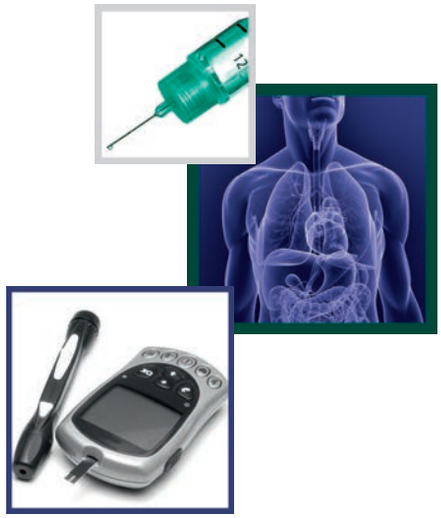
REVIEW



A novel approach for diabetes: recent evidence on endoluminal liners

Héctor Romero-Talamás[1] & Stacy A Brethauer*[1]

Practice Points

- Two modern pandemics, obesity and diabetes, are considered the most significant causes of morbidity and mortality in the 21st century.
- There is a strong association between obesity and diabetes and they need to be managed in tandem for many patients.
- Bariatric surgery has proven to be the only durable effective therapy for patients with severe obesity and related comorbidities.
- Procedures that bypass the foregut and deliver the nutrients directly to the distal bowel have a favorable metabolic effect on glucose homeostasis.
- Several novel endoscopic therapies are available for the treatment of morbid obesity. Only the endoscopic duodenal–jejunal liner has been designed to replicate the effect of the surgical duodenal–jejunal bypass.
- Although promising, the endoscopic duodenal–jejunal liner is still an investigational device.

SUMMARY The obesity–diabetes pandemic is a devastating contemporary public health issue that for decades has been steadily on the rise. As knowledge and experience have been progressively acquired, numerous strategies and techniques for its management have arisen. Currently, only surgical treatment offers significant and durable results in terms of weight loss, and remission or improvement of comorbidities. With the objective of offering less invasive alternatives, several endoscopic devices have been introduced. Only the endoscopic duodenal–jejunal liner effectively simulates the bypass component of certain bariatric procedures. Initially designed for weight loss, this endoluminal artifact later proved to also provide a powerful metabolic effect. Although it is still in an investigational phase, the device is a promising tool for the treatment of obesity.

In the last few decades, increasing recognition has been given to the obesity pandemic. The 1991 NIH consensus conference statement on gastrointestinal (GI) surgery for severe obesity has defined morbid obesity as a BMI of ≥40 kg/m^2 or ≥35 kg/m^2 in the presence of associated comorbidities [1]. Individuals that meet these criteria have an increased risk of associated morbidity and mortality and are, therefore, offered surgical therapy, the only durable therapy for this disease

[1]Bariatric & Metabolic Institute, Cleveland Clinic, 9500 Euclid Avenue, M61, Cleveland, OH 44195, USA
*Author for correspondence: Tel.: +1 216 444 9244; Fax: +1 216 445 1586; brethas@ccf.org

Future Medicine part of fsg

that is currently available. The mean BMI for the global citizen has been increasing steadily since 1980. The dimension of the disease has reached such an alarming point that by 2008, 502 million adults in the world were obese [2], and even though different strategies have been implemented to stop this trend, no country has developed an effective preventative or treatment system to combat this illness [3]. During the same time period, the prevalence of diabetes worldwide has followed a similar pattern. It is now estimated that the number of adult diabetic subjects doubled from 1980 to 2008, affecting more than 300 million individuals [4]. A total of 60% of these cases are directly attributable to weight gain [5]. This emphasizes the close relationship of these two pathological entities in the modern era.

As would be expected, the appearance and growth of these public health issues have led to the development of numerous innovations and strategies intended for their management. Bariatric surgery has proven to be a safe and effective therapy for the morbidly obese, producing durable weight loss and control of obesity-related comorbidities [6]. The most recent evidence shows that obese patients with poorly controlled Type 2 diabetes mellitus (T2D) who undergo a bariatric procedure achieve significantly better glycemic control than those that receive intensive medical therapy [7]. While complication rates and mortality after bariatric surgery are extremely low in the modern era, there is still a widely held perception that bariatric surgery is risky and should only be utilized as a last resort. Major complication rates after bariatric surgery occur in less than 5% of patients and postoperative mortality rates in large population studies are reported as 0.3% or less [8,9]. These rates are far less than many other elective operations today and are consistent with commonly performed procedures, such as laparoscopic cholecystectomy and elective hip arthroplasty [10,11].

Regardless of the current safety data, many physicians are reluctant to refer patients for bariatric surgery and many patients are not interested in this option. It is, therefore, necessary that innovative, less invasive approaches are developed to manage both obesity and diabetes. The ideal intervention would, therefore, produce similar metabolic effects to surgery without the risk of surgical complications. In an effort to produce this technology, several endoscopic devices have been developed, aiming to mimic the complex effects of the bariatric operations. In this article, the authors will focus on the novel endoscopic devices that were designed to modify the physiology of the GI tract, providing an effective endoscopic option for the management of diabetes mellitus.

