver steatosis score, but the difference was not statistically significant.[63] In terms of liver histology, there were no significant changes in lobular inflammation, hepatocellular ballooning, or fibrosis score.[63] Regarding weight loss, the decrease in BMI in the BIB group was significantly greater than that in the sham control group (median 1.52 [range: 0.36–3.37] kg/m² vs. 0.8 [range: −0.74 to 1.33] kg/m², $p=0.0008$).[63] Altogether, this short-term pilot study suggests that IGBs is a useful novel approach for managing NAFLD/NASH.

More recently, Bazerbachi *et al*.[24] performed an open-label, prospective study (NCT02880189) to evaluate the effects of a 6-month treatment with a single fluid-filled IGB (Orbera) on the metabolic and histological features of NASH in 20 obese people. Improvement in NAS and fibrosis regression were both observed.[24] NAS improved in 18/20 subjects (90%), with a median decrease of 3 (range: 1–4) points; histologic fibrosis improved in 3/20, remained unchanged in 12/20, and worsened in 5/20 subjects.[24] Fibrosis detected by magnetic resonance elastography improved by 1.5 stage in 10/20 individuals.[24] Overall, half the people met FDA-defined endpoints for NASH resolution and fibrosis improvement. The study indicated that IGB was safe and effective for NAFLD/NASH management, and resulted in reversal of the natural history of NAFLD and NASH despite the short duration of the intervention.

Nonhistological evidence

As liver biopsy is an invasive method associated with risk of pain, bleeding, and bile duct injury, most studies have evaluated liver steatosis and fibrosis using noninvasive tests that have been previously validated and are widely used in clinical practice. Liver stiffness detected by elastography[78] and blood-based noninvasive fibrosis scoring systems, including NAFLD fibrosis score (NFS)[79] and fibrosis-4 (FIB-4),[80] are used to assess the presence of fibrosis. Among these, reduction in FIB-4 was reported to be positively correlated with histological improvement in liver fibrosis in people with NASH.[81] The controlled attenuation parameter (CAP) assessed by transient elastography,[78] proton density fat fraction measured by magnetic resonance imaging (MRI-PDFF), and blood-based scoring system hepatic steatosis

Table 2. Summary of studies reporting the effects of EBMTs on biomarkers of NAFLD

Study	Type of EBMT	Participants	Study design	Total subjects (Follow-up)
Frutos *et al*. 2007[75]	IGB	obese patients	prospective noncomparative	31 (6 mo)
Ricci *et al*. 2008[67]	IGB	obese patients	retrospective noncomparative	103 (6 mo)
Donadio *et al*. 2009[65]	IGB	obese patients	prospective noncomparative	40 (6 mo)
Stimac *et al*. 2011[66]	IGB	obese patients	prospective noncomparative	171 (6 mo)
Lee *et al*. 2012[63]	IGB	obese patients with NAFLD	RCT (vs. sham)	8 (6 mo)
Nguyen *et al*. 2017[64]	IGB	obese patients with NAFLD	retrospective noncomparative	135 (6 mo)
Bazerbachi *et al*. 2021[24]	IGB	obese patients with NAFLD	prospective noncomparative	21 (6 mo)
Salomone *et al*. 2021[23]	IGB	obese patients with NAFLD	retrospective noncomparative	26 (6 mo)
Hajifathalian *et al*. 2020[25]	ESG	obese patients with NAFLD	prospective noncomparative	118 (24 mo)
Lopez-Nava *et al*. 2020[68]	POSE-2	obese patients	prospective noncomparative	41 (6 mo)
Thompson *et al*. 2016[33]	aspiration therapy	obese patients	RCT (vs. lifestyle counseling)	111 (12 mo)
de Jonge *et al*. 2013[39]	DJBL	obese patients with T2DM	prospective noncomparative	17 (12 mo)
Forner *et al*. 2017[72]	DJBL	obese patients with T2DM	combined retrospective and prospective noncomparative	114 (12 mo)
Gollisch *et al*. 2017[69]	DJBL	obese patients with T2DM	retrospective noncomparative	20 (12 mo)
Karlas *et al*. 2018[70]	DJBL	obese patients with T2DM	prospective noncomparative	31 (12 mo)
Ryder *et al*. 2019[71]	DJBL	obese patients with T2DM	prospective noncomparative	61 (12 mo)
Haidry *et al*. 2019[74]	DMR	patients with T2DM	prospective noncomparative	44 (24 w)
van Baar *et al*. 2020[21]	DMR	patients with T2DM	prospective noncomparative	46 (12 mo)
Mingrone *et al*. 2021[73]	DMR	patients with T2DM	RCT (vs. sham)	56 (24 w)

