REVIEW

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Mechanism of action and selection of endoscopic bariatric therapies for treatment of obesity

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Endoscopic bariatric therapies (EBTs) are minimally invasive and safe procedures with favorable weight loss outcomes in obesity treatment. We aimed to present the weight loss mechanism of action of EBTs and an individualized selection method for patients with obesity. We searched PubMed, Medline, Scopus, Embase, and Google Scholar databases for studies on the topic from databases inception to July 1, 2023, written in English. We focused on EBTs potential mechanism of action to induce weight loss. We also present an expert opinion on a novel selection of EBTs based on their mechanism of action. EBTs can result in weight loss through variable mechanisms of action. They can induce earlier satiation, delay gastric emptying, restrict the accommodative response of the stomach, decrease caloric absorption, and alter the secretion of gastrointestinal hormones. Selecting EBTs may be guided through their mechanism of action by which patients with abnormal satiation may benefit more from tissue apposition devices and aspiration therapy while patients with fast gastric emptying may be better candidates for intragastric devices, endoscopic anastomosis devices, and duodenal mucosal resurfacing. Consequently, the selection of EBTs should be guided by the mechanism of action which is specific to each type of therapy.

Keywords: Bariatric surgical procedures; Obesity; Weight loss

INTRODUCTION

Obesity is a chronic and relapsing disease with a wide range of economic and medical consequences.[1] Assuming this rise continues unabated, over half of the United States population will suffer from obesity by 2030.[2] Worldwide, obesity represents one of the largest economic burdens costing more than US $700 billion each year. In fact, the estimated annual cost of this disease is approximately US $480 billion in the United States only.[3] Furthermore, obesity increases the risk of several comorbid conditions: type-two diabetes mellitus (T2DM), coronary heart disease, stroke, respiratory problems, gallbladder disease, and some cancers.[4]

Endoscopic bariatric therapies (EBTs) represent an emerging and effective weight loss method and have been increasingly used owing to their safety profile.[5] For example, space-occupying intragastric devices (IGDs), aspiration therapy (AT), tissue apposition devices (TADs), duodenal mucosal resurfacing (DMR), incisionless anastomosis devices, and the duodenal-jejunal bypass line (DJBL) induce weight loss through a different mechanism of action. Here, we review their mechanism of action and weight loss outcomes and provide an expert opinion on an innovative method of EBT selection for each patient.

METHODS

We searched for research articles on the topic of EBTs on PubMed, Medline, Scopus, Embase, and Google Scholar databases from database inception to July 1, 2023, written in English. We focused

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on the potential weight loss mechanism of action. In particular, we included data from systematic reviews and meta-analysis, randomized clinical trials (RCTs), and cohort studies that assess the weight loss outcomes of EBTs and their mechanism of action. We also present an expert opinion in the field of bariatric endoscopy on a novel selection of EBTs based on their mechanism of action.

RESULTS

A summary of EBTs is presented in Table 1 and Figure 1.[6]

Endoscopic bariatric therapies

1) Intragastric balloons

Currently, four devices are approved by the Food and Drug Administration (FDA), two of which are fluid-filled (Orbera and ReShape), one is air-filled (Obalon), and the last is silicone-filled (BAROnova). Orbera was approved by the FDA in 2015 and can be filled with up to 400 to 700 mL of sterile saline to achieve its optimal functionality. Furthermore, 10 mL of methylene-blue was added as an indicator of deflation or perforation during the time of use. ReShape Duo is a dual balloon system approved in 2015 and includes two balloons filled with 750 to 900 mL of liquid that are connected by a flexible wire-band. This double balloon modality makes this device more resistant to migration in case one of two malfunctions. Meanwhile, Obalon was approved by the FDA in 2016 and is currently the only gas-filled device that has several advantages, including the ability to swallow the deflated balloon capsule guided by fluoroscopy in addition to placing three 250 mL balloons together.[7,8]

