The future of bariatrics: endoscopy, endoluminal surgery, and natural orifice transluminal endoscopic surgery

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submitted 10 October 2008
accepted after revision 16 July 2009

Bibliography
DOI http://dx.doi.org/10.1055/s-0029-1243876
Endoscopy 2010; 42: 155–162 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

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This review considers the evolving role of endoscopic techniques in the treatment of obesity, and developments in minimally invasive procedures in endoscopy, endoluminal surgery and natural orifice transluminal endoscopic surgery (NOTES). Endoscopic approaches that are similar to surgery but less invasive, relying on gastric restriction and/or malabsorption, show some promise. Intragastric injection of botulinum toxin is also considered, as is the role of minimally invasive bariatric endoscopic interventions. Gastrointestinal stimulation with implanted electrodes may have potential in the treatment of obesity and endoscopic applications have a role to play in post-surgical interventions. Evolving research into endosurgical approaches is described. Current work on the feasibility of a NOTES approach to bariatric procedures is described.

Introduction

Obesity is a major cause of morbidity and mortality, and the effectiveness of bariatric surgery suggests an important role for gastrointestinal tract procedures in the regulation of body weight (**Table 1**). However, although bariatric surgery is the keystone of current therapy of morbid obesity, it has limitations and risks. With regard to endoscopic approaches, for many years intragastric balloons have been the only available treatment option.

Preclinical research in the field of therapeutic endoscopy and minimally invasive surgery promises to expand the bariatric armamentarium. First reports from human studies testify to interesting progress in the development of less invasive approaches. However little is known about these. Several minimally invasive procedures are being tested for feasibility, safety and efficacy, and we review here the development of such procedures in the fields of endoscopy, endoluminal surgery, and natural orifice transluminal endoscopic surgery (NOTES).

Methods

Data were identified by bibliographic research in Medline and Pubmed for all English-language full papers, using the following keywords alone or in combination: obesity, endoscopic, endoluminal, transoral, bariatric, treatment, botulinum toxin, gastroplasty, bypass sleeve, electrical stimulation, natural orifice transluminal endoscopic surgery, natural orifice, gastroenteric, gastrojejunal, and anastomosis. The references of the retrieved articles were also reviewed.

Intragastric injections of botulinum toxin

The endoscopic administration of botulinum toxin type A (Botox) is thought to have a role in the management of weight loss. The rationale is that botulinum toxin inhibits acetylcholine release at the neuromuscular junction, with subsequent local paralysis of the injected muscle.

Injection into the gastric wall has been shown experimentally to produce weight loss and reduction of food intake, by inhibiting antral motility and slowing down gastric emptying [1]. Human pilot studies have suggested that antral injections were safe and well-tolerated but the results for satiety changes and weight loss were varied [2–4]. Published randomized placebo-controlled trials do not lend enough support to continue investigation because no statistically significant weight loss was shown ($P > 0.05$) [5,6]. However, when fundal injections were also given, significantly greater short-term weight loss (11 ± 1.09 versus 5.7 ± 1.1 kg; $P < 0.001$), reduction in body

Table 1 Bariatric surgical procedures in current use.

Gastric restriction-only
Laparoscopic adjustable gastric banding
Sleeve gastrectomy
Vertical banded gastroplasty
Diversionary malabsorption
Biliopancreatic diversion (BPD)
BPD with duodenal switch
Roux-en-Y gastric bypass (combined restriction and diversion)

mass index (BMI) (4 ± 0.36 versus 2 ± 0.58; $P < 0.001$), prolongation of emptying ($P < 0.05$), and decrease in maximal gastric capacity for liquids ($P < 0.001$) were achieved compared with controls [7]. Ghrelin, which is primarily secreted from the fundal glands, gastric accommodation, or other unknown mechanisms might be involved in these results.

These favorable results need to be validated by further research. At the very least, they might facilitate progress towards resolving new areas of gastric physiology.