DJBL, duodenal-jejunal bypass liner; DMR, duodenal mucosal resurfacing; EBMTs, endoscopic bariatric and metabolic therapies; ESG, endoscopic sleeve gastroplasty; IGB, intragastric balloon; NAFLD, nonalcoholic fatty liver disease; POSE, primary obesity surgery endoluminal; RCT, randomized clinical trial; T2DM, type 2 diabetes mellitus.

index (HSI),[82] are used to evaluate the degree of steatosis.

IGBs: IGBs are the most frequently studied EBMTs for the treatment of NAFLD. A retrospective study in Italy investigated the effects of Orbera IGBs in 26 people with NAFLD and advanced fibrosis.[23] After 6 months of IGB treatment, significant reduction in liver stiffness as measured using transient elastography (from 13.3 ± 3.2 kPa to 11.3 ± 2.8 kPa, $p<0.001$), FIB-4 (from 3.2 ± 0.7 to 2.7 ± 0.8, $p<0.001$), and CAP (from 355 [range: 298–400] dB/m to 296 [range: 255–352] dB/m, $p<0.001$) were observed, indicating that IGB ameliorated liver fibrosis and steatosis in patients with NASH.[23] In addition, there was a significant improvement in the serum levels of ALT (from 84.5 ± 42.3 U/L to 46.7 ± 24.6 U/L, $p<0.001$) and AST (from 72.1 ± 40.3 U/L to 34.3 ± 22.4 U/L, $p<0.001$). Improvements in liver function were also observed in many studies following IGB implantation.[64–67,83,84]

A recently published meta-analysis of 13 studies with a combined enrollment of 624 participants explored the effects of IGBs on the known biomarkers of NAFLD.[85] The results showed that IGBs significantly decreased HOMA-IR by 1.56 (95% CI: 1.16–1.95), ALT by 11.53 (95% CI: 7.10–15.96) U/L, AST by 6.79 (95% CI 1.69–11.90) U/L, and gamma glutamyltransferase (GGT) by 10.54 (95% CI 6.32–14.75) U/L.[85] Moreover, the beneficial effects of endoscopic IGB were comparable to those of swallowable IGBs.[85] In another meta-analysis of nine studies comprising 442 IGB placements, short-term improvement in steatosis observed in 79.2% individuals and NAS in 83.5% after 6 months.[86]

Endoscopic gastroplasty: Endoscopic gastroplasty appears to have prolonged therapeutic effects on NAFLD.

In a prospective single-arm study, 118 obese people with NAFLD received ESG and completed a 2-year follow-up.[25] Noninvasive measurements (NFS and HSI) were used to evaluate liver fibrosis and steatosis, respectively. The results showed that ESG significantly reduced the average NFS by 0.3 points (95% CI: 0.02–0.6) per year ($p=0.034$) and the average HSI by four points (95% CI: 2–4) per year ($p<0.001$), indicating improvement in liver fibrosis and steatosis. Moreover, serum ALT levels decreased by 5 (95% CI: 3–7) U/L per year ($p<0.001$), AST levels decreased by 3 (95% CI: 2–4) U/L per year ($p<0.001$), and HOMA-IR decreased by 1.7 (95% CI: 0.2–3.2) per year ($p=0.029$).[25] Although liver biopsy and elastography were not performed, the results suggested that ESG is a promising alternative treatment in the management of NAFLD. In a prospective multicenter trial, POSE-2, which uses an incisionless operating platform initially designed to target gastric accommodation, was reported to significantly improve CAP by 79 dB/m ($p=0.00024$, $n=15$) and ALT by 14.3 mg/dL ($p=0.0074$, $n=36$) at 6 months after the procedure.[68]