Classification

Traditionally, bariatric procedures have been classified in three broad categories: restrictive, malabsorptive or mixed. This terminology has largely fallen out of favor as it is overly simplistic and does not represent our current knowledge of these operations. While some procedures only produce gastric restriction (gastric banding), other procedures, such as sleeve gastrectomy, reduce gastric volume and also produce gut hormone changes that effect hunger, satiety and glucose homeostasis. In gastrojejunal bypass (GJB), a diverting route between the stomach and the distal bowel is created after surgical exclusion of the duodenum has been achieved. This allows food to have early contact with this portion of the intestine. Gastric bypass adds a restrictive component to the bypass of the proximal bowel that is responsible for many of the metabolic effects of the operation. Biliopancreatic diversion and duodenal switch procedures cause nutrient malabsorption, but also have a restrictive component and metabolic mechanisms that affect diabetes. For this review, we will limit the endoluminal categories to gastric restriction and metabolic types of procedures.

Mechanisms

Two operations have taught us about the metabolic consequences of bypassing the proximal gut: the GJB and the Roux-en-Y gastric bypass (RYGB). The GJB has been clinically tested, mostly in small studies of low-BMI patients, with a relatively short follow-up. The majority of these studies have shown significant improvement in patient glycemic status [12–14]. This effect is achieved through a weight loss-independent mechanism. This phenomenon is supported by the absence of significant weight loss but also by other factors, such as the lack of improvement in insulin resistance [14] and the moderate increase in serum C-peptide that occurs a few months after the operation [13]. However, the positive impact that RYGB has on T2D has been repeatedly demonstrated in clinical studies over the last 20 years. Several authors have reported high rates of partial or total remission [6,7,15,16]. This is particularly true

for individuals with diabetes of shorter duration [16]. Similar to the duodenal–jejunal bypass (DJB), patients who undergo RYGB can have normalization of their glycemic status within a few days of the operation; even before considerable weight loss takes place [15]. This weight loss-independent effect has been the focus of much research to find targets of therapy that do not require surgery. In 2004, Rubino and Marescaux, published a study involving nonobese, diabetic rats who underwent GJB [17]. In this study, glucose tolerance improved when nutrient flow was excluded from the duodenum and proximal jejunum. This occurred without weight loss. The findings of this study provided evidence that exclusion of nutrient flow through the duodenum and proximal bowel plays a role in glucose homeostasis after these procedures. Incretins, such as gastric inhibitory peptide and GLP-1, are key factors in the rapid changes in glucose control after bypass procedures. Rubino's foregut theory proposed that, by bypassing the proximal part of the intestine, an 'anti-incretin' mechanism present in diabetic patients is then turned-off [18]. However, the hindgut theory suggests that improvement in glycemic parameters results from an early stimulation of the distal bowel that, in turn, promotes the early, exaggerated secretion of GLP-1 from the L cells in the distal ileum [19]. Newer operations, such as the sleeve gastrectomy, seem to produce metabolic changes through a hindgut effect [20]. The two mechanisms are not mutually exclusive and both are likely to contribute to the overall effects that are seen clinically. To further elucidate the relative contribution of each, however, a number of experimental models for selective gut stimulation have been designed [21–24]. In one of these studies, the authors assigned a number of Goto–Kakizaki rats to receive one of the three designed operations. The first group underwent a DJB to effectively exclude the passage of food through the proximal bowel. The second group was submitted to a standard gastro-jejunostomy with the purpose of allowing the food to come in contact with the distal bowel in an early phase without entirely bypassing the proximal segment. Finally, the third group received an ileal bypass to avoid the passage of the bolus at the level of the distal bowel. As expected, the animals that underwent the DJB showed significantly better glucose homeostasis in the postoperative period even when no differences in food intake, body weight or nutrient absorption was seen among all groups. Interestingly, when surgical exclusion of the foregut was added to the animals in the gastro-jejunostomy group, the previously unchanged glycemic status rapidly improved. The same phenomenon was inversely observed when surgical restoration of duodenal transit was performed in the DJB group [22]. An interesting experimental study by Rubino *et al.* was also based on the concept of duodenal exclusion [25]. The design included three groups of Goto–Kakizaki rats assigned to surgically receive an endoluminal duodenal sleeve, a fenestrated equivalent or a sham procedure. The group that received the nonfenestrated endoluminal sleeve showed significant improvement of glucose tolerance over the other two groups that were subjected to pair-feeding. These rudimentary models were used to establish the principles that later led to the development of current endoluminal technology [25]. Although these findings strongly support the role of the proximal bowel in the improvements in T2D after bypass procedures, other metabolic pathways that implicate different neuro–hormonal jejunal signaling processes have been proposed as primary glucose-regulating mechanisms [26–28]. These newly recognized mechanisms are clear evidence that the physiology of glucose control in subjects that have undergone a bypass procedure is extremely complex and multifactorial. They also provide solid proof that glucose regulation occurs, at least partially, independent of weight loss. Despite the increasing amount of available data, the conclusions from these experimental studies are heterogeneous and more precise mechanistic studies are necessary.

