






Future of Metabolic Endoscopy

Rabih Ghazi¹  Eric J. Vargas¹  Donna Abboud¹  Farah Abdul Razak¹ Tala Mahmoud¹
Andrew C. Storm¹ Vinay Chandrasekhara¹ Barham K. Abu Dayyeh¹

¹Division of Gastroenterology and Hepatology, Mayo Clinic, Minnesota, United States

J Digest Endosc 2022;13:170–178.

Address for correspondence Barham K. Abu Dayyeh, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905, United States (e-mail: Abudayyeh.barham@mayo.edu).

Abstract

Keywords

- ▶ endoscopic bariatric and metabolic therapies (EBMT)
- ▶ endoscopic obesity
- ▶ endoscopic sleeve gastropasty (ESG)
- ▶ intragastric balloons (IGB)
- ▶ metabolic endoscopy
- ▶ primary obesity surgery endoluminal (POSE)

Obesity has been escalating as one of the worst public health epidemics. Conservative therapies including lifestyle modifications and weight loss medications have limited efficacy and long-term sustainability. Bariatric surgeries, although effective, remain underutilized due to their cost, safety concerns, and patient acceptance. In the past two decades, endoscopic bariatric and metabolic therapies (EBMTs) have emerged as safe, effective, and less invasive options for the treatment of obesity and its comorbidities, with recent studies reporting favorable outcomes in terms of weight loss and metabolic parameters. This article reviews the major and newly developed EBMTs, with emphasis on their metabolic effects and potential use in the management of metabolic conditions.

Introduction

Obesity is markedly rising as one of the worst global public health epidemics. According to the World Health Organization, its prevalence has nearly tripled since 1975, affecting more than 650 million individuals worldwide in 2016.¹ The increasing burden of obesity and its associated comorbidities, such as type 2 diabetes mellitus (T2DM), chronic renal disease, coronary artery disease, and nonalcoholic fatty liver disease (NAFLD), represent a major concern to the healthcare sector. In India, it is estimated that around 40% of the population suffers from obesity, 9.6% from T2DM, and 9 to 53% from NAFLD.^{2–4}

Conservative therapies including exercise, dietary modification, and weight loss medications remain a mainstay

component of weight loss and weight maintenance programs but have limited long-term sustainability. Bariatric surgery, despite its proven effectiveness at inducing weight loss and metabolic changes, remains underutilized, with only 1% of eligible patients undergoing surgical intervention for the treatment of obesity. The underutilization of bariatric surgery is multifactorial, such as cost, safety, and patient acceptance. Additionally, some of the patients who fail conservative management do not meet the eligibility criteria for bariatric surgery.

Endoscopic bariatric and metabolic therapies (EBMT) have emerged as safe and effective options for patients who are ineligible for bariatric surgery or for those who opt for a less invasive, anatomy preserving treatment approach. Various EBMT are currently used in clinical practice, while others

DOI <https://doi.org/10.1055/s-0042-1754335>.
ISSN 0976-5042.

© 2022. Society of Gastrointestinal Endoscopy of India. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

are still under investigation. In addition to resulting in favorable weight loss outcomes, EBMT also seem to improve several metabolic parameters including insulin sensitivity, lipid profile, liver enzymes, steatosis, fibrosis, and others, independent of weight loss. In this article, we review the most current literature assessing the efficacy and safety of different EBMT in the management of obesity and its associated comorbidities, with a special focus on their potential use in the management of metabolic conditions such as T2DM, NASH, and others.

Intragastric Balloons

Intragastric balloons (IGBs) are one of the most widely used space-occupying devices for the treatment of obesity. In addition to decreasing the gastric volume, IGBs seem to delay gastric emptying and alter the gut hormones, leading to early satiety and decreased food intake. ► **Table 1** describes the different types of IGBs.

Studies have shown favorable outcomes with IGBs in terms of weight loss and improvement in metabolic parameters and comorbid conditions. A multicenter, open-label, randomized clinical trial (RCT) evaluated the efficacy and safety of the Orbera Intragastric Balloon (Apollo Endosurgery, Austin, Texas, United States), one of the most commonly used IGB.⁵ The IGB plus lifestyle group was found to have a significantly higher percent total body weight loss (%TBWL) at 6 months (10.2 vs. 3.3%), 9 months (9.1 vs. 3.4%), and 12 months (7.6 vs. 3.1%) after implantation, compared with the lifestyle group. The rate of device- or procedure-related serious adverse events (SAE) was 10%, while 18.8% of patients had their device removed before 6 months due to an SAE or subject request. The most common SAE was device intolerance. In a 2020 meta-analysis, the %TBWL at 6, 12, and 18 to 24 months was 12.16, 10.35, and 6.89%, respectively.⁶ The overall adverse event (AE) rate was 3.97%, and included abdominal pain and nausea, and 5.92% of patients had an early removal of the IGB due to esophagitis, severe dehydration, and others.

The results of a multicenter randomized trial that assessed the efficacy and safety of the adjustable Spatz IGB (Spatz FGIA, Great Neck, New York, United States) were recently published.⁷ The study reported a significantly higher %TBWL at 32 weeks in the IGB group compared with the lifestyle intervention alone group (15.0 vs. 3.3%, respectively). Overall, 92% of patients in the IGB group achieved more than or equal to 5% TBWL. Device-related SAEs were observed in 4% of patients. These favorable results recently led the Food and Drug Administration (FDA) to approve the use of this device for patients with a body mass index (BMI) between 30 and 40 kg/m² who have previously failed to reach and maintain target weight loss despite a supervised weight loss program.

The effect of IGBs on metabolic parameters and comorbidities has also been assessed in multiple studies. A 2017 systematic review and meta-analysis⁸ found a significant decrease in fasting blood glucose (FBG) (mean difference [MD], -11.0%), hemoglobin A1c (HbA1c) (MD, -0.6%), triglycerides (MD, -22.0%), and systolic blood pressure (SBP) (MD, -9.1 mm Hg) from baseline in patients with an IGB.