2) TransPyloric Shuttle

The TransPyloric Shuttle (TPS; BAROnova) was approved in 2019 and is an endoscopic device inserted trans-orally that can be removed after 12 months. It is mechanically constructed using solid silicone material, which eliminates the inflation/deflation risk. The TPS consists of a large balloon connected to a smaller and cylindrical bulb by a flexible silicone connection. The large bulb aims to prevent migration from the stomach while the smaller bulb travels freely to the proximal duodenum. Ultimately, the larger bulb intermittently seals the pylorus, reducing the gastric outflow rate and caloric intake.[9]

IGDs are approved for patients with obesity classes 1 and 2 (body mass index [BMI], 30–40 kg/m^2), particularly patients who failed other lifestyle and nutritional modifications. In fact, a patient must have one or more obesity-related comorbidities for BMI ranges of 30 to 40 and 30 to 34.9 kg/m^2, respectively to be a candidate for BAROnova and ReShape.[7] Moreover, IGDs

Table 1. Different endoscopic bariatric and metabolic therapies with their corresponding total percentage of weight loss at 12 months and duration of placement

Endoscopic bariatric and metabolic therapies	Mechanism of action in weight loss	Devices in market	Total body weight loss at 12 mo (%)	Duration of placement (mo)
Intragastric balloons	1. Decrease gastric emptying	ReShape	10–15	6
	2. Increase gastric accommodation	Orbera	10–12	6
	3. Increased GLP-1 and PYY	Obalon	5–10	6
		BAROnova	10–12	12
Aspiration therapy	1. Aspiration of undigested food	AspireAssist	15–20	>12
	2. Lifestyle modification associated with AT			
Tissue apposition devices	1. Increased gastric restriction	ESG	15–20	NA
	2. Decreased gastric accommodation	POSE	10–20	NA
	3. Increased cholecystokinin	EGP	7–12	NA
Duodenal mucosal resurfacing	Not well understood	Revita	Minimal	NA
		Diagone	Minimal	NA
Endoscopic anastomosis devices	Anastomosis enhances the passage of partially undigested food into the distal ileum, increasing GLP-1 and PYY secretion	IMAS	10–15	NA
		Magnamosis	Limited data	NA
		EasyByPass	Limited data	NA
Duodenal-jejunal bypass liner	Undigested nutrients bypass the proximal intestine, increasing GLP-1 and PYY secretion	EndoBarrier	15–20	3–12
		ValenTx	Limited data	Limited data

GLP-1, glucagon-like-peptide-1; PYY, peptide YY; ESG, endoscopic sleeve gastrectomy; POSE, primary obesity surgery endoluminal; EGP, endoscopic gastric plication; IMAS, incisionless magnetic anastomosis system; NA, not applicable.