Available devices

Of the available novel endoscopic devices being developed to treat obesity, only two were specifically designed to mimic the metabolic effects of a gastric bypass and thus are considered suitable for the treatment of T2D. The EndoBarrier™ (GI Dynamics Inc., MA, USA), an endoscopic duodeno–jejunal liner (EDJL), has been the most widely tested device in humans in this area. A second device, the Valentx® (ValenTx Inc., CA, USA) is still at a very early stage of development. This endoluminal sleeve is implanted endoscopically with laparoscopic assistance. The Valentx has been designed to mimic both the restrictive and malabsorptive components of the RYGB, but in its current form requires laparoscopic assistance for placement **(Figure 1)**. The

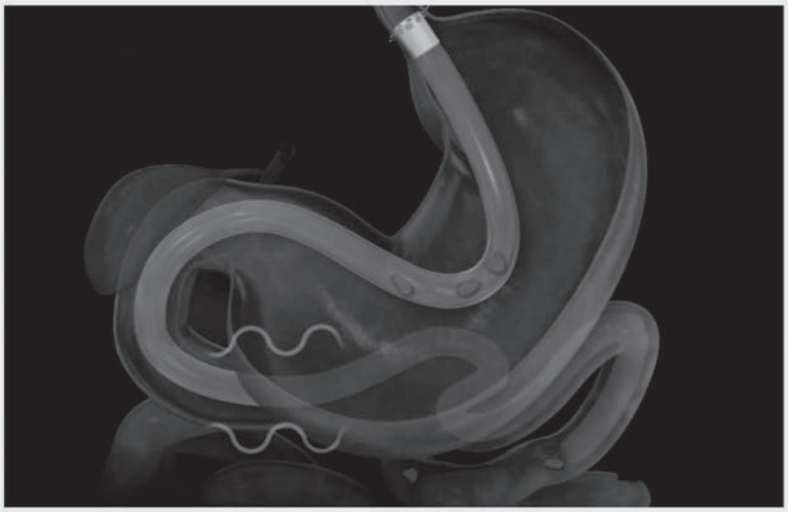


Figure 1. The Valentx® (ValenTx Inc., CA, USA) is an endoluminal gastrointestinal sleeve that is designed to be restrictive and malabsorptive. Implantation is performed endoscopically, assisted by laparoscopy. The device is anchored at the level of the gastroesophageal junction to allow bypassing of the stomach, duodenum and part of the jejunum.
Image courtesy of ValenTx Inc. (CA, USA).

first human study suggests that it is a safe device that will offer good results in terms of weight loss [29].

■ EndoBarrier

The EndoBarrier is a thin and flexible liner made of a fluoro-polymer that is impermeable to nutrients (Figure 2). This endoluminal 'sleeve' measures 60 cm in length and is intended to cover the duodenum and the proximal segment of the jejunum. The device is placed endoscopically and is anchored at the level of the duodenal bulb by deploying a self-expandable metallic stent that is integrated in the proximal aspect of the liner (Figure 3). This placement of the device allows the biliopancreatic secretions to transit freely from the papilla outside of the barrier without coming into contact with ingested nutrients until they both have reached the end of the liner. This is an especially attractive choice for patients who are interested in the benefits of a bariatric operation but are unwilling to undergo an operation. Currently, the EndoBarrier is considered a temporary therapy, designed to be used continually for up to 12 months. Trials with longer placement of the device are being planned.

Figure 2. The EndoBarrier™ (GI Dynamics Inc., MA, USA) is an endoscopic duodenal–jejunal liner designed to mimic the metabolic effect of the duodenal–jejunal bypass.
Image courtesy of GI Dynamics Inc. (MA, USA).

■ Implantation & explantation technique

The device is placed using a standard endoscope under sedation or general anesthesia. After a guidewire is placed into the duodenum, the device is placed in the lumen over the wire and the sleeve is advanced distally into the jejunum using a pushing device under fluoroscopic guidance. The anchoring system is then deployed to secure the proximal end of the liner in the duodenal bulb. With some experience, the procedure can be performed in less than 30 min. For explantation, an endoscopic grasper is advanced through the working channel and is used to pull on one of the drawstrings attached to the stent anchoring mechanism. This maneuver collapses the self-expanding anchor system to allow its placement inside a retrieval chamber on the end of the endoscope [30–32].

■ Data on endoluminal barrier

The initial feasibility studies for the placement of the endoscopic duodenal sleeve were conducted in a porcine model in 2008 [33,34]. Each experiment evaluated a safety and feasibility at different time points. They were able to demonstrate that implantation and explantation were safe in an animal model [34]. However, the implanted device developed anchoring malfunction on several occasions while in place for a longer period of time and this prompted modifications of the anchoring system. No significant morbidity or tissue damage was observed [33]. After initial safety and feasibility were effectively demonstrated, these studies set the stage for a number of human trials.