Small intestine EBMTs: The role of small intestine EBMTs (DJBL and DMR) in the treatment of NAFLD is less well investigated. A retrospective study in Germany performed transient elastography to measure liver stiffness and CAP in 20 people with T2DM with DJBL implantation. At 12 months after implantation, median liver stiffness was significantly reduced from 10.4 (IQR: 6.0–14.3) kPa at baseline to 5.3 (IQR: 4.3–7.7) kPa ($p<0.01$). The median CAP had also significantly decreased from 343 (IQR: 326–3,840) dB/m at baseline to 317 (IQR: 269–375) dB/m ($p<0.05$).[69] Simi-

lar results were obtained by Karlas *et al*.,[70] who found that 12 months after DJBL implantation, the median CAP had improved from 332 (range: 249–368) dB/m at baseline to 283 (range: 180–368) dB/m (p=0.003) in 29 people with T2DM.[70] Moreover, serum ALT, AST, and GGT levels were considerably improved after DJBL treatment.[39,70–72,87] Collectively, the findings show that DJBL implantation improved liver steatosis and fibrosis, as measured using transient elastography, as well as serum liver enzyme levels.

Three studies have reported the effects of DMR therapy on liver-related outcomes. The REVITA-2 feasibility trial (NCT02879383) was a randomized, double-blind, sham-controlled, multicenter study evaluating the safety and efficacy of DMR in people with T2DM, approximately 85% of whom had fatty liver.[73] Among people with baseline liver MRI-PDFF >5%, the change in liver fat after 12 weeks was not significantly different between the DMR group and the sham group (median, −5.4 [IQR: 5.6] % vs. median −2.9 [IQR: 6.2] %, p=0.096). In contrast, in a European cohort with a baseline liver MRI-PDFF >5%, a greater, clinically significant reduction in liver fat content was observed at week 12 in the DMR group than in the sham group (median, −32.1 [IQR: 20.6] % vs. median, −17.9 [IQR: 25.6] %, p=0.020).[73] The data provide insights into a potential therapeutic role of DMR for NAFLD in selected populations. In the first human study of DMR, a significant reduction of FIB-4 score at week 24 was observed in individuals with baseline FIB-4 >1.3 (−0.4±0.41, p=0.0246, n=8), indicating improvement in liver fibrosis.[74] Serum liver enzyme levels were also improved following DMR treatment.[21,74]

However, all studies till date have focused on the role of DJBL/DMR in achieving glycemic control and weight loss in people with T2DM, with additional reporting on liver parameters. Further research exploring the exact therapeutic role of small intestine EBMTs in people with NAFLD/NASH is warranted. At the time of writing, a prospective single-arm study investigating the safety and efficacy of a new DJBL device (Tangji Medical, Hangzhou, China) in obese people with NAFLD is underway. The findings should provide new insights into the role of small intestine EBMTs for the treatment of NAFLD/NASH.

EBMTs for obese LT candidates

Owing to the increasing prevalence of obesity in LT candidates, management of obesity in these individuals is a key challenge. NASH is now the second most frequent indication for LT in the US, and the leading indication in women. Obesity is associated with increased long-term mortality in LT candidates, mostly resulting from cardiovascular events.[88] Pretransplant obesity is also associated with poor post-LT outcomes, primarily increased infective complications associated with longer intensive care unit and hospital stays.[89] Therefore, weight loss should be recommended for obese people awaiting LT.