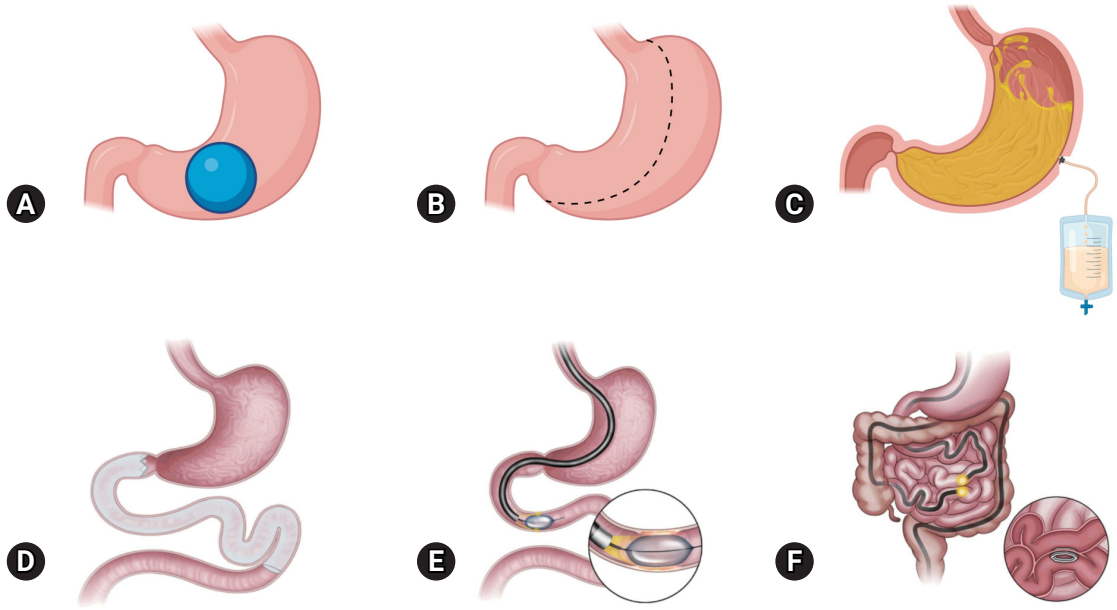

Fig. 1. Illustration of endoscopic bariatric therapies. (A) Intragastric balloon. (B) Endoscopic sleeve gastroplasty. (C) Aspiration therapy. (D) Duodenal-jejunal bypass liner. (E) Duodenal mucosal resurfacing. (F) Incisionless magnetic anastomosis system. (D–F) Adapted from Gong and Kim. Clin Endosc 2018;51:425–429, according to the Creative Commons license.[6]

can be pursued as a bridge therapy in patients with a BMI >40 kg/m^2 undergoing bariatric surgery or some other non-bariatric needed interventions (such as heart and liver transplants).[10-13]

3) Weight loss mechanism

Mechanical and hormonal stimuli of intragastric balloons (IGBs) interplay to regulate satiety (sensations that inhibit eating in the postprandial period[14]) and satiation (the process that brings an eating episode to an end[15]), which leads to decreased caloric intake and ultimately decreasing body weight. Mion et al.[16] showed a decrease in ghrelin levels (an orexigenic hormone) at the time of IGB removal which positively correlates with weight loss. Other contributors to weight loss include IGB-induced delay in gastric emptying (GE) and accommodations[17-20] as well as parasympathetic afferent neurons stimulating secondary gastric distension.

4) Outcomes

IGB placement resulted in weight loss and BMI reduction of about 33.9% and 4.9 kg/m^2, respectively, in a study performed on 2,515 patients with obesity.[21] However, other studies show that the total body weight loss percentage (TBWL%) ranges 5% to 15%.[22] A prospective, multicenter, open-label RCT shows that patients with IGB lost 15.0% (95% confidence interval [CI], 13.9%–16.1%; *n*=187) compared with 3.3% (2.0%–4.6%; *n*=101) in the control group.[23] A systematic review and meta-analysis including 10 RCTs and 30 observational studies (total of 5,668 patients) shows that metabolic parameters (such as fasting blood glucose, glycated hemoglobin [HbA1c], blood pressure, and waist circumference) improved compared to non-surgical therapies.[24]

Tissue apposition devices

1) Device description and indications

TADs involve endoscopic suturing or plication of the gastric pouch to modify its native anatomy. Currently, two TADs are available: endoscopic sleeve gastroplasty (ESG) via the Apollo OverStitch Endoscopic Suturing System which is FDA approved,[25] and the primary obesity surgery endoluminal (POSE) procedure. The Apollo Overstitch System is used to achieve transoral endoscopic gastric volume reduction similarly to sleeve gastrectomy. Full-thickness closely spaced interrupted sutures are placed from the prepyloric antrum to the gastroesophageal junction.[26,27] The POSE procedure reduces the gastric volume by using an incisionless operating platform system. This technique uses specialized suture anchors to plicate the stomach in a total average of 11 to 13 locations: 8 to 9 in the fundus

and 3 to 4 in the distal body. Consequently, this mechanically and physiologically restricts ingested food from contacting the full surface area of the stomach.[28] One of the main differences between POSE and ESG is the inclusion of plications near the stomach fundus in POSE.[29]

This technique targets patients with a BMI range of 30 to 39.9 kg/m^2 and is semi-permanent owing to the involvement of suturing. These devices can be the primary or supplementary treatment for obesity in patients experiencing weight regain after bariatric surgery.[22]

2) Weight loss mechanism

TAD-induced weight loss is achieved by increased satiation, whether from peripheral signaling from distal gut to the hypothalamus and brainstem or secondary to restriction of gastric accommodation.[30,31] Furthermore, GE impairment and retention of food in the gastric pouch cause increased satiety. The distal plications can slow the antral mill contractions which further delays the complete GE. A delay in GE was observed in patients who underwent ESG compared to patients with lifestyle intervention at 3 (152.3±47.3 vs. 89.1±27.9 min, p<0.001) and 12 months (137±37.4 vs. 90.1±23.4 min, p<0.001). Importantly, a GE delay at 3 months is associated with a greater weight loss.[32] However, IGBs can cause a greater delay in GE compared to ESGs. On the other hand, ESGs have a greater impact on satiation than IGBs[33] (Fig. 2).