■ Human studies

Early experience & preliminary data

The first reported case of successful placement of the endoluminal duodenal–jejunal liner in the USA was published in 2007. The authors reported no complications related to the procedure and the patient tolerated the device without complaints for a total of 3 months. Significant weight loss was observed after this time (9.09 kg) [30]. The first human prospective series was presented soon after that and involved 12 patients (seven females and five males) with a mean BMI of 43 kg/m^2. Four patients in this initial trial had T2D. A total of ten individuals tolerated the liner for 12 weeks. The two premature device retrievals took place 9 days after the implantation and occurred because of abdominal pain. In the remaining subjects, several episodes of nausea, vomiting and abdominal pain were observed, especially during the first week. However, no severe complications were reported. The investigators observed that there was normalization of blood glucose in three of the four diabetic subjects that occurred 24 h after implantation [31]. In an effort to add a restrictive mechanism to the liner, a similar study with the addition of a 'restrictor' orifice to slow the transit time was conducted in ten patients with an average BMI of 40.8 ± 4 kg/m^2. As before, the device was left in place for 12 weeks. The 'restrictor' was a 4 mm wide inlet situated proximally in the liner. Using scintigraphic studies, the team showed a significant delay in gastric emptying, however, the majority of the patients experienced nausea, vomiting and abdominal pain, which required endoscopic dilation of the restrictive orifice. The average excess weight loss percentage (EWL%) at 12 weeks was 40 ± 3% [35]. Finally, during this early experience phase, a small-randomized study (EDJL vs sham) evaluating the effect of the EDJL on T2D was published with promising results [36]. The study included 18 obese subjects (BMI ≥30–≤50 kg/m^2) subjects with T2D of less than 10 years duration, an HbA1c ≥7–≤10% and a fasting glucose ≤240 mg/dl. Although originally planned for 24 weeks, the treatment period was extended to 52 weeks for safety analysis. The baseline caloric intake of all individuals was determined by a survey and then maintained for the first 2 weeks after the endoscopy. After this period, all patients received counseling on adequate dieting and lifestyle. By week 1, the EDJL arm experienced a difference in glucose levels of -55 ± 21 mg/dl while the patients in the sham group had an increase of 42 ± 30 mg/dl. At week 24, the change in HbA1c was -2.4 ± 0.7% in the intervention group versus a -0.8 ± 0.4% in the sham group. A total of 30% of the EDJL group suffered from upper abdominal pain and 10.8% from nausea. There were no major complications.

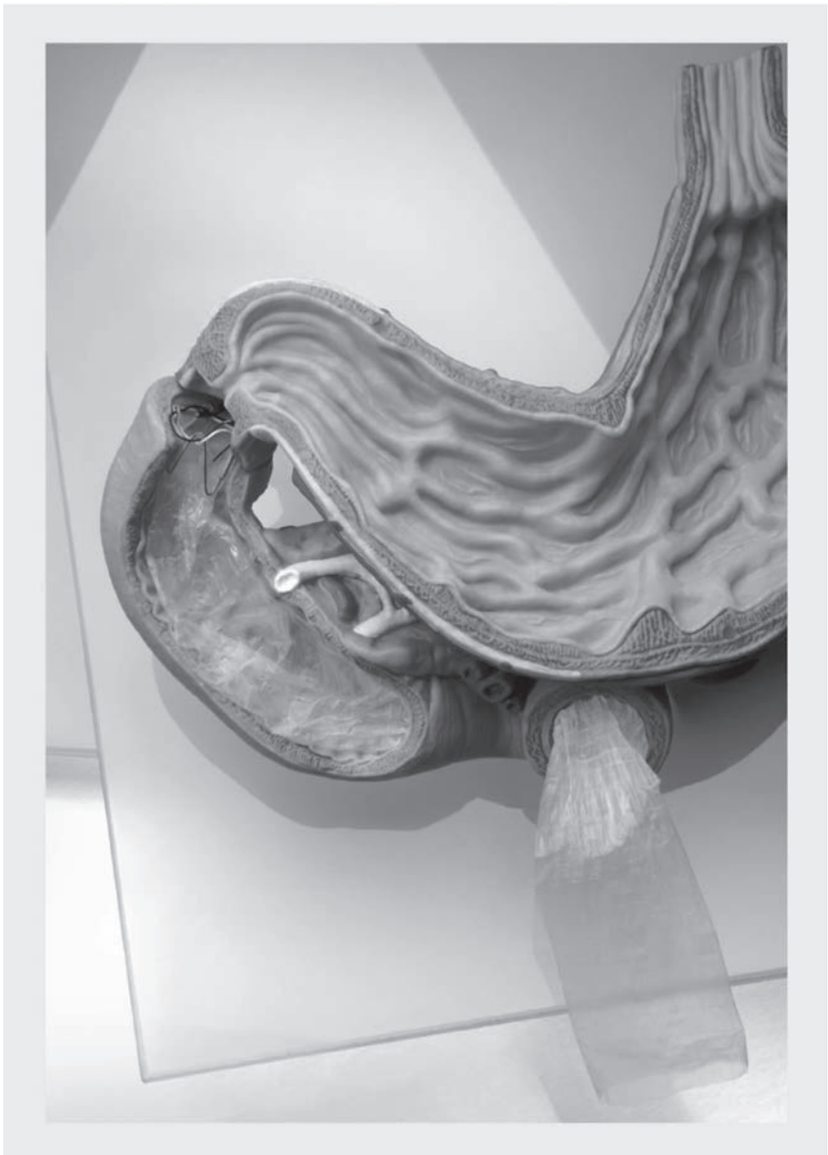


Figure 3. Anatomical configuration of the EndoBarrier™ (GI Dynamics Inc., MA, USA). Notice the anchoring system at the duodenal bulb.
Image courtesy of GI Dynamics Inc. (MA, USA).

Clinical trials

The EDJL has been primarily tested in South America (Brazil and Chile), USA and Europe (The Netherlands). So far, the best available data

Table 1. Available clinical trials.