The optimal approach for the management of obese LT candidates, including lifestyle modifications and/or concurrent or staged bariatric surgery with LT, has not yet been determined. A recent meta-analysis of eight studies enrolling 96 obese people undergoing LT evaluated the perioperative and long-term outcomes of bariatric surgery in these individuals. The mean EWL at 12 and 24 months was 44.08% and 49.2%, respectively. The mean bariatric surgery-related morbidity and mortality rates were 37% and 0.6%, respectively.[90]

Several studies have explored the efficacy and safety of EBMTs in obese patients undergoing LT. In 2013, in a study enrolling eight people, Choudhary *et al*.[91] were the first to report IGB placement in a morbidly obese person (BMI=48.3 kg/m²) with cirrhosis awaiting LT. Significant short-term weight loss was observed, with a decrease in BMI from 48.3 to 39.2 kg/m², which made the patient eligible for LT and reducing the incidence of perioperative complications. The remaining seven people in the same cohort had similar results.[92] More recently, a clinical pilot study of eight patients assessed weight loss, metabolic improvement, and safety of IGB in people with cirrhosis awaiting LT.[26] A significant short-term IGB-induced weight loss, from 146±22.2 kg to 127±21.6 kg (p=0.005), was achieved at 6 months, but the weight was at least partially regained in most participants. Prolonged nausea and vomiting were frequent, possibly resulting from splenomegaly or portal hypertension. Two people developed liver decompensation and one developed HCC, which may have been related to the rapid weight loss. Of note, the sample size of studies investigating the use of EBMTs in LT recipients is relatively small, which may lead to over- or underappreciation of AEs. Therefore, further large-scale studies are required to obtain more definitive evidence of the benefit-risk ratio of EMBTs in people with cirrhosis awaiting LT.

EBMTs for reducing liver volume in bariatric surgery candidates

Owing to the high prevalence of NAFLD in obese people, those qualified for bariatric surgery usually have an enlarged and fatty liver. Elevation of the left liver lobe is an essential step in Roux-en-Y-gastric bypass (RYGB) surgery, and an enlarged liver makes it difficult to expose the gastroesophageal junction. Moreover, the softer fatty liver is vulnerable, thereby increasing the risk of intraoperative bleeding. The most commonly reported reason for conversion from laparoscopic to open RYGB is insufficient exposure of the esophagogastric junction owing to enlarged liver (29.3%).[93]

The potential utility of IGBs for reducing liver volume in bariatric surgery candidates has been studied in small clinical samples. Frutos *et al*.[75] investigated the impact of IGBs on liver volume using computed axial tomography and pre-operative weight loss in super-obese people prior to laparoscopic RYGB. The results showed that 6 months of IGB treatment significantly reduced liver volume by 31.8±18.2% from 2,938.5±853.1 cm³ to 1,918.0±499.8 cm³ and body weight by 12.7% from 149.3±26.3 kg to 128.0±20.1 kg (n=29).[75] In total, 27 patients (93%) experienced nausea and 25 (86%) experienced vomiting, which abated 1 week after placement. The effect of IGBs on the liver volume of bariatric surgery candidates was also reported in a retrospective Japanese study of eight super-obese people with a median BMI of 44.0 kg/m². IGBs reduced liver volume by 6.4%, from 1,873.3 (range: 1,442.5–3,043.3) cm³ to 1,751.6 (range: 904.5–2,583.3) cm³ (p=0.006).[27] There was also a nonsignificant change in visceral fat area from 333.9 (range: 252.9–395.2) cm² to 295.8 (range: 187.7–387.7) cm² (p=0.1755). No severe complications were observed. All in all, EBMTs can reduce liver volume and thereby reduce the incidence of surgical complications in bariatric surgery candidates. They can also serve as a bridge for super-obese people who are not eligible for bariatric surgery.