3) Outcome

Several studies show that TAD can result in a 15–20% of TBWL.[22] In a systematic review and meta-analysis involving 1,772 patients, the TBWL was 15.1%, 16.5%, and 17.2% in 6, 12, and 18 to 24 months, respectively.[34] Furthermore, a RCT involving 9 United States centers demonstrated a TBWL of 13.6% (standard deviation [SD], 8.0; n=85) in patients who underwent ESG compared to 0.8% (SD, 5.0; n=124; p<0.0001) in the control group.[35] This technique has shown significant improvement in several parameters including HbA1c, systolic blood pressure, alanine transferase, and triglycerides levels in metabolic and obesity comorbid conditions.[36,37] Some studies favor ESG over POSE in terms of weight loss,[38] while others show that the difference in TBWL% is insignificant between both procedures.[29] A more recent, prospective, multicenter POSE 2.0 trial shows that a TBWL% of 15.7±6.8% was achieved in 44 patients at 12 months with a significant improvement in the lipid profile, liver enzymes, and hepatic steatosis.[39]

Aspiration therapy

1) Device description and indications

The aspiration technique involves using a gastrostomy tube and siphon assembly to aspirate gastric content from the patients' stomach 20 minutes after meals thrice daily.[40] Importantly, the timing of aspiration after the meal determines the efficacy of AT. Aspiration 20 minutes after a 450-kcal meal is ingested removes approximately 30% of undigested calories, while aspirating after 60 miniutes decreases this percentage to 17%.[41]

AspireAssist is FDA approved for 22 years or older patients with a BMI range of 35 to 55 kg/m^2 who have previously tried non-surgical weight loss therapies but failed to lose or maintain weight loss.[42]

2) Weight loss mechanism

Aspiration-therapy-induced weight loss is achieved through different mechanisms of action, such as undigested food aspiration and lifestyle modifications. The aspiration of undigested food particles before absorption reflects approximately 30% of the ingested energy if aspirated within 20-min of meal ingestion. Interestingly, this can only explain 80% of the total amount of weight loss experienced by fully compliant patients. Other weight loss mechanisms include the need for increased chewing and drinking more water with every meal,[43,44] and limiting their between-meal snacks to avoid any additional aspiration inside or outside their home.[45]

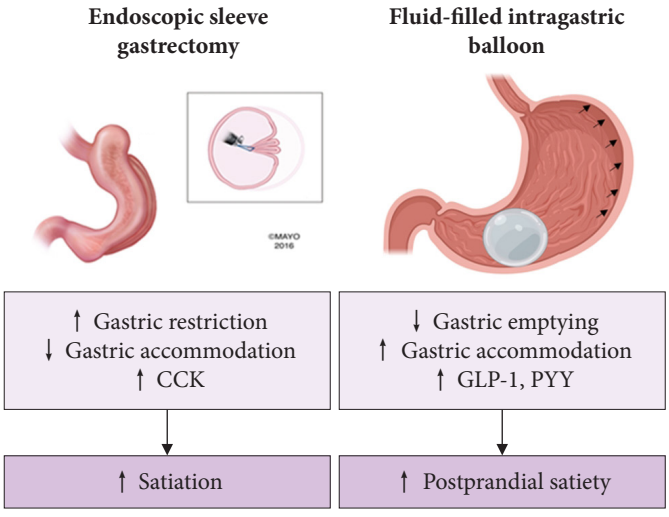

Fig. 2. Main mechanism of action of endoscopy sleeve gastrectomy and intragastric balloons. CCK, cholecystokinin; GLP-1, glucagon-like-peptide-1; PYY, peptide YY.