Study (year)	Region	Design	Patient (n)	Primary end point	Mean age (years)	Mean BMI (kg/m^2)	Other characteristics (mean)	Follow-up (weeks)	Results (completers)	Complications (EDJL group)	Ref.
Escalona *et al.* (2012)	Chile	Prospective	42[†]; obese Successful implantation: 39 Completers: 24	Safety Weight change	36 ± 10	43.7 ± 5.9	Weight (baseline): 109 ± 18 kg	52	Total weight change: -22.1 ± 2.1 kg ($p < 0.0001$) 6 T2D: change in HbA1c: -1.4 ± 0.6% ($p = 0.0525$) 15 early removals	Upper abdominal pain: 81.0%; nausea: 41.0%; vomiting: 33.0%; gastroenteritis: 4.8%	[37]
de Moura *et al.* (2012)	Brazil	Prospective	22[†]; T2D Completers: 13	Changes in FBG and insulin Change in HbA1c	46.2 ± 10.5	44.8 ± 7.4	HbA1c: 8.9 ± 1.7% FBG: 179.4 ± 68.8 mg/dl Insulin: 19.5 ± 14.7 µU/ml	52	Change in FBG: -37.1 ± 11.8 mg/dl ($p < 0.01$) Change in insulin level: -10.1 ± 4.2 µU/ml ($p < 0.05$) Change in HbA1c: -2.3 ± 0.3% ($p < 0.0001$)	Procedure related: upper abdominal pain (n = 11); nausea (n = 7); vomiting (n = 7); diarrhea (n = 1); Procedural complication (n = 6); back pain (n = 5)	[38]
Tarnoff *et al.* (2009)	Multicenter (Brazil, Chile, USA)	RCT (LFD + EDJL vs LFD)	40[†]; obese EDJL: 26 (25 successful implantation, 20 completers) Control: 14	Weight loss	EDJL: 38 ± 10.1 Control: 43 ± 10.6	EDJL: 42 ± 5.1 Control: 40 ± 3.5	Weight (baseline): EDJL: 114 ± 20.9 kg Control: 108 ± 5.1 kg	12	Mean EWL%: EDJL: 22.1 ± 8% Control: 5.3 ± 6.6% ($p < 0.02$) Mean total weight loss: EDJL: 10.3 ± 3.2 kg Control: 2.6 ± 3.5 kg	Patients with ≥1 AE: EDJL: 100% Mild-to-moderate: abdominal pain (n = 15); nausea (n = 7); vomiting (n = 7); distension (n = 11); GI bleeding (n = 1) Severe: GI bleeding (n = 3); abdominal pain (n = 1); vomiting (n = 1)	[39]

[†]Total enrolled before any exculsion.
AE: Adverse event; EDJL: Endoluminal duodenal–jejunal liner; EWL%: Excess weight loss percentage; FBG: Fasting blood glucose; GI: Gastrointestinal; LCD: Low calorie diet; LFD: Low fat diet; RCT: Randomized controlled trial; T2D: Type 2 diabetes mellitus; Tx: Treatment.

Table 1. Available clinical trials (cont.).

Study (year)	Region	Design	Patient (n)	Primary end point	Mean age (years)	Mean BMI (kg/m^2)	Other characteristics (mean)	Follow-up (weeks)	Results (completers)	Complications (EDJL group)	Ref.
Schouten *et al.* (2010)	Multicenter (The Netherlands)	RCT (EDJL + LCD vs LCD)	41†; obese EDJL: 30 (26 successful implantation, 24 completers, 8 T2D) EDJL subgroup: 10 patients for 24-week follow-up (3 completers) Control: 11 (2 T2D)	Weight loss	EDJL: 40.9 Control: 41.2	EDJL: 48.9 Control: 49.2	Baseline HbA1c: EDJL (T2D): 8.8 ± 1.7% Control (T2D): 7.3 ± 0.1%	12 Subgroup (n = 10) followed for 24 (safety)	Mean EWL%: EDJL: 19.0 ± 10.9% Control: 6.9 ± 6.1% ($p < 0.00$) Mean BMI: EDJL: 43.4 ± 6.7 kg/m^2 Control: 47.3 ± 6.7 kg/m^2 ($p < 0.23$) Mean HbA1c (T2D): EDJL: 7.7 ± 1.8% Control: 6.9 ± 0.6% ($p < 0.32$)	Patients with ≥1 AE: EDJL: 100% Mild (61.3%) Moderate (38.7%) Nausea (n = 20); abdominal pain (n = 13); pseudopolyp formation (n = 13); implant site inflammation (n = 10); vomiting (n = 6); other (n = 21)	[40]
Gersin *et al.* (2010)	Multicenter (USA)	RCT (EDJL vs sham)	56†; obese EDJL: 27 (2 withdrawals before Tx, 4 unsuccessful implantations, 13 completers) Sham: 29 (3 withdrawals before Tx, 24 completers)	EWL% difference	EDJL: 45 ± 7 Control: 43 ± 10	EDJL: 46 ± 5 Control: 46 ± 6	Not applicable	12	Mean EWL%: EDJL: 11.9 ± 1.4% Sham: 2.7 ± 2.0% ($p < 0.001$) Total weight change: EDJL: -8.2 ± 1.3 kg Sham: -2.1 ± 2.2 kg ($p < 0.05$)	Upper abdominal pain (n = 14); nausea (n = 6); vomiting (n = 3.7); constipation (n = 3); GI bleeding (n = 3); hematemesis (n = 3); abdominal pain (n = 2); other (n = 6)	[41]
Cohen *et al.* (2013)	Brazil	Prospective	23; low BMI, diabetic Successful implantation: 20 Completers: 16	AEs Changes in body weight, FBG, HbA1c	49.8 ± 6.7	30 ± 3.6	Body weight: 84 ± 16.6 kg FBG: 207 ± 61 mg/dl HbA1c: 8.7 ± 0.9%	52	Mean body weight: 77.2 ± 17.6 kg Mean FBG: 155 ± 52 mg/dl Mean HbA1c: 7.5 ± 1.6% Mean BMI: 28.5 ± 3.3 kg/m^2	GI symptoms (n = 13); metabolic and nutritional disorders (n = 14)	[42]