Endoluminal endoscopic interventions

Research interest in approaches that are similar to surgery but less invasive has intensified. The aim is to develop durable, reversible, easy, adjustable, reproducible, and safe endoluminal procedures, to eliminate incision of the skin and thickened abdominal wall and reduce perioperative complications and recovery time.

Restriction techniques

Several endoscopic suturing devices have been developed for creating tissue plication by apposition of adjacent tissue folds. Although their long-term effectiveness in gastroesophageal reflux disease (GERD) has been debated, extension of their therapeutic potential to obesity has been suggested.

The Endo-Cinch device (C.R. Bard Inc, Murray Hill, New Jersey, USA) was initially used for an experimental vertical banded gastroplasty (VBG) procedure [8]. The device is mounted on an endoscope and fires a straight threaded needle through a tissue fold formed by suction. A proximal gastric pouch with an outlet ring was created by using the device to suture a flexible plastic ring along the lesser curvature and to suture together the anterior and posterior gastric walls. However, it frequently delivers submucosal stitches resulting in early suture loss [9].

Another experimental gastric partitioning procedure that used a prototype suturing device (Eagle Claw VII; Apollo Group and Olympus Corporation) has been described [10]. This device is also advanced through an overtube alongside an endoscope. Under direct visualization a curved needle is driven into tissue, allowing intracorporeal knotting. In this procedure, a long fishing line was sutured to the proximal gastric walls at the greater curvature and tightened. A flexible plastic sheath segment was placed and additional knots formed an outlet ring. Despite an initially large pouch and wide outlet, the dimensions achieved later were similar to those obtained with surgery [11]. With the successful achievement of a consistent suturing depth within the muscularis layer, the aim is for results that last longer than those of the Endo-Cinch.

Endoluminal vertical gastroplasty (EVG) and transoral sleeve gastroplasty (TSG) have been carried out, following Savary dilation, in appropriately selected patients (hiatal hernia < 2 – 3 cm)

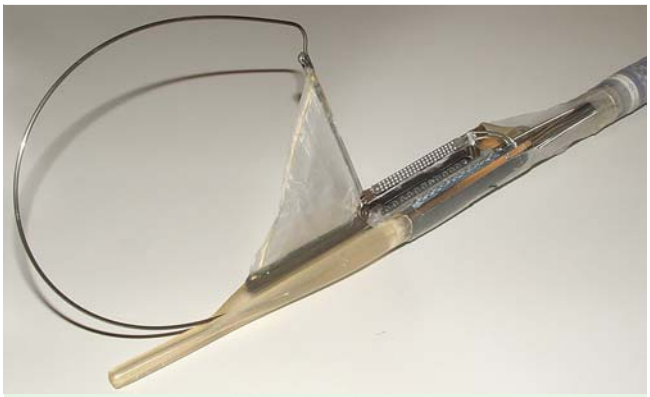

Fig. 1 Transoral gastroplasty device (TOGA system). (Courtesy of Dr. J. Devière, Université Libre de Bruxelles, Hôpital Erasme, Belgium).

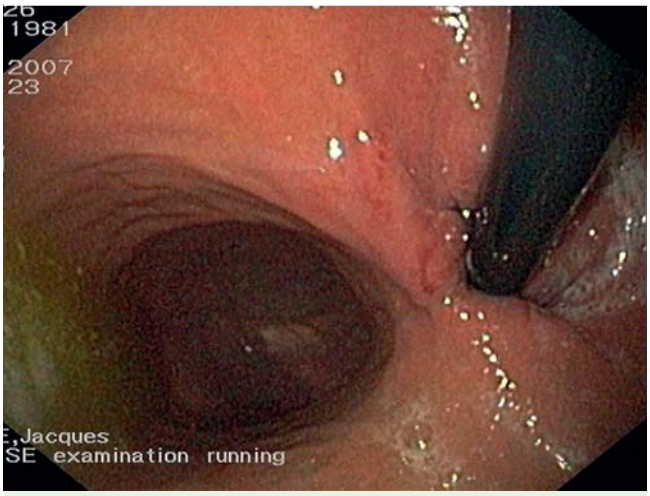

Fig. 2 Endoscopic view of transoral sleeve gastroplasty (TSG). (Courtesy of Dr. J. Devière, Université Libre de Bruxelles, Hôpital Erasme, Belgium).