3) Outcome

Several large trials have assessed the efficacy of AT. The USPATHWAY study demonstrates a TBWL% of approximately 14.2%, 15.3%, 16.6%, and 18.7% at 1, 2, 3, and 4 years of therapy, respectively.[46,47] Several other studies support the efficacy of AT in achieving significant weight loss in patients with obesity.[40] Hence, AT is considered an effective weight loss therapy in the short- and long-term. In addition to weight loss, a post-market study in five European countries showed cardiometabolic improvement in HbA1C, fasting glucose, and triglycerides levels and systolic and diastolic blood pressure. Meanwhile, cholesterol levels significantly increased.[48]

Duodenal-jejunal bypass liner

1) Device description and indications

The DJBL consists of a liner, delivery, and retrieval system. The liner represents an impermeable fluoropolymer that spans approximately 60 cm into the small intestine and can be affixed and secured to the duodenal bulb between the ampulla of Vater and pylorus by anchors located proximally to the liner. This liner bypasses the duodenum by allowing chyme to pass directly from the stomach to the jejunum. Therefore, pancreatic juices exiting the ampulla of Vater do not mix with the gastric content separated by the liner. This technique resembles gastric bypass surgery without permanently altering the gastrointestinal anatomy. This device can remain in the duodenum up to 12 months after deployment.[49]

EndoBarrier is appropriate for patients with poorly controlled T2DM who are poor surgical candidates. Although it is not FDA approved, it can be used as a bridge weight loss therapy before surgery. Furthermore, patients with poorly controlled T2DM precluding a non-bariatric elective surgery can improve their glycemic levels with this procedure.[49]

2) Weight loss mechanism

The DJBL can induce weight loss through a mechanism involving incretin theory. Food intake causes changes in hormonal cues which influences insulin secretion. This incretin effect is altered in patients with obesity or T2DM. However, undigested nutrients bypass the proximal intestine rapidly to reach the distal small bowel following DJBL, resulting in increased secretion of glucagon-like-peptide-1 (GLP-1) hormone by L-cells. Consequently, GLP-1 stimulates insulin secretion, increases insulin sensitivity, and inhibits glucagon. Centrally, GLP-1 also acts to increase satiety and reduce appetite.[49,50] Another explanation for the increased level of incretin hormones is the increased bile acid levels caused by enterohepatic circulation disruption induced by DJBL.[51,52] A RCT shows that the postprandial levels of glucose-dependent insulinotropic polypeptide (GIP) and glucagon decrease after 24 weeks of DJBL implantation. The homeostatic model assessment for insulin resistance (HOMA-IR, an indicator of insulin sensitivity) significantly improves in 14/17 patients in this study.[50]

3) Outcome

EndoBarrier is the most studied DJBL. Five RCTs were launched to test the efficacy of EndoBarrier. The most extensive study followed 73 patients for 12 months; 6 months of device usage, and another 6 months of follow-up after removal. The DJBL group lost 32% of their excess weight versus only 16.4% in the control group ($p<0.05$). Although some trials also showed a significant increase in weight loss and improvement of T2DM,[49,53] one trial was halted by the FDA owing to the development of seven liver abscesses (3.5%). One possible explanation for this finding is the creation of a nidus of infection that spreads to the liver bed.[49]

A systematic review and meta-analysis of 10 RCTs (681 patients) comparing weight loss and glycemic control between DJBL and control groups shows that the DJBL group has a major excess weight loss percentage (11.39%; 95% CI, 7.75%–15.03%; $p<0.00001$) and greater decrease in HbA1c level (–1.03%; 95% CI, –1.56 to –0.50]; $p<0.0001$).[54] Adverse events included early device removal in 17.8% (from nine studies including 321 patients) and gastrointestinal bleeding, DJBL migration, device obstruction, and liver abscess in 6.5% (8 studies including 276 patients) of patients.