†Total enrolled before any exculsion.
AE: Adverse event; EDJL: Endoluminal duodenal–jejunal liner; EWL%: Excess weight loss percentage; FBG: Fasting blood glucose; GI: Gastrointestinal; LCD: Low calorie diet; LFD: Low fat diet; RCT: Randomized controlled trial; T2D: Type 2 diabetes mellitus; Tx: Treatment.

come from two prospective nonrandomized, noncomparative trials and three randomized, controlled trials. The first study enrolled 42 subjects with a mean BMI of 43.7 ± 5.9 kg/m^2. In three patients implantation was not achieved due to anatomical problems (short duodenal bulb). Twenty-four completed the 1-year follow-up, the rest underwent early explantation due to anchor dislodgement (n = 8), device obstruction (n = 3), abdominal pain (n = 2), acute cholecystitis (n = 1) and patient request (n = 1). Total weight loss for completers at 52 weeks was 22.1 ± 2.1 kg ($p < 0.0001$) or a 47.0 ± 4.4 EWL%. In the six diabetic patients, the change in HbA1c was -1.4 ± 0.6% ($p = 0.0525$). No severe associated complications were observed [37]. A more metabolic-focused trial was conducted with the participation of 22 T2D subjects. This population had a mean age of 46.2 ± 10.5 years, a mean BMI of 43.7 ± 5.9 kg/m^2 and was followed for 52 weeks. The device was successfully implanted in all patients. Only 13 patients completed the 1-year follow-up with device migration being the main reason for explantation (n = 3). There was one GI bleed that took place 4 weeks after placement. In the completers' group at 52 weeks, change in fasting glucose was -37.1 ± 11.8 mg/dl, -2.3 ± 0.3% in HbA1c and -10.1 ± 4.2 µU/ml in insulin levels. All parameters reached statistical significance. Upper abdominal or back pain, nausea and vomiting were frequent but usually mild [38]. The first randomized controlled trial tested the EDJL for short-term weight loss as the primary end point. Two arms, the EDJL (n = 25) and the control (n = 14) received baseline counseling on diet and behavior modification. A total of 80% were able to complete the 3-month follow-up with the liner in place. The treatment group had an EWL% of 22%, in comparison with a 5% in the control group. The early device removals occurred because of upper GI bleeding (n = 3), migration (n = 1) and obstruction (n = 1) [39]. A multicenter trial studied 41 morbidly obese patients, of whom 30 were randomly allocated to the EDJL and 11 served as controls. In four individuals, the device could not be implanted for technical–anatomical reasons and four individuals had to undergo early explantation due to migration, dislocation of the anchor, upper abdominal pain and obstruction. All patients experienced at least one episode of mild abdominal pain or nausea but these symptoms occurred more frequently in the first week and then typically subsided. At 3 months, the mean EWL% was 19, compared with 6.9 in the control group ($p < 0.002$). Six out of the eight T2D patients in the EDJL arm were able to lower the dosage of their oral antidiabetic medication and insulin in 1 week [40]. The only multicenter, randomized, sham controlled trial was published in 2010. The study enrolled 41 patients distributed in two groups: the EDJL (n = 21) and the sham (n = 26). Implantation was unsuccessful in four individuals, three because of a short duodenal bulb and one because of endoscopist inexperience. All patients were counseled on their diet. Thirteen (EDJL) and 24 (sham) patients completed the 3-month follow-up. Early explantations were necessary because of GI bleeding (n = 3), nausea and vomiting (n = 2), and abdominal pain (n = 2). At this point, the EDJL group achieved an 11.9 ± 1.4 EWL% versus a 2.7 ± 2.0 EWL% in the sham arm ($p < 0.05$) [41]. Recently, Cohen *et al.* published their experience on the metabolic effects of this therapy in low BMI patients. They enrolled 23 diabetic subjects with an average BMI of 30 ± 3.6 kg/m^2 and a mean HbA1c of 8.7 ± 0.9%, the device was implanted in 20 patients. Patients were kept on a liquid diet for the first week after placement, and encouraged to continue a low calorie diet for the rest of the 52-week trial. Four early explantations occurred due to poor compliance, abdominal pain and displacement or migration. At 52 weeks, mean BMI dropped to 28.5 ± 3.3 kg/m^2 and mean HbA1c to 7.5 ± 1.6%. Mild-to-moderate GI symptoms occurred in 13 subjects and metabolic (hypoglycemia), as well as nutritional disorders (iron deficiency) occurred in 14 subjects [42]. Currently, a large, multicenter trial is being conducted in the USA to determine the percentage of change in HbA1c after 1 year of implantation. **Table 1** shows a summary of available clinical trials.