Table 1 Intragastric balloons (IGBs)

IGB device	Manufacturer	FDA	Balloon characteristics	Filling material	Volume (mL)	Number of balloons	Adjustable	Duration of placement	Placement	Removal
Orbera	Apollo Endosurgery	Yes	Silicone	Saline	400–700	One	No	Up to 6 months	Endoscopy	Endoscopy
Obalon	Obalon Therapeutics	Yes	Gelatin	Air	250	Three	No	Up to 6 months	Swallowing capsule/ verification via fluoroscopy or pressure reading	Endoscopy
Spatz	Spatz FGIA	Yes	Silicone	Saline	400–800	One	Yes	Up to 12 months	Endoscopy	Endoscopy
Elipse	Allurion Technologies	No	Polymer film	Saline	450–550	One	No	Up to 4 months	Swallowing capsule/ verification via fluoroscopy or pressure reading	Natural excretion
Heliosphere Bag	Helioscope Medical Implants	No	Polyurethane and silicone	Air	550	One	No	Up to 6 months	Endoscopy	Endoscopy
End-Ball	Endalis	No	Polyurethane	Air/ Saline	600	One	No	Up to 6 months	Endoscopy	Endoscopy

Abbreviation: FDA, U.S. Food and Drug Administration.

Moreover, the study reported an increased probability of remission from T2DM (odds ratio [OR] = 1.4), hypertension (OR = 2.0), and dyslipidemia (OR = 1.7) after 6 months of IGB therapy.

Several studies evaluated the effect of IGBs on hepatic steatosis and fibrosis in patients with NAFLD or nonalcoholic steatohepatitis (NASH). One study prospectively assessed the impact of IGBs on the histologic and metabolic features of NASH in 21 consecutive patients with obesity, radiologically proven hepatic steatosis, and early hepatic fibrosis.⁹ At 6 months of follow-up, there was an improvement in the NAFLD activity score (NAS) in 90% of patients, with a median decrease of three points. Fifteen percent of patients improved their fibrosis by 1.17 stages, while the magnetic resonance enterography-detected fibrosis improved by 1.5 stages in 50% of patients. Moreover, 50% of patients reached the United States FDA's defined end points for NASH resolution and fibrosis improvement. Finally, the study reported a mean %TBWL of 11.7%, with significant reductions in waist circumference (MD, -14.4 cm) and HbA1c (MD, -1.3%). Another study¹⁰ found a significant decrease in alanine aminotransferase (ALT) (MD, -10.02 U/l), gamma-glutamyl transferase (MD, -9.82 U/l), FBG (MD, -7.0 mg/dL), triglycerides (MD, -30.8 mm/dL), and SBP (MD, -8.3 mm Hg), at 6 months following IGB insertion. The study additionally reported a significantly lower NAS in the IGB group (NAS = 2) compared with the sham procedure and diet group (NAS = 4) at 6 months, and an improvement in hepatic steatosis by magnetic resonance imaging and ultrasound. A more recent systematic review and meta-analysis in 2021 also assessed the safety of IGB in 452 patients with NAFLD.¹¹ The study found improved steatosis in 79.2% of patients, in NAS in 83.5% of patients, and in homeostatic model assessment of insulin resistance (HOMA-IR) in 64.5% of patients. Liver volume measured on computed tomographic (CT) scan was also significantly reduced in 93.9% of patients. ► **Table 2** summarizes the impact of EBMTs on metabolic parameters.

The IGB is an effective and relatively safe EBMT that improves several metabolic parameters, including insulin sensitivity, lipid profile, and liver fibrosis and steatosis but remains underutilized in obesity. The device seems to have favorable weight independent effects on metabolic parameters that warrant further use and investigation in various metabolic conditions such as T2DM and NASH.

Transpyloric Shuttle

The transpyloric shuttle (TPS, BAROnova Inc., Goleta, California, United States), is another endoscopically placed space-occupying device that is deployed at the level of the pylorus. It consists of two silicone bulbs that are connected by a flexible tether. The large spherical bulb resides in the pyloric antrum with the purpose of preventing the migration of the device, while the smaller cylindrical bulb resides freely in the duodenum, allowing the device to position across the pylorus. Few studies have evaluated the safety and efficacy of TPS (► **Fig. 1**).

An initial small Australian trial¹² reported promising results, with 25.1% excess weight loss (EWL) at 3 months and 41.0% EWL at 6 months following device insertion. However, 10% of patients had their device removed earlier than expected due to symptomatic gastric ulceration. A recent randomized sham-controlled trial reported a significantly higher %TBWL in the TPS group compared with control at 12 months (9.5 vs. 2.8%).¹³ Moreover, at 12 months follow-up, the TPS group showed significantly greater improvement in insulin levels (MD, -2.8 vs. 0.4 µIU/mL) and HOMA-IR (MD, -0.6 vs. 0.0), compared with control. An improvement in lipid profile and blood pressure measurements was also reported and was more prominent in patients with elevated baseline values, with the TPS group showing significantly greater improvement in low-density lipoprotein (LDL) (MD, -15.2 vs. 1.7 mg/dL), triglycerides (MD, -47.9 vs. -29.0 mg/dL), cholesterol (MD, -13.5 vs. -4.5 mg/dL), SBP (MD, -8.0 vs. -0.4 mm Hg), and diastolic blood pressure (MD, -5.3 vs. -0.9 mm Hg) compared with control.

Although the TPS was approved by the FDA in 2019, publications regarding its use and effectiveness in clinical practice are limited.

Primary Obesity Surgery Endoluminal

Primary obesity surgery endoluminal (POSE) is a transoral endoscopic suturing technique that utilizes the Incisionless Operative Platform (USGI Medical, San Clemente, California, United States). In this procedure, full-thickness plications are created at the level of the gastric fundus and distal body, resulting in a decrease in stomach size, gastric accommodation, and rate of gastric emptying.