Limited long-term effects data of DJBL is available. Seventy-two percent of 30 patients regain weight within 6 months of EndoBarrier removal.[55] A second-generation EndoBarrier device studied in Chile offered the patients who tolerated the device an opportunity to keep it in for up to 3 years. Significant weight loss maintenance was observed over 52 weeks (71 patients), 104 weeks (40 patients), and 156 weeks (11 patients). Similarly, HbA1c levels significantly decreased after 12 and 24 months of device placement. However, current guidelines do not recommend the placement of this device for over 1 year.[56]

Duodenal mucosal resurfacing

1) Device description and indications

DMR is an endoscopic, minimally invasive, catheter-based procedure requiring hydrothermal ablation of the duodenal mucosa with subsequent mucosal healing. Duodenal ablation starts at the post-papilla area and extends just proximal to the ligament of Treitz. The procedure usually creates five longitudinally separated ablations of 9 to 10 cm in length.[57]

This procedure is promising in patients with obesity, T2DM, and elevated liver enzyme levels as is the case in metabolic dysfunction-associated steatotic liver disease (MASLD). Although several studies show the effectiveness of such procedures in reducing weight and improving glycemic control, more studies are needed to further establish the potentially favorable results in patients with MASLD.[58,59] In fact, DMR is indicated for patients with T2DM to improve their glycemic control irrespective of their BMI.[60]

2) Weight loss mechanism

Animal and human studies have proposed foregut non-stimulation secondary to diversion as a weight loss mechanism in bariatric surgery. Proximal diversion induces an increase in incretins such as GLP-1 and GIP secondary to decreased anti-incretins release as well as distal delivery of undigested nutrients.[61,62] These modified pathways have a significant role in major diseases including obesity and T2DM. Restoring the mucosal interface in the duodenum can correct the malfunctioning metabolic signals seen in patients with obesity and T2DM.[58] More research is needed to fully understand the mechanism behind the weight loss and metabolic benefit.

3) Outcome

Revita is the most studied DMR, followed by DiaGone which as is an ongoing multicenter, open-label study (NCT03390322). The first DMR study in humans included 39 patients with T2DM. In this trial, two groups of patients were included. The first group had a 9.3 cm segment ablated (long segment [LS]), while the other group had a 3.4 cm ablation segment (shorter segment [SS]). HbA1c levels significantly decreased by 1.2% at 6 months (p<0.001). Remarkably, the glycemic improvement was higher in the LS group at 3 (2.5% vs. 1.2%) and 6 months (1.4% vs. 0.7%). There was a modest weight reduction at three and six months: 3.9% and 2.5%, while glycemic improvement did not correlate with weight reduction.[58] Subsequent studies on DMR shows an improvement in patients' liver function tests and lipid profiles with a statistically significant reduction in alanine aminotransferase in 36 patients over 12 months.[59]

Endoscopic anastomosis devices

1) Device description and indications

The incisionless magnetic anastomosis system (IMAS) is one of the most studied devices in the group of endoscopic anastomosis device (EAD). This technique uses self-assembling magnets to create a jejunoileal bypass and generate a dual-path enteral bypass. The magnets are deployed through simultaneous enteroscopy and colonoscopy, which create a large-bore compression anastomosis. Furthermore, no additional intervention is required to remove this device since the magnets spontaneously pass through the stool.[6]

2) Weight loss mechanism

The anastomosis created by EAD enhances the passage of partially undigested food into the distal ileum[63] which leads to increased secretion of GLP-1, peptide YY (PYY), and other gastrointestinal hormones promoting improvement in glucose homeostasis and weight loss enhancement.[64]

3) Outcome

The IMAS can result in a TBWL of 10% to 15%. One study assessed the jejunal diversion of ten patients with obesity plus prediabetes, diabetes, or no diabetes. This diversion remained patent in all patients after twelve months. The average weight loss was 14.6%, while HbA1c decreased by 1.9% and 1% in diabetic and prediabetic patients, respectively.[63] Further studies are needed to assess the efficacy of this innovative treatment.