Conclusion & future perspective

Contemporary medicine has been largely defined by the development and implementation of medical technology. Obesity and diabetes, two of the present major pandemics we face, have traditionally been managed medically. In the last two decades, surgery has become a more acceptable option for the management of these diseases, but there is still reluctance among referring physicians and patients to accept surgery as an early treatment option despite strong evidence favoring the benefits over the risks in the majority of patients. The need for less invasive options with a

risk–benefit profile between medical and surgical therapy is needed. For the treatment of diabetes, there is only one device currently being tested that could potentially meet this need. Current evidence shows a moderate but consistent effect on weight loss and the metabolic effects occur soon after implantation of the device. The need for early explantation (removal of therapy) has been addressed by the device manufacturer with improved patient tolerance, but there will be a small percentage of patients who do not tolerate the effects of this device. It is currently unclear what the lasting effects of the device will be after planned explantation, or how often the device may need to be reimplanted to achieve long-term effects. Larger, randomized, sham-controlled trials are necessary to further assess its value in the treatment of diabetes and such studies are underway.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1 NIH. Gastrointestinal surgery for severe obesity. *Consens. Statement* 9(1), 1–20 (1991).

2 Finucane MM, Stevens GA, Cowan MJ *et al.* National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 377(9765), 557–567 (2011).

3 Swinburn BA, Sacks G, Hall KD *et al.* The global obesity pandemic: shaped by global drivers and local environments. *Lancet* 378(9793), 804–814 (2011).

4 Danaei G, Finucane MM, Lu Y *et al.* National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 378(9785), 31–40 (2011).

5 Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nat. Med.* 12(1), 62–66 (2006).

6 Pories WJ, Swanson MS, Macdonald KG *et al.* Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann. Surg.* 222(3), 339–350; discussion 350–332 (1995).

7 Schauer PR, Kashyap SR, Wolski K *et al.* Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N. Engl. J. Med.* 366(17), 1567–1576 (2012).

■ **Only published high-quality randomized controlled trial on the effects of bariatric surgery versus intensive medical therapy in obese patients with diabetes.**

8 Smith MD, Patterson E, Wahed AS *et al.* Thirty-day mortality after bariatric surgery: independently adjudicated causes of death in the longitudinal assessment of bariatric surgery. *Obes. Surg.* 21(11), 1687–1692 (2011).

9 Demaria EJ, Pate V, Warthen M, Winegar DA. Baseline data from American Society for Metabolic and Bariatric Surgery-designated Bariatric Surgery Centers of Excellence using the Bariatric Outcomes Longitudinal Database. *Surg. Obes. Relat. Dis.* 6(4), 347–355 (2010).

10 Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality: the problem with small sample size. *JAMA* 292(7), 847–851 (2004).

11 Giger UF, Michel JM, Opitz I *et al.* Risk factors for perioperative complications in patients undergoing laparoscopic cholecystectomy: analysis of 22,953 consecutive cases from the Swiss Association of Laparoscopic and Thoracoscopic Surgery database. *J. Am. Coll. Surg.* 203(5), 723–728 (2006).

12 Geloneze B, Geloneze SR, Fiori C *et al.* Surgery for nonobese Type 2 diabetic patients: an interventional study with duodenal–jejunal exclusion. *Obes. Surg.* 19(8), 1077–1083 (2009).

13 Ramos AC, Galvao Neto MP, De Souza YM *et al.* Laparoscopic duodenal–jejunal exclusion in the treatment of Type 2 diabetes mellitus in patients with BMI <30 kg/m^2 (LBMI). *Obes. Surg.* 19(3), 307–312 (2009).

14 Cohen R, Caravatto PP, Correa JL *et al.* Glycemic control after stomach-sparing duodenal–jejunal bypass surgery in diabetic patients with low body mass index. *Surg. Obes. Relat. Dis.* 8(4), 375–380 (2012).

15 Rubino F, Gagner M, Gentileschi P *et al.* The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. *Ann. Surg.* 240(2), 236–242 (2004).

16 Schauer PR, Burguera B, Ikramuddin S *et al.* Effect of laparoscopic Roux-en-Y gastric bypass on Type 2 diabetes mellitus. *Ann. Surg.* 238(4), 467–484; discussion 484–465 (2003).

17 Rubino F, Marescaux J. Effect of duodenal–jejunal exclusion in a non-obese animal model of Type 2 diabetes: a new perspective for an old disease. *Ann. Surg.* 239(1), 1–11 (2004).

■ **Classic experimental study of the effects of duodenal–jejunal bypass on glucose control in an animal model.**

18 Rubino F. Is Type 2 diabetes an operable intestinal disease? A provocative yet reasonable hypothesis. *Diabetes Care* 31(Suppl. 2), S290–S296 (2008).

19 Patriti A, Aisa MC, Annetti C *et al.* How the hindgut can cure Type 2 diabetes. Ileal transposition improves glucose metabolism and beta-cell function in Goto–Kakizaki rats through an enhanced Proglucagon gene expression and L-cell number. *Surgery* 142(1), 74–85 (2007).

20 Lee WJ, Chen CY, Chong K, Lee YC, Chen SC, Lee SD. Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. *Surg. Obes. Relat. Dis.* 7(6), 683–690 (2011).

21 Eldar S, Heneghan HM, Dan O, Kirwan JP, Schauer PR, Brethauer SA. Gastrostomy tube

placement in gastric remnant at gastric bypass: a rat model for selective gut stimulation. *Surg. Obes. Relat. Dis.* doi:10.1016/j.soard.2011.11.019 (2011) (Epub ahead of print).

22 Rubino F, Forgione A, Cummings DE *et al.* The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of Type 2 diabetes. *Ann. Surg.* 244(5), 741–749 (2006).