The efficacy and safety of POSE have been assessed in several studies and trials. A recently published systematic review and meta-analysis¹⁴ reported a pooled mean %TBWL of 13.45 and 12.68% at 3 to 6 months and 12 to 15 months, respectively. The overall rate of SAE was 2.84%, with reported cases of gastrointestinal and extra-gastric bleeding, hepatic abscess, severe pain, nausea, and vomiting. The MILEPOST multicenter RCT¹⁵ found a significantly higher %TBWL in the POSE group compared with the conventional medical therapy group at 12 months (13.0 vs. 5.3%). Moreover, in the POSE group, patients showed significant reductions in caloric intake, gastric volume, and time to satiety, with the latter found to be significantly related to %TBWL. However, the ESSENTIAL randomized sham-controlled trial¹⁶ reported significant but less %TBWL than other trials, with a 12-month %TBWL of 4.95% in the POSE group compared with 1.38% in the control group. Additionally, a significantly higher percentage of patients achieved more than or equal to 5% TBWL in the POSE group compared with control (41.55 vs. 22.11%). Interestingly, patients in the POSE group showed significantly more improvement in T2DM defined as a decrease in diabetic medications, as well as fasting plasma glucose (MD, -2.18 vs. 1.23 mg/dL) and LDL (-6.81 vs. 0.87 mg/dL), compared with the control group despite the lower weight loss. Other comorbidities and metabolic parameters improved in the POSE group at 12 months compared with baseline, with a reported

Table 2 The effect of EMBTs on metabolic parameters

EBMT	Time of follow-up	HbA1c (%)	HOMA-IR	HDL (mg/dL)	LDL (mg/dL)	Triglyceride (mg/dL)	Total cholesterol (mg/dL)	SBP (mm Hg)	ALT (IU/L)	Hepatic steatosis	Hepatic fibrosis
IGB ⁸⁻¹¹	3 mo										
	6 mo	-0.6 ^a	Improved in 64.5% of patients with NAFLD			-30.8 ^a		-9.1 ^a -8.3 ^a	-10.02 ^a	Significant decrease in fat fraction (16.7 at baseline, 7.6 post-IGB)	-3 points in NAS. Improvement in 90% of patient
	12 mo										
TPS ¹³	3 mo	-	-	-	-	-	-	-	-	-	-
	6 mo	-	-	-	-	-	-	-	-	-	-
	12 mo	-	-0.6 ^a	-	-15.2 ^a	-47.9 ^a	-13.5 ^a	-8.0 ^a	-	-	-
POSE ¹⁶	3 mo	-	-	-	-	-	-	-	-	-	-
	6 mo	-0.09	+1.72	-	-5.51	-10.9	-5.95	-8.64	-	-	-
	12 mo	-0.07	+3.15	-	-6.81 ^a	-11.5	-7.07	-4.78	-	-	-
ESC ^{25,31,32}	3 mo	-	-	-	-	-	-	-	-	-	-
	6 mo	-	-	-	-	-	-	-	-10.04 ^a	-	-0.43 ^a NFS
	12 mo	-1.0 ^a	-1.7/year ^a	-	-	-39.48 ^a	-	-6.79 ^a	-11.6 ^a	-4 points/year in HSI ^a	-0.78 ^a NFS -0.3 points/year in NAS
DMR ^{38,39}	3 mo	-1.72 ^a	-	-	-	-	-	-	-10.48 ^a	-6.59 ^a HSI	-
	6 mo	-0.94 ^a	-	-	-	-	-	-	-16.84 ^a	-	-
	12 mo	-0.9 ^a	-2.9 ^a	-	-	-	-	-	-10	-	-
DJBL ^{40,41}	3 mo	-	-	-	-	-	-	-	-	-	-
	6 mo	-1.3 ^a	-4.6 ^a	-0.73	-11.6 ^a	-11.6	-27.1 ^a	-15.0	-	-	-
	12 mo	-	-	0.0	+3.9	+7.7	0.0	-17.0	-	-	-
PJD ⁴²	3 mo	-	-	-	-	-	-	-	-	-	-
	6 mo	-	-	-	-	-	-	-	-	-	-
	12 mo	-1.9 ^a	-	-	-	-	-	-	-	-	-

Abbreviations: ALT, alanine transaminase; AT, aspiration therapy; DJBL, duodenal jejunal bypass liner; DMR, duodenal mucosal resurfacing; EMBT, endoscopic metabolic and bariatric therapies; ESC, endoscopic sleeve gastroplasty; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HIS, hepatic steatosis index; HOMA-IR, homeostatic model assessment of insulin resistance; IGB, intragastric balloons; LDL, low-density lipoproteins; NAS, NAFLD activity score; NFS, NAFLD fibrosis score; PJD, partial jejunal diversion; POSE, primary obesity surgery endoluminal; SBP, systolic blood pressure; TPS, transpyloric shuttle.
^ap-Value <0.05.

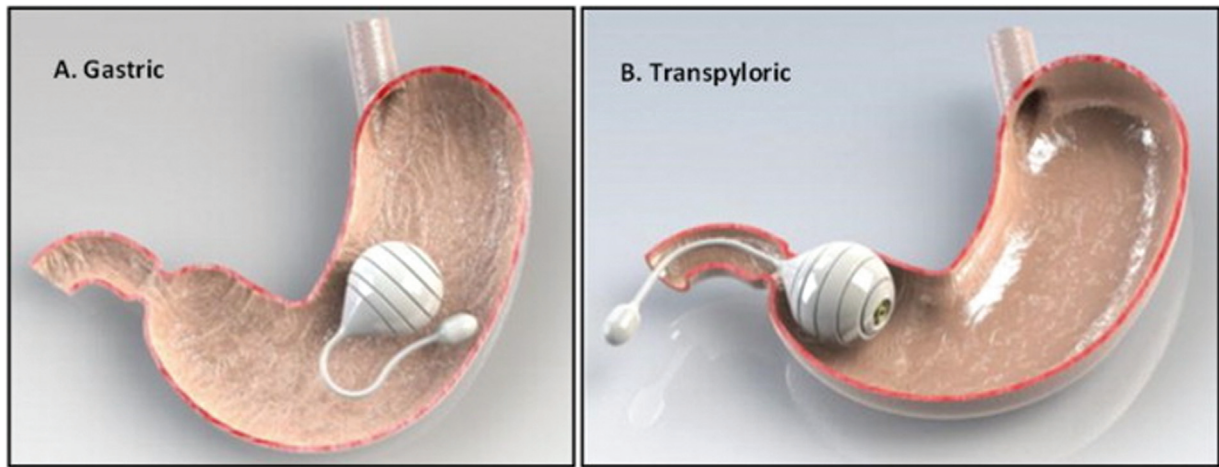


Fig. 1 Transpyloric shuttle in the (A) gastric and (B) transpyloric positions.¹²

decrease in SBP (MD, -4.78 mm Hg) and total cholesterol (MD, -7.07 mg/dL), and an improvement in dyslipidemia and hypertension in 35.71 and 19.39% of patients, respectively. However, these changes were not statistically significant when compared with control.