who were under general anesthesia. A total of 64 patients with a mean BMI of 39.9 ± 5.1 kg/m^2 and a wide BMI range (28 – 60.2 kg/m^2) were followed up for 12 months after undergoing EVG with the Endo-Cinch device on an outpatient basis [12]. The first two stitches were placed on the anterior proximal fundus and distal body walls respectively and anterior and posterior sutures were alternated in a proximal direction. This simple procedure was completed in approximately 45 minutes with only minimal adverse events. At follow-up, three disrupted and five loose but intact suture configurations were seen endoscopically. At study completion, the extremely obese subgroup exhibited a significantly higher percent excess weight loss (EWL) compared with the other groups ($P = 0.001$). Surprisingly, the reported total weight loss results (mean BMI 30.6 ± 4.7 kg/m^2, $P = 0.001$; %EWL 58.1 ± 19.9) were comparable to those obtained with surgery. The plication did not start at the angle of His unlike surgical VBG, it was not parallel to the lesser curvature, and neither was there formation of a narrow outlet to delay gastric emptying.

TSG was performed using a transoral gastroplasty stapling system (TOGA; Satiety Inc., Palo Alto, California, USA) under direct retroflexed visualization (**Figs. 1** and **2**) [13]. A septum with a retraction wire was deployed to orientate tissue for capture and 11 titanium staples were delivered in three rows by aspirating anterior and posterior gastric tissues (**Fig. 3 a – c**). The anterior and posterior walls were connected by a transerosal vertical staple line beginning at the angle of His along the lesser curvature