23 Hansen EN, Tamboli RA, Isbell JM *et al.* Role of the foregut in the early improvement in glucose tolerance and insulin sensitivity following Roux-en-Y gastric bypass surgery. *Am. J. Physiol. Gastrointest. Liver Physiol.* 300(5), G795–G802 (2011).

24 Pournaras DJ, Aasheim ET, Bueter M *et al.* Effect of bypassing the proximal gut on gut hormones involved with glycemic control and weight loss. *Surg. Obes. Relat. Dis.* 8(4), 371–374 (2012).

25 Rubino F, Schauer PR, Kaplan LM, Cummings DE. Metabolic surgery to treat Type 2 diabetes: clinical outcomes and mechanisms of action. *Annu. Rev. Med.* 61, 393–411 (2010).

26 Breen DM, Rasmussen BA, Kokorovic A, Wang R, Cheung GW, Lam TK. Jejunal nutrient sensing is required for duodenal–jejunal bypass surgery to rapidly lower glucose concentrations in uncontrolled diabetes. *Nat. Med.* 18(6), 950–955 (2012).

27 Jiao J, Bae EJ, Bandyopadhyay G *et al.* Restoration of euglycemia after duodenal bypass surgery is reliant on central and peripheral inputs in zucker fa/fa rats. *Diabetes* 62(4), 1074–1083 (2013).

28 Salinari S, Debard C, Bertuzzi A *et al.* Jejunal proteins secreted by db/db mice or insulin-resistant humans impair the insulin signaling and determine insulin resistance. *PLoS One* 8(2), e56258 (2013).

29 Sandler BJ, Rumbaut R, Swain CP *et al.* Human experience with an endoluminal, endoscopic, gastrojejunal bypass sleeve. *Surg. Endosc.* 25(9), 3028–3033 (2011).

■ **First and only publication about safety and feasibility in gastrojejunal bypass liner placement.**

30 Gersin KS, Keller JE, Stefanidis D *et al.* Duodenal–jejunal bypass sleeve: a totally endoscopic device for the treatment of morbid obesity. *Surg. Innov.* 14(4), 275–278 (2007).

■ **Initial description of endoscopic duodeno–jejunal liner (EDJL) technology.**

31 Rodriguez-Grunert L, Galvao Neto MP, Alamo M, Ramos AC, Baez PB, Tarnoff M. First human experience with endoscopically delivered and retrieved duodenal–jejunal bypass sleeve. *Surg. Obes. Relat. Dis.* 4(1), 55–59 (2008).

32 Galvao Neto MP, Campos JM, De Moura EGH, Rodriguez L. Duodenal-jejunal endoluminal prosthetic GI sleeve. In: *Endoscopy in obesity surgery.* Campos JM, Galvao Neto MP, De Moura EGH (Eds). Santos, Sao Paolo, Brazil, 111–120 (2008).

33 Tarnoff M, Shikora S, Lembo A, Gersin K. Chronic *in vivo* experience with an endoscopically delivered and retrieved duodenal–jejunal bypass sleeve in a porcine model. *Surg. Endosc.* 22(4), 1023–1028 (2008).

34 Tarnoff M, Shikora S, Lembo A. Acute technical feasibility of an endoscopic duodenal–jejunal bypass sleeve in a porcine model: a potentially novel treatment for obesity and Type 2 diabetes. *Surg. Endosc.* 22(3), 772–776 (2008).

35 Escalona A, Yanez R, Pimentel F *et al.* Initial human experience with restrictive duodenal–jejunal bypass liner for treatment of morbid obesity. *Surg. Obes. Relat. Dis.* 6(2), 126–131 (2010).

36 Rodriguez L, Reyes E, Fagalde P *et al.* Pilot clinical study of an endoscopic, removable duodenal–jejunal bypass liner for the treatment of Type 2 diabetes. *Diabetes Technol. Ther.* 11(11), 725–732 (2009).

37 Escalona A, Pimentel F, Sharp A *et al.* Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal–jejunal bypass liner. *Ann. Surg.* 255(6), 1080–1085 (2012).

■ **Largest long-term prospective study evaluating the outcomes of EDJL placement in morbidly obese subjects.**

38 de Moura EG, Martins BC, Lopes GS *et al.* Metabolic improvements in obese Type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal–jejunal bypass liner. *Diabetes Technol. Ther.* 14(2), 183–189 (2012).

39 Tarnoff M, Rodriguez L, Escalona A *et al.* Open label, prospective, randomized controlled trial of an endoscopic duodenal–jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. *Surg. Endosc.* 23(3), 650–656 (2009).

40 Schouten R, Rijs CS, Bouvy ND *et al.* A multicenter, randomized efficacy study of the EndoBarrier gastrointestinal liner for presurgical weight loss prior to bariatric surgery. *Ann. Surg.* 251(2), 236–243 (2010).

41 Gersin KS, Rothstein RI, Rosenthal RJ *et al.* Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. *Gastrointest. Endosc.* 71(6), 976–982 (2010).

■■ **Largest multicenter randomized controlled trial evaluating the effects of the EDJL versus sham.**

42 Cohen RV, Neto MG, Correa JL *et al.* A pilot study of the duodenal–jejunal bypass liner in low body mass index Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 98(2), E279–E282 (2013).

■■ **Only long-term prospective study evaluating the effects of EDJL in low-BMI patients.**