Another study investigated the gastrointestinal physiological changes and potential mechanisms of weight loss in 18 patients who underwent a POSE procedure.¹⁷ The authors reported significantly enhanced postprandial Peptide YY (PYY) stimulation and postprandial ghrelin inhibition, and significantly decreased fasting ghrelin levels. Moreover, there was a significant decrease in caloric intake capacity at 2- and 6 months, and a delay in gastric emptying at 2 months. However, the rate of gastric emptying normalized at 12 months. Finally, the best predictor model (R^2 : 66%, $p = 0.006$) for EWL at 15 months following the procedure included postprandial PYY increase, pre-POSE BMI, and post-POSE gastric emptying. Taken together this suggests that the technique has weight independent effects on metabolism that warrant further investigation.

The traditional POSE technique has been recently revised into what is now known as the POSE 2.0 procedure, with the premise to enhance the durability of the plication and improve weight loss outcomes.¹⁸ The POSE 2.0 utilizes the same Incisionless Operative Platform (USGI Medical, San Clemente, California, United States) to create multiple full-thickness interrupted plications at the level of the gastric body while sparing the fundus, resulting in a short and narrow stomach (**Fig. 2**). In their initial experience on 73 patients with obesity, the authors reported promising weight loss results with a %TBWL of 15.7% at 6 months. This was later confirmed in an international multicenter prospective trial¹⁹ that showed a %TBWL of 13.9, 17.3, and 17.5% at 3, 6, and 9 months, respectively. At 6 months follow-up, there was a significant improvement in fasting and postprandial satiety and satiation scores, and 85% of patients had significant changes in gastric emptying. Moreover, POSE 2 improved liver parameters and hepatic steatosis, with a significant decrease in ALT (MD, -14.3 mg/dL) and controlled attenuation parameter (MD, -79 dB/m) at 6 months com-

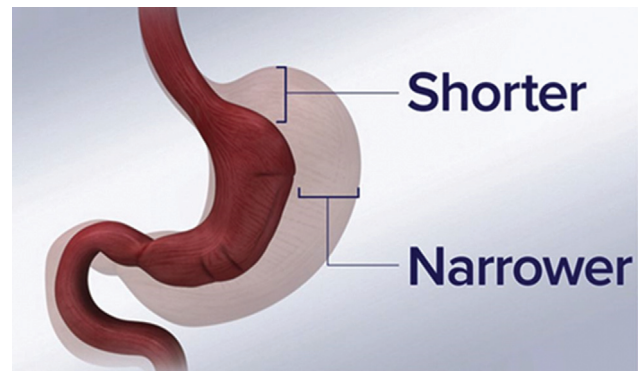


Fig. 2 Primary obesity surgery endoluminal 2.0 (Abu Dayyeh et al.)¹⁹

pared with baseline. A more recent study similarly reported a %TBWL of 17.8% 1 year after the procedure.²⁰ Four out of 46 patients experienced an adverse event, which included two gastric perforations treated intraprocedurally, and two asymptomatic hemoglobin drops treated conservatively. The favorable weight loss outcomes were also demonstrated in a recent prospective, international, multicenter study.²¹ The authors reported a %TBWL of 13.4% at 3 months, 16.7% at 6 months, 16.2% at 12 months, and 14.17% at 18 months, with 86 and 56% of patients achieving more than or equal to 10% and more than or equal to 15% TBWL at 12 months, respectively. There were no SAEs reported.

A prospective study comparing the changes in gastric physiology between POSE 1 and POSE 2 demonstrated a diverging impact of each procedure on gastric emptying.²² At 6 months of follow-up, POSE 2 had induced a significant acceleration in gastric emptying ($GE_{1/2}$) (MD, -19.34 minutes) and decrease in gastric retention (GE_{2h}) (MD, -12.52%) compared with baseline. These changes were not demonstrated with POSE 1. Moreover, the two groups had significant differences in ($GE_{1/2}$) and (GE_{2h}) at 6 months, and in change in (GE_{2h}) from baseline to 6 months.

Additional studies assessing the safety, efficacy, and changes in gastric hormones and motility are ongoing.

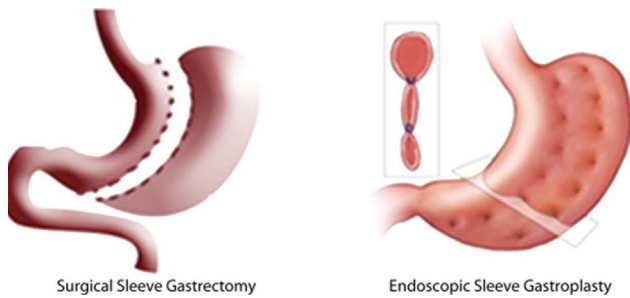


Fig. 3 Surgical sleeve gastrectomy compared with endoscopic sleeve gastroplasty.²¹

Endoscopic Sleeve Gastroplasty

The endoscopic sleeve gastroplasty (ESG) is a transoral endoscopic gastric reduction technique involving a full-thickness endoscopic suturing device (OverStitch, Apollo Endosurgery, Austin, Texas, United States). During ESG, a restrictive sleeve is created by placing full-thickness sutures along the greater curvature of the stomach, extending from the prepylorus to the proximal stomach, sparing the fundus (► Fig. 3).²³

Several studies have assessed the efficacy and safety of ESG, reporting a %TBWL ranging from 13.7 to 16.4% at 6 months, 15.0 to 17.6% at 12 months, and 17.2 to 19.5% at 24 months, with a SAE rate of 1.1 to 2.7%.^{24–27} A meta-analysis that included 1,772 patients reported a pooled % TBWL of 15.1, 16.5, and 17.2% at 6, 12, and 18 to 24 months, respectively, after ESG.²⁴ The pooled rate of SAE was 2.2%, and included nausea and pain requiring hospital admission, upper gastrointestinal bleed, and perigastric leak or fluid collection that were all managed conservatively without further sequelae. One study assessed the long-term weight loss outcomes following ESG.²⁸ The authors found a %TBWL of 15.9% at 5 years follow-up, with 90% of patients maintaining 5% TBWL and 60% maintaining 10% TBWL.