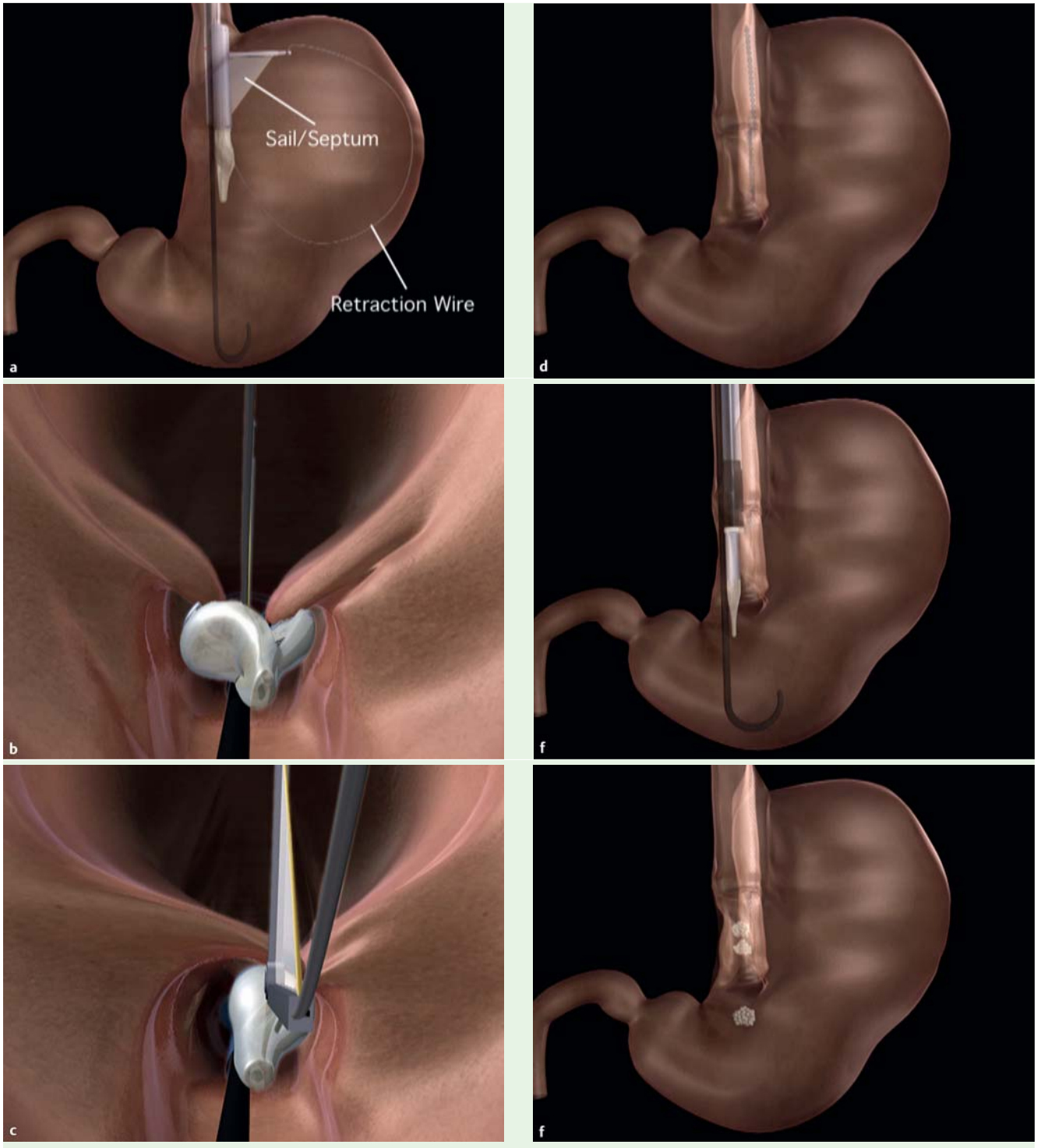

Fig. 3 **a** Transoral gastroplasty device (TOGA system): septum with retraction wire. **b, c** Stapling procedure. **d** Vertical staple line. **e** Transoral gastroplasty restrictor. **f** Created sleeve with outlet. (Courtesy of Dr. J. Devière, Université Libre de Bruxelles, Hôpital Erasme, Belgium).

(**Fig. 3 d**). A second one distally extended the created sleeve to a length of 80 – 90 mm. By using the TOGA system restrictor, a single suction pod stapler for pleat formation, an adjustable outlet of dimensions similar to those obtained by surgery was formed (**Fig. 3 e, f**). Out of 21 patients with morbidity (mean BMI 43.3 kg/m^2, range 35 – 53), 18 received two sleeves, 1 a single sleeve, and 2 a partial second one. Although the average procedure duration was quite long (131 minutes), the mean hospitalization was short (1.6 days). The most frequent adverse events included transient vomiting, pain, nausea, and dysphagia. However, there was a high number of early staple line gaps (n = 11). By the end of the 6-month study, there were three incomplete distal sleeves, two additional gaps, and one re-created restriction. From the clinical point of view, TSG resulted in significant improvements in body weight (average BMI 38.5 kg/m^2, $P < 0.0001$, %EWL 26.5), and in overall as well as specific quality-of-life (QoL) measures ($P < 0.05$). Its effects on comorbidities were less favorable.

The same technique was later improved with closer apposition of the two staple lines and the perioperative administration of methylprednisolone and diclofenac [14]. In this study 11 patients (mean BMI 41.6 kg/m^2, range 37.2 – 52.6) received two sleeves with only two early mid-stoma gaps. The average procedure time was lower (84 minutes) and hospital stay was a single night. After 6 months, despite recording of four gaps (< 1 cm) in total and two re-created restrictions, no statistically significant difference in weight loss between patients with or without gaps was observed. The total mean BMI was 33.1 kg/m^2 ($P < 0.01$), %EWL was 46.0 ($P < 0.05$), and the QoL measures were remarkably improved.