DISCUSSION

Obesity phenotypes

An innovative way to classify obesity relies on pathophysiology rather than BMI and other parameters (such as waist circumference).[1] Homeostatic food intake consists of three stages: hunger (desire to eat), satiation, and postprandial satiety.[65,66] We previously showed that the prevalence of abnormal satiation and abnormal postprandial satiety was 32% for each in 450 patients with obesity.[67] These obesity phenotypes were used to guide the selection of anti-obesity medications and enhance weight loss.[67-70] Furthermore, we reported that ESG mainly decreases caloric

intake to reach fullness.[31] Meanwhile, IGB has a pronounced effect on delaying GE.[71] Our recently published data suggest that the change in $T_{1/2}$ at 3 months correlated with TBWL% at 3 months for IGB and ESG (p=0.01 for both). However, a greater impact on TBWL% was demonstrated in IGB compared to ESG (R2=0.42 vs. 0.26). Furthermore, the change in $T_{1/2}$ at 3 months in the IGB group was predictive of weight loss at 6 months (p=0.01) but not in ESG (p=0.11). Moreover, ESG was associated with a greater decrease in the maximum tolerated volume (MTV) compared to IGB (340.25±297.97 mL vs. 183.00±217.13 mL, p=0.08). Hence, ESG is associated with an enhanced effect on satiation through decreased gastric accommodation. In fact, changes in MTV trended toward significance for predicting TBWL% at 6 months for ESG (p=0.06) but not IGB (p=0.19).[72] Hence, the choice of EBT based on obesity phenotypes is a promising step in improving weight loss outcomes.

No previous studies assessed for the weight loss outcomes of other EBTs with respect to different phenotypes. However, a hypothetical proposed mechanism can be suggested based on the mechanism of action of these EBTs. AT can benefit patients with abnormal satiation since those patients consume more calories. Patients with abnormal satiation may benefit more from this technique compared to patients with abnormal postprandial satiety by preventing the absorption of excess calories via aspiration. Moreover, EAD and DJBL techniques increase GLP-1 levels.[49,64] Hence, this can delay the GE which may be a significant advantage for patients with rapid GE. In summary, patients with abnormal satiation may benefit more from TAD or AT while patients with abnormal postprandial satiety can be suitable candidates for IGB, EAD, and DJBL (Fig. 3).

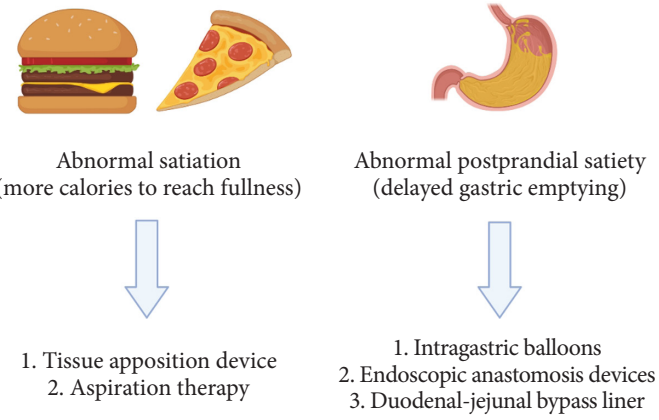

Fig. 3. A working hypothesis of endoscopic bariatric therapy selection based on the mechanism of action and pathophysiology.

CONCLUSIONS

Obesity is a complex metabolic disease that is associated with multiple serious comorbid conditions. Lifestyle modifications, pharmacotherapies, bariatric surgeries and EBTs constitute the major weight loss interventions. As more EBTs become FDA approved, patients with obesity have a wide variety of options for weight loss. The utilization of EBTs as a sole therapy or combined with surgery and pharmacotherapy are proving to be important contributors for treating obesity. Although significant data support the safety and efficacy of EBTs, more research is needed to learn about the outcomes and individualized selection of these innovative techniques.

Conflicts of Interest

Dr. Andres Acosta is a stockholder in Gila Therapeutics, Phenomix Sciences; he served as a consultant for Rhythm Pharmaceuticals, General Mills, and Amgen Pharmaceuticals. Dr. Barham K. Abu Dayyeh is a consultant for Endogenex, Endo-TAGSS, Metamodix, and BFKW; a consultant and grant/research support from USGI, Cairn Diagnostics, Aspire Bariatrics, Boston Scientific; he had speaker roles with Olympus, Johnson and Johnson; speaker and grant/research support from Medtronic, Endogastric solutions; and research support from Apollo Endosurgery, and Spatz Medical. The other authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: WG, AA; Methodology: WG, GC, AA; Supervision: BKAD, AA; Validation: AA; Writing–original draft: WG, GC; Writing–review & editing: all authors.

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