When compared with laparoscopic sleeve gastrectomy (LSG), ESG has been shown to result in lower %TBWL at 6 months follow-up (7.6 vs. 17.1%), but lower risks of AEs (5.2 vs. 16.9%) and new-onset gastroesophageal reflux disease (1.9 vs. 14.5%).²⁹ Interestingly, LSG weight loss superiority was clearly significant in patients with BMI more than 40, but borderline significant in patients with BMI less than 40 ($p = 0.05$).

Interestingly, one study assessed ESG outcomes in the pediatric population and demonstrated high efficacy with a %TBWL of 14.4% at 6 months, 16.2% at 12 months, and 13.7% at 24 months.³⁰ No SAE were reported.

ESG's impact on obesity-related comorbidities and metabolic parameters has also been observed in recently published studies. One study²⁵ reported a significant reduction in HbA1c (MD, -1.0%), serum triglycerides (MD, -39.48 mg/dL), SBP (MD, -6.79 mm Hg), and ALT (MD, -11.6 mg/dL), at 12 months after ESG compared with baseline. Another observational study published in 2021³¹ reported a significant improvement in HOMA-IR (from 6.7 to 3.0) score 1-week after ESG, with continued improvement in the subsequent 2 years. Additionally, there was a significant decrease in hepatic steatosis index

(4-points decrease per year) and NAFLD fibrosis score (0.3-point decrease per year). At the end of the study, 20% of patients had improvement in their risk of hepatic fibrosis from F3-F4 or intermediate to F0-F1. Another prospective study assessed the impact of ESG on liver parameters, steatosis, and fibrosis in NAFLD patients and reported significant improvement in ALT, hepatic steatosis index, NAFLD fibrosis score, Fibrosis-4 (FIB-4), and AST to platelet ratio index (APRI) scores at both 6 and 12 months.³² Additionally, the %TBWL was 18% at 12 months with no observed AEs.

Few studies have compared ESG to lifestyle interventions or other endoscopic procedures. One study compared ESG to high intensity diet and lifestyle intervention and found a significantly higher %TBWL with ESG compared with control (14.0 vs. 11.3% at 6 months, and 20.6 vs. 14.3% at 12 months).³³ Another study compared the weight loss outcomes between ESG and IGB and reported significantly higher %TBWL in the ESG group compared with the IGB group at 6 and 12 months (19.5 vs. 15.0% and 21.3 vs. 13.9%, respectively).³⁴ Most studies in the literature report favorable outcomes with ESG. However, additional studies are required to compare ESG with conservative therapy or other EBMT. The results of an ongoing RCT (NCT03406975) are expected to be published soon.

The alterations in gastric physiology following ESG were assessed in four patients.³⁵ Three months after the procedure, there was a significant delay in solid gastric emptying compared with baseline, with a 90-minute increase in time for 50% emptying (T50) of solid. Moreover, there was a significant increase in satiety following ESG, with 59% decrease in caloric intake required to achieve maximum fullness on a meal tolerance test, resulting in earlier termination of a meal compared with baseline (11.5 vs. 35.2 minutes). Finally, the study reported a decrease in active fasting and postprandial ghrelin by 29.4% ($p = 0.1$), and no significant changes in PYY, glucagon-like peptide 1 (GLP-1), and leptin following ESG. It is postulated that the changes in metabolic parameters after the ESG have weight independent factors, similar to the IGB. Further studies investigating the changes in gastric hormones and motility after this procedure are ongoing.

The Endomina System (Endo Tools Therapeutics SA, Gosselies, Belgium) is another novel device used to perform gastric remodeling for weight loss. An initial prospective study on 51 patients reported a %TBWL of 7.4% and a %EWL of 29.0% at 1 year following the Endomina procedure, with no observed SAEs.³⁶ A recently published RCT³⁷ compared the weight loss outcome between Endomina procedure plus lifestyle modification with lifestyle modification alone. At 6 months, the Endomina procedure group had a significantly higher %TBWL (11.0 vs. 2.7%) compared with the control group. Patients in the Endomina procedure group were able to maintain their weight loss a year after the procedure, with a reported %TBWL of 11.9%. No procedure- or device-related SAE were observed.

ESG is currently one of the most commonly performed EBMT for the treatment of obesity due to its efficacy and favorable safety profile. ESG has also been shown to improve several metabolic parameters such as insulin sensitivity,

lipid profile, and liver enzymes, and could potentially play a role in the treatment of NAFLD.

Duodenal Mucosal Resurfacing

Duodenal mucosal resurfacing (DMR) is a novel EBMT that utilizes the Revita Device (Fractyl, Lexington, Massachusetts, United States). This technique involves the circumferential hydrothermal ablation of the postpapillary duodenal mucosa, with subsequent mucosal healing and possible “resetting” of the gut-brain entero-neuro-hormonal axis; however, the exact mechanism of action is not fully understood.

A 1-year international multicenter study assessed the role of DMR in the treatment of T2DM and reported a significant improvement in metabolic parameters at 24 weeks of follow-up compared with baseline.³⁸ The study showed a significant reduction in HbA1c (MD, -0.9%) and FBG (MD, -1.7 mmol/L), an improvement in HOMA-IR (MD, -2.9), and a decrease in ALT (MD, -9 U/L), and these observed effects were sustained at 12-months of follow-up. The study additionally reported a modest weight loss (MD, -2.5 kg at 24 weeks), with no correlation between HbA1c changes and weight reduction.