Although transoral gastroplasty has yielded promising short-term results, the long-term effects are yet to be seen. So far, the endoscopic restriction procedures have not shown an advantage over surgery in eliminating general anesthesia. There is in any case some scepticism about efficacy and indications, as several surgical gastric partitioning procedures have been abandoned as failures. VBG, for example has become unpopular because of discouraging long-term results and the sleeve gastrectomy has only specific indications. Sleeve gastrectomy can be done as a first stage, prior to the duodenal switch procedure for high-risk patients. It can constitute the definitive surgical procedure or, at a later stage, be combined with duodenoileostomy [15].

Malabsorption techniques

Roux-en-Y gastric bypass (RYGB) is the dominant bariatric procedure, especially in the USA, with well-documented effectiveness by all definitions of efficacy. Its principal mechanism is rerouting the passage through the gastrointestinal tract, as ingested nutrients enter the jejunum in the absence of biliopancreatic juice via a Roux limb that is anastomosed to a small gastric pouch.

A similar concept is applied with the endoscopic duodenal–jejunal bypass sleeve (EDJBS) (**Fig. 4**). The Endobarrier (GI Dynamics, Inc., Watertown, Massachusetts, USA) is placed over a wire catheter system. It consists of a self-expanding nickel–titanium alloy anchor (diameter 25–50 mm) with barbs for engaging proximal duodenal tissue and a 60-cm polyethylene sleeve that is extended into the jejunum, with drawstrings in the proximal end for removal. As only food and no biliopancreatic juice passes through its impermeable liner, a proximal intestinal bypass can be created without anastomosis or stapling. Theoretical effects include early satiety, delayed gastric emptying, partial duodenal mechanical obstruction, and enhanced delivery of bile salts and undigested nutrients to the distal bowel with alteration of incretin pathways. These effects also suggest a potential for diabetes treatment.

In live porcine models, the EDJBS was shown to be feasible, easy, and reversible with a quite favorable 120-day safety profile and significantly less average weight gain ($P = 0.01$) [16, 17]. However several concerns about anchor stability and associated risks were raised. While a Food and Drugs Administration (FDA)-approved clinical trial is underway, the preliminary results in humans are encouraging. In 12 patients with mean BMI 43 kg/m^2, mean procedure times for implantation and removal were short (26.6 and 43.3 minutes, respectively), with two early removals attributed to poor placement [18]. It was generally safe. Minor complications included implant site inflammation, self-limited functional disorders and two removal-related pharyngeal tears. Patients who completed a 12-week treatment with EDJBS had an average EWL of 23.6%. The glycemic control results were promising.