Liver abscess: a common SAE of DJBL implantation

Liver abscesses are the most serious complications associated with DJBL and typically occur 9 months after DJBL implantation. In a systematic review of 38 studies, 11 of 1,056 people with T2DM who received DJBL (1.04%) were found to have developed liver abscesses.[94] All were managed with antibiotics and/or drainage. The ENDO trial (NCT01728116) was a multicenter, double-blind randomized clinical trial by

Table 3. Research agenda for future studies

Key areas for future research
1. Change in liver histological features following EBMTs in NAFLD/NASH patients
2. Long-term effects of EBMTs for treating NAFLD/NASH
3. Large-scale, well-designed RCTs
4. Role of EBMTs in combination with other treatments or drugs for treating NAFLD/NASH
5. Therapeutic role of small intestine EBMTs in people with NAFLD/NASH
6. Benefit-risk ratio of EMBTs in obese people with end-stage liver disease awaiting liver transplantation
7. A new anchoring system for the DJBL device to reduce the incidence of liver abscesses

EBMTs, endoscopic bariatric and metabolic therapies; DJBL, duodenal-jejunal bypass liner; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RCT, randomized clinical trial.

the FDA to investigate the safety and efficacy of DJBL (Endobarrier) for achieving glycemic control. Unfortunately, it was terminated early in 2015 because of a higher than anticipated rate of liver abscesses (3.5%).

The cause of liver abscess formation is unclear, but is most likely the anchor of the DJBL device. It is well known that venous drainage of the duodenum, where the anchor of the device is fixed into the mucosa, enters the portal vein. The barbs on the anchor of the DJBL can cause microperforations of the duodenal bulb. Therefore, it has been suggested that the long-term placement of the anchoring system may serve as a breeding ground for bacteria that results in liver abscess formation. On the other hand, ascending cholangitis resulting from obstruction of the device may also contribute to the formation of liver abscesses.

It is necessary to improve the DJBL device, especially the anchoring system, with the aim of reducing the incidence of SAEs including abscesses and possibly to extend the length of time over which each device can be continuously used. Recently, Frydenberg *et al*.[95] developed a new anchoring system for the DJBL, and confirmed the feasibility of this modified device in a pig model. The device held a modified liner in place for 1 month and functioned correctly without serious complications. Further studies focusing on adjustments of the barbs are the key to improving the benefit-risk balance of DJBL.

Conclusions

An increasing number of studies have investigated the potential role of EMBTs for the treatment of NAFLD/NASH. EBMTs have been shown to improve the serological, imaging, and histological markers of NAFLD. Two studies demonstrated histological improvement following IGB treatment. However, almost all the studies focused on short-term results. Large, well-designed randomized studies evaluating histological features and long-term change in liver-related outcomes are warranted. In addition, EBMTs can be used in combination with other treatments or drugs as part of multidisciplinary treatment plans for NAFLD/NASH. Research agendas for future studies on the safety and efficacy of EBMTs for treating liver disease are summarized in Table 3.

Studies with small sample sizes have shown that IGBs induced short-term weight loss and reduced the rates of surgical complications in obese people with end-stage liver disease and awaiting LT. However, prolonged nausea and vomiting were common, and some patients developed liver decompensation and HCC that may have been associated with rapid weight loss. Large long-term studies are required to evaluate the benefit-risk ratio and therapeutic utility of EMBTs in such populations.

The available evidence supports the use of EBMTs to achieve preoperative weight loss and liver volume reduction in bariatric surgery candidates to lower the rate of perioperative complications. Future prospective studies with large sample sizes are required for confirmation. In addition, a new anchoring system for the DJBL device is required to reduce the incidence of liver abscesses and prolong the action time.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (MR, FJ), acquisition of data (MR, XZ), analysis and interpretation of data (MR, XZ, LL), drafting of the manuscript (MR), critical revision of the manuscript for important intellectual content (MR, XZ, LL, FJ), administrative, technical, or material support, study supervision (FJ).

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