The improvement in metabolic parameters was also observed in a recent meta-analysis.³⁹ The study reported a significant improvement in HbA1c at 3 (MD, -1.72%) and 6 months (MD, -0.94%), in FBG at 6 months (MD, -15.84 mg/dL), in ALT at 3 (MD, -10.48 IU/L) and 6 months (MD, -16.84 IU/L), and in hepatic steatosis at 3 months (MD, -6.59), compared with baseline. While the study reported modest but significant reduction in weight at 3 months (MD, -3.10 kg), there was no significant weight loss at 6 months (MD, -1.84 kg).

While initial reports suggest modest effect on weight loss, DMR was shown to have beneficial metabolic effects. Additional studies are needed to assess the efficacy of DMR as an adjunct metabolic technique to other endoscopic weight loss therapies.

Duodenal Jejunal Bypass Liner

EndoBarrier duodenal jejunal bypass liner (DJBL) (GI Dynamics, Lexington, Massachusetts, United States) is an endoscopically deployed, nutrient-impermeable fluoropolymer sleeve that is proximally anchored in the duodenal bulb, spanning 60 cm through the duodenum and jejunum. This creates a barrier between the ingested food and the absorptive mucosa of the small intestine, preventing nutrient absorption.

An initial 2014 multicenter RCT assessed the safety and efficacy of DJBL placed for 6 months.⁴⁰ The study reports a significantly higher %TBWL in the DJBL group compared with the diet group at 6 (10.0 vs. 4.7%, respectively) and at 12 months (5.8 vs. 3.5%, respectively) after the device placement. The DJBL group additionally showed a significantly greater decrease in HbA1c at 6 months (MD, -1.3 vs. -0.4), and 85.3% of patients in the DJBL achieved a decrease in postprandial glucose excursion compared with 48.7% in the diet group ($p < 0.05$). However, 23.5% of patients in the

DJBL group had an AE that required hospitalization, five of which were related to the device.

A 2018 meta-analysis assessed the effect of DJBL on glycemic control in patients with T2DM and obesity.⁴¹ At the time of device removal, the %TBWL was 18.9%, and there was a significant decrease in HbA1c levels (MD, -1.3%) and HOMA-IR (MD, -4.6) from baseline. DJBL was also shown to impact the gut hormones, with a significant increase in postprandial GLP-1, PYY, and ghrelin, and decrease in gastric inhibitory polypeptide following device insertion. However, the study showed a SAE rate of 15.7% and included gastrointestinal bleeding and hepatic abscess.

Although studies showed favorable outcomes with DJBL in terms of weight loss and metabolic improvement, the safety profile of this device remains a concern. A prospective study utilizing a revised protocol of use is ongoing.

Partial Jejunal Diversion

Partial jejunal diversion is another EBMT that utilizes the Incisionless Magnetic Anastomosis System (IMAS; GI Windows, Boston, Massachusetts, United States). This system consists of two self-assembling magnets placed in the jejunum and ileum via anterograde enteroscopy and colonoscopy, respectively. The magnets are then coupled under endoscopic and fluoroscopic guidance, resulting in a side-to-side anastomosis 1 week after their placement. As a result, a portion of the digested food bypasses the jejunum and is delivered directly to the ileum.

An initial single-arm pilot study assessed the efficacy and safety of PJD in 10 patients.⁴² The study reported a %TBWL of 14.6% at 12 months, with a significant reduction in HbA1c in diabetic (MD, 1.9%) and prediabetic subjects (MD, 1.0%) compared with baseline. One procedure-related SAE occurred during the insertion of the trochar and subsequent penetration of the gastric serosa. All patients experienced diarrhea following the procedure, while 40% had recurrent diarrhea that resolved with conservative treatment. The current device is anticipated to require laparoscopic guidance for deployment, thus not a purely endoscopic/natural orifice procedure.

Comparison of Different EBMTs

A 2019 meta-analysis⁴³ compared the weight loss outcomes between ESG ($n = 369$) and POSE ($n = 447$) and reported a significantly higher %EWL with ESG compared with POSE at 6 and 12 months (MD, 6.17 and 7.84%, respectively). To note, this study did not include the POSE 2.0 procedure in the analysis. Similarly, a meta-analysis compared the weight loss outcomes between ESG ($n = 1979$) and IGBs ($n = 3025$).⁶ The study reported a significantly higher %TBWL with ESG compared with IGB at 12 months (MD, 7.33%). Additionally, while the weight loss with ESG was durable, this was not observed with IGB, with a significant decrease in %TBWL and %EWL reported at 18 and 24 months compared with 6 months after IGB removal.

Conclusion

EBMTs have revolutionized the treatment of morbid obesity by bridging the gap between conservative and surgical management. Several techniques have been recently developed or revised with the goal of improving weight loss and metabolic outcomes. This review summarizes the latest evidence on the efficacy and safety of the different EBMT techniques that are currently utilized in clinical practice or under investigation.

Incisionless gastric remodeling techniques have shown the most substantial development in recent years. They have been proven to be safe and effective in inducing weight loss and improving the metabolic parameters of T2DM, NAFLD, and dyslipidemia. ESG, POSE 2.0, and IGB could potentially play a role in the management of NASH, as studies have shown significant improvement in hepatic steatosis and fibrosis following these procedures. Similarly, DMR appears to have a great impact on metabolic parameters such as HbA1c, liver enzymes, and hepatic steatosis. Finally, PJD, DJBL, and TPS have also shown promising results; however, additional comparative studies are required to assess the safety and efficacy of the different EBMTs and determine superiority. Patient preference, endoscopist expertise, procedure and device training, and device availability should also be considered when choosing the optimal EBMT.