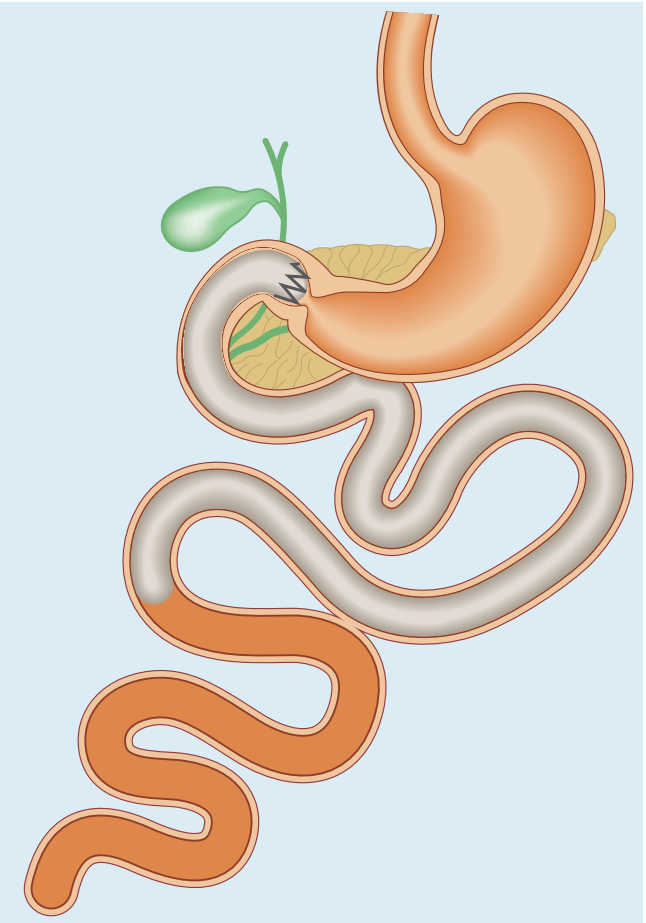

Fig. 4 Diagram of fully deployed endoscopic duodenal–jejunal bypass sleeve (EDJBS). (Courtesy of l'Institut de Recherche contre les Cancers de l'Appareil Digestif [IRCAD]).

As in endoscopic gastroenteroanastomosis, there may be potential for the use of magnets in bariatric endoluminal endosurgery [19].

Bariatric endoluminal interventions extend the range of endoscopic treatments. Although further research and development is needed to prove their potential advantages over surgery, they hold some promise as potential bariatric alternatives. Their favorable short-term results suggest that they might evolve as useful antiobesity strategies when surgery is not desirable either for medical or personal reasons. If they fail to provide any long-lasting benefits, they might at least be employed as the first component of a two-stage procedure or they might simply be revised.

Post-surgical endoscopic interventions

Ineffective weight loss or complications following bariatric surgery may require a corrective re-intervention. As surgical revisions carry high morbidity rates, post-surgical endoscopic interventions may prove to be a valuable alternative.

Anastomotic bleeding, strictures, leaks, or large gastric stomas with a subsequent weight regain can be managed by standard endoscopic techniques such as epinephrine injection, heater probe cautery, argon plasma coagulation, balloon dilation, bougienage, endoclipping, stent insertion, fibrin glue application, or sclerotherapy [20 – 27]. Transoral anastomotic tightening with sutures has been shown to be safe, with preliminary weight re-

sults being variable but significant [28]. Post-RYGB sutures and post-VBG eroded bands can be endoscopically cut and removed [29,30]. Radiofrequency ablation with the Stretta procedure via endoscopic balloon-mounted needles was used for persistent post-RYGB GERD with favorable results [31].

Endotherapy after surgical revision has also been shown to be technically possible, with post-revision anastomotic leak repair being achieved with a through-the-scope suturing T-tag device [32]. Two propylene threads are loaded into a hollow needle, sequentially pushed out after tissue puncture, then tied and locked together with a plastic ring and pin. Also, post-revision pouch leaks have been repaired by means of an incisionless transoral fastening device (StomaphyX; EndoGastric Solutions Inc., Redmond, Washington, USA) [33]. This was previously applied in post-RYGB stoma revision and pouch reduction [34]. The endoscope is inserted through its shaft, tissue is drawn into its chamber and polypropylene fasteners are delivered for serosa-to-serosa plication.

In experimental studies, transoral tissue anchors or a T-tag device have also been applied for pouch and/or stoma reduction [35,36]. However, the T-tag device was associated with moderate reductions and low risks of injury or attachment to adjacent organs (**Fig. 5**).

Endosurgical interventions

Both endoscopic and surgical bariatric approaches have their drawbacks. Several efforts to minimize these have given birth to experimental endosurgical procedures.

Endolaparoscopic gastric partition was carried out by securing a transorally delivered mesh in the gastric lumen with laparoscopic intragastric suturing [37].

An adjustable gastric band (Ethicon Endo-Surgery, Johnson and Johnson, Cincinnati, Ohio, USA) was endoscopically placed around the cervical esophagus following exposure with open dissection [38]. The procedure was generally safe, well tolerated, and resulted in significantly lower weight gains than in the sham group ($P = 0.005$). However, it is conceivable that early regurgitation may occur after swallowing.

A duodenojejunal bypass procedure using a polyethylene cylindrical endoluminal tube has also been proposed [39]. The device was implanted in pigs by duodenotomy and circumferentially sutured for proximal fixation with no major complications. Significantly slower weight gains were seen compared with the control group ($P = 0.005$) with a trend to even slower gains when longer tubes were used.

In an evolving research process, the utilization of endoluminal stapling represents another challenge. The FDA-approved SurgASSIST (Power Medical Interventions, New Hope, Pennsylvania, USA), which is a transoral, computer-mediated circular stapler with a flexible shaft, has been used in gastrojejunostomy during RYGB. Its theoretical advantages include consistent stapling force, better accuracy and access, no need for trocar dilation, and decreased complications. Despite several technical limitations, its use seems generally easy and safe with significantly lower wound infection rates than conventional staplers [40].

Fig. 5 T-tag threads (Courtesy of Wilson-Cook Medical).

Gastrointestinal electrical stimulation via intraluminal electrodes

The ability to normalize gastric dysrhythmia and entrain gastric slow waves, using implantable stimulation electrodes and a pulse generator for the gastrointestinal delivery of long pulses or long pulse-trains has suggested the therapeutic potential of gastrointestinal pacing in obesity. It can induce food intake reduction, gastric emptying delay, decrease in appetite-stimulating gut hormones and increase in appetite-inhibiting gut hormones in gastric and duodenal tissues [41–43]. Gastric electrical stimulation (GES) may also have an impact on the central expression of appetite-related hormones [44].

Implanted GES, though still under investigation, has yielded promising weight loss results. Not all patients respond, however, and moreover, it cannot be reversed without re-operation. Despite the lack of appropriate generators, these problems might be overcome by short-term GES via endoscopically placed electrodes. In experimental studies, these have been either transabdominally placed in contact with the full thickness of the gastric wall similarly to a percutaneous endoscopic gastrostomy (PEG) procedure or transgastrically inserted into the gastric serosa while attached to the sides of a PEG tube [45,46]. In humans, the electrodes have been advanced either transorally or transabdominally via a PEG tract and fixed onto the mucosa [47–50]. In another study, electrodes have been percutaneously inserted through a plastic cannula into the gastric muscle layer, without mucosal penetration [51].

These procedures are technically different. Some resemble the surgical implantation of serosal electrodes more than others. The abdominal exit route seems more suitable for humans, and PEG placement is technically more difficult in obese patients. Nevertheless none of these approaches was associated with notable adverse events.

Pilot studies in humans demonstrated reductions in gastric accommodation and emptying, supporting the idea that GES via intraluminal electrodes might serve to predict long-term outcomes and, therefore, help in the selection of appropriate candidates for implantable GES [47,49].

Duodenal electrical stimulation was done in a similar way [52]. A pair of ring electrodes was incorporated into a nasal–jejunal feeding tube, and preliminary experience in humans showed significant reductions in maximum water intake and delay in gastric emptying without dyspeptic symptoms [53]. A decrease in nutrient absorption, induction of mild-to-moderate dyspeptic and malabsorption symptoms and small bowel transit acceleration

has been recently reported for intestinal pacing, suggesting a potential antiobesity role [54].

Gastrointestinal electrical stimulation via intraluminal electrodes is in an early developmental stage and several practical and technical issues need to be addressed for longer-term application. However, its potential contribution to the treatment of obesity seems worthy of further exploration. Furthermore, this might trigger future research towards a potential endoscopically delivered pacemaker.

Natural orifice transluminal endoscopic surgery (NOTES)

Endoscopic access through natural orifices for performance of traditional surgical procedures promises several benefits, including improved cosmesis and reductions in postoperative complication rates, anesthesia, analgesia, and recovery period. Obesity seems to be an attractive indication for NOTES owing mainly to the potential advantages in decreasing incision-related complications (such as hernias). Several experimental devices and gastrojejunostomy techniques might represent possible platforms for bariatric NOTES procedures [55–60]; even though they are still of a hybrid nature, their feasibility has recently been demonstrated.