EBMTs, when used in sequence or combination, could enhance weight loss outcomes and improve the metabolic profiles of patients. For instance, one study assessed the efficacy of combined IGB and DJBL in an animal study.⁴⁴ The study reported a significantly lower rate of weight gain in the combination group (MD, 0.63 kg) compared with IGB alone and DJBL alone (MD, 1.00 and 0.75 kg, respectively). Other combination therapies could be potentially further studied, namely the conjunction of DMR with either ESG or POSE with the aim of enhancing the metabolic outcomes in patients with high-risk conditions such as T2DM or NASH.

EBMT will certainly play a pivotal role in the management of morbid obesity. Coupled with lifestyle modifications, pharmacotherapy, and psychosocial support, EBMTs may provide promising weight loss and metabolic outcomes comparable to those seen with the more invasive surgical approaches. Identifying patient level and technique specific markers of improved efficacy will further propel the field of metabolic endoscopy.

Authors' Contributions

BKA, RG, and EV were involved in manuscript concept and design.

RG, EV, DA, FA, and TM drafted the manuscript.

BKA, VC, ACS, RG, EV, DA, FA, and TM critically revised the manuscript.

Conflict of Interest

RG, EV, DA, FA, TM: No relevant conflicts of interest to disclose.

BKA: Consulting for Endogenex, Endo-TAGSS, Metamodix, and BFKW; consultant and grant/research support from USGI, Cairn Diagnostics, Aspire Bariatrics, Boston Scientific; 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.

VC: Consulting for Covidien LP and Boston Scientific; Shareholder in Nevakar Corporation.

ACS: Consulting for Apollo Endosurgery, GI Dynamics, Olympus, ERBE, and Intuitive, and the recipient of research support from Apollo Endosurgery, Endo-TAGSS, Enterasense, Endogenex, and Boston Scientific.

References

- World Health Organization. Obesity and overweight. 9 June 2021; Accessed June 30, 2022 from: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
- Venkatrao M, Nagarathna R, Majumdar V, Patil SS, Rathi S, Nagendra H. Prevalence of obesity in India and its neurological implications: a multifactor analysis of a nationwide cross-sectional study. *Ann Neurosci* 2020;27(3-4):153-161
- De A, Duseja A. Nonalcoholic fatty liver disease: Indian perspective. *Clin Liver Dis (Hoboken)* 2021;18(03):158-163
- International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Accessed June 30, 2022 at: <https://www.diabetesatlas.org/>
- Courcoulas A, Abu Dayyeh BK, Eaton L, et al. Intra-gastric balloon as an adjunct to lifestyle intervention: a randomized controlled trial. *Int J Obes* 2017;41(03):427-433
- Singh S, de Moura DTH, Khan A, et al. Intra-gastric balloon versus endoscopic sleeve gastroplasty for the treatment of obesity: a systematic review and meta-analysis. *Obes Surg* 2020;30(08):3010-3029
- Abu Dayyeh BK, Maselli DB, Rapaka B, et al. Adjustable intra-gastric balloon for treatment of obesity: a multicentre, open-label, randomised clinical trial. *Lancet* 2021;398(10315):1965-1973
- Popov VB, Ou A, Schulman AR, Thompson CC. The impact of intra-gastric balloons on obesity-related co-morbidities: a systematic review and meta-analysis. *Am J Gastroenterol* 2017;112(03):429-439
- Bazerbachi F, Vargas EJ, Rizk M, et al. Intra-gastric balloon placement induces significant metabolic and histologic improvement in patients with nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol* 2021;19(01):146-154.e4
- Popov VB, Thompson CC, Kumar N, Ciarleglio MM, Deng Y, Laine L. Effect of intra-gastric balloons on liver enzymes: a systematic review and meta-analysis. *Dig Dis Sci* 2016;61(09):2477-2487
- Chandan S, Mohan BP, Khan SR, et al. Efficacy and Safety of Intra-gastric Balloon (IGB) in Non-alcoholic Fatty Liver Disease (NAFLD): a comprehensive review and meta-analysis. *Obes Surg* 2021;31(03):1271-1279
- Marinos G, Eliades C, Raman Muthusamy V, Greenway F. Weight loss and improved quality of life with a nonsurgical endoscopic treatment for obesity: clinical results from a 3- and 6-month study. *Surg Obes Relat Dis* 2014;10(05):929-934
- Rothstein RI, Woodman G, Swain J, Cruz N, Kushnir V, Pryor A. Transpyloric shuttle treatment improves cardiometabolic risk factors and quality of life in patients with obesity: results from a randomized, double-blind, Sham-Controlled Trial. *Gastroenterology* 2019;156(06):237
- Singh S, Bazarbashi AN, Khan A, et al. Primary obesity surgery endoluminal (POSE) for the treatment of obesity: a systematic review and meta-analysis. *Surg Endosc* 2021;36(01):252-266