Sleeve gastrectomy was initially done in a porcine model [61]. Gastric retraction and exposure were achieved using stay sutures applied with the Endostitch device (Auto-Suture, Norwalk, Connecticut, USA). A transgastric dual-channel endoscope was used through an overtube for gastric manipulation. Stapler placement necessitated gastric fixation with stay sutures. The esophagogastric junction (EGJ) was visualized by means of minilaparoscopy for gastric division. An initial duration of approximately 5 hours for transrectal pouch removal was later reduced to 2.5 hours, and the suture lines were intact at autopsy. However no closure of the rectal defect was attempted.

Another surgical team described a more complex RYGB procedure in a human cadaver [62]. Abdominal trocar placement was used for pneumoperitoneum maintenance and visualization. A transgastric single-channel endoscope was used for exposure of the ligament of Treitz, a transvaginal laparoscopic grasper for lifting the mesocolon, and a transvaginal endoscope via a second trocar for bowel manipulation. Performing proximal jejunotomy and distal enterotomy, required both endoscopes, along with endograspers, endoscopic and laparoscopic scissors, and computer-mediated linear staplers. After removal of the transgastric scope, a gastric pouch was formed with a triple-stapling technique and a transvaginal anvil. The gastrojejunostomy, jejunojejunostomy, and gastrotomy were intact on abdominal inspection but the mesenteric defects and the vaginotomies were left unclosed.

Several technical issues of RYGB were highlighted in a second cadaver study carried out by surgeons as well as gastroenterologists [63]. Under only umbilical laparoscopic supervision, the transvaginal access seemed easy and safe. A transgastric single-channel endoscope was suitable for gastric retraction and advantageous over laparoscopy in creating the retrogastric passage to the EGJ. Transumbilical articulated linear staplers were used for pouch formation, employing guide wires because of the unavailability of long staplers and the difficulty of guidance with flexible instruments. A transgastric scope was less useful for measurement of the small bowel than flexible and/or rigid graspers. For performance of gastrojejunostomy, placement of the stapler shaft and anvil in the small bowel was difficult. Docking of the stapler was almost impossible with flexible instruments. No jejunostomy was done using flexible transesophageal stapling. Small-bowel manipulation was facilitated by laparoscopic graspers, and it was resected transvaginally with linear staplers. Not all procedures were completed; those that were took 6–9 hours. Several perforations occurred.

The first four sleeve gastrectomies with minilaparoscopic assistance in human patients have recently been reported [64]. With the use of a transvaginal endoscope, enterotomy was avoided. Sleeve gastrectomy required two abdominal trocars and an umbilical trocar for stapling. It was uneventfully completed by surgeons in 90–100 minutes with the additional use of an harmonic scalpel, an orogastric bougie, and sutures for staple line reinforcement, as well as vaginal closure and drain placement for 5 days. Hospital stay was only 2 days. No follow-up details were available.

As the benefits should outweigh the risks, further progress in instrumentation, techniques, and skills are mandatory for the performance of advanced bariatric NOTES procedures in humans. Despite several technical challenges such as the point of entry, visualization, intra-abdominal manipulation, port closure, complication management, infection prevention, and procedure duration, NOTES suggests a new research approach for the management of obesity.

Conclusions

Endoscopic bariatric treatment is an evolving concept. Preclinical research in the fields of therapeutic endoscopy and minimally invasive surgery promises to expand this therapeutic armamentarium with several alternatives for bariatric treatment. As the need for minimally invasive procedures grows, more research opportunities will be available. Preliminary results in humans testify to interesting progress in the development of minimally invasive bariatric procedures. Today, these procedures are at an early stage. However, with further technical improvements, they might evolve as attractive alternatives for selected obese patients. Randomized prospective studies are warranted.

Competing interests: None

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