- 15 Miller K, Turró R, Greve JW, Bakker CM, Buchwald JN, Espinós JC. Medical Therapy. MILEPOST multicenter randomized controlled trial: 12-month weight loss and satiety outcomes after poseSM vs. *Obes Surg* 2017;27(02):310–322
- 16 Sullivan S, Swain JM, Woodman G, et al. Randomized sham-controlled trial evaluating efficacy and safety of endoscopic gastric plication for primary obesity: the ESSENTIAL trial. *Obesity (Silver Spring)* 2017;25(02):294–301
- 17 Espinós JC, Turró R, Moragas G, et al. Gastrointestinal physiological changes and their relationship to weight loss following the POSE procedure. *Obes Surg* 2016;26(05):1081–1089
- 18 Lopez-Nava G, Asokkumar R, Turró Arau R, Neto MG, Dayyeh BA. Modified primary obesity surgery endoluminal (POSE-2) procedure for the treatment of obesity. *VideoGIE* 2020;5(03):91–93
- 19 Lopez-Nava G, Turro R, Maselli DB, et al. 720 Primary obesity surgery endoluminal 2 (POSE2): an international multicenter prospective trial. *Gastrointest Endosc* 2020;91(06):AB60
- 20 Lopez Nava G, Asokkumar R, Laster J, et al. Primary obesity surgery endoluminal (POSE-2) procedure for treatment of obesity in clinical practice. *Endoscopy* 2020
- 21 Abu Dayyeh BK, Turro R, Maselli DB, et al. Primary obesity surgery endoluminal 2 (POSE 2.0): an international multicenter prospective trial with plication durability assessment. In *Gastrointestinal Endoscopy*. New York, NY: Mosby-Elsevier; 2021
- 22 Maselli DB, Matar R, Vargas EJ, et al. Sa1992 primary obesity surgery endoluminal 1 and 2 have distinct impacts on gastric physiology in a prospective cohort study. *Gastroenterology* 2020; 158(06):S-492
- 23 Abu Dayyeh BK, Rajan E, Gostout CJ. Endoscopic sleeve gastroplasty: a potential endoscopic alternative to surgical sleeve gastrectomy for treatment of obesity. *Gastrointest Endosc* 2013;78(03):530–535
- 24 Hedjoudje A, Abu Dayyeh BK, Cheskin LJ, et al. Efficacy and safety of endoscopic sleeve gastroplasty: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020;18(05):1043–1053.e4
- 25 Sharaiha RZ, Kumta NA, Saumoy M, et al. Endoscopic sleeve gastroplasty significantly reduces body mass index and metabolic complications in obese patients. *Clin Gastroenterol Hepatol* 2017; 15(04):504–510
- 26 Sartoretto A, Sui Z, Hill C, et al. Endoscopic sleeve gastroplasty (ESG) is a reproducible and effective endoscopic bariatric therapy suitable for widespread clinical adoption: a large, international multicenter study. *Obes Surg* 2018;28(07):1812–1821
- 27 Lopez-Nava G, Galvão MP, Bautista-Castaño I, Fernandez-Corbelle JP, Trelle M, Lopez N. Endoscopic sleeve gastroplasty for obesity treatment: two years of experience. *Arq Bras Cir Dig* 2017;30(01): 18–20
- 28 Sharaiha RZ, Hajifathalian K, Kumar R, et al. Five-year outcomes of endoscopic sleeve gastroplasty for the treatment of obesity. *Clin Gastroenterol Hepatol* 2021;19(05):1051–1057.e2
- 29 Fayad L, Adam A, Schweitzer M, et al. Endoscopic sleeve gastroplasty versus laparoscopic sleeve gastrectomy: a case-matched study. *Gastrointest Endosc* 2019;89(04):782–788
- 30 Alqahtani A, Elahmedi M, Alqahtani YA, Al-Darwish A. Endoscopic sleeve gastroplasty in 109 consecutive children and adolescents with obesity: two-year outcomes of a new modality. *Am J Gastroenterol* 2019;114(12):1857–1862
- 31 Hajifathalian K, Mehta A, Ang B, et al. Improvement in insulin resistance and estimated hepatic steatosis and fibrosis after endoscopic sleeve gastroplasty. *Gastrointest Endosc* 2021;93 (05):1110–1118
- 32 Jagtap N, Kalapala R, Katakwar A, et al. Endoscopic sleeve gastroplasty - minimally invasive treatment for non-alcoholic fatty liver disease and obesity. *Indian J Gastroenterol* 2021;40(06):572–579
- 33 Cheskin LJ, Hill C, Adam A, et al. Endoscopic sleeve gastroplasty versus high-intensity diet and lifestyle therapy: a case-matched study. *Gastrointest Endosc* 2020;91(02):342–349.e1
- 34 Fayad L, Cheskin LJ, Adam A, et al. Endoscopic sleeve gastroplasty versus intragastric balloon insertion: efficacy, durability, and safety. *Endoscopy* 2019;51(06):532–539
- 35 Abu Dayyeh BK, Acosta A, Camilleri M, et al. Endoscopic sleeve gastroplasty alters gastric physiology and induces loss of body weight in obese individuals. *Clin Gastroenterol Hepatol* 2017;15 (01):37–43.e1
- 36 Huberty V, Machytka E, Boškoski I, Barea M, Costamagna G, Deviere J. Endoscopic gastric reduction with an endoluminal suturing device: a multicenter prospective trial with 1-year follow-up. *Endoscopy* 2018;50(12):1156–1162
- 37 Huberty V, Boskoski I, Bove V, et al. Endoscopic sutured gastroplasty in addition to lifestyle modification: short-term efficacy in a controlled randomised trial. *Gut* 2020:gutjnl-2020-322026
- 38 van Baar ACG, Holleman F, Crenier L, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study. *Gut* 2020;69(02):295–303
- 39 de Oliveira GHP, de Moura DTH, Funari MP, et al. Metabolic effects of endoscopic duodenal mucosal resurfacing: a systematic review and meta-analysis. *Obes Surg* 2021;31(03):1304–1312
- 40 Koehestanie P, de Jonge C, Berends FJ, Janssen IM, Bouvy ND, Greve JW. The effect of the endoscopic duodenal-jejunal bypass liner on obesity and type 2 diabetes mellitus, a multicenter randomized controlled trial. *Ann Surg* 2014;260(06):984–992
- 41 Jirapinyo P, Haas AV, Thompson CC. Effect of the duodenal-jejunal bypass liner on glycemic control in patients with type 2 diabetes with obesity: a meta-analysis with secondary analysis on weight loss and hormonal changes. *Diabetes Care* 2018;41(05): 1106–1115
- 42 Machytka E, Bužga M, Zonca P, et al. Partial jejunal diversion using an incisionless magnetic anastomosis system: 1-year interim results in patients with obesity and diabetes. *Gastrointest Endosc* 2017;86(05):904–912
- 43 Khan Z, Khan MA, Hajifathalian K, et al. Efficacy of endoscopic interventions for the management of obesity: a meta-analysis to compare endoscopic sleeve gastroplasty, aspire assist, and primary obesity surgery endoluminal. *Obes Surg* 2019;29(07): 2287–2298
- 44 Ghaz H, Jaruvongvanich V, Matar R, et al. A preclinical animal study of combined intragastric balloon and duodenal-jejunal bypass liner for obesity and metabolic disease. *Clin Transl Gastroenterol* 2020;11(09):e00234