Endoscopic Treatment of Obesity: From Past to Future

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Abstract
Background: Conventional approaches in the management of obesity offer only a limited potential for sustained weight loss. Moreover, bariatric surgery, although momentarily being the most effective weight-loss treatment, has some serious pitfalls, such as significant morbidity rate, high substantial costs and limited patient applicability. Hence, there is a substantial need for endoscopic approaches to obesity. ***Summary:*** The aim of this article is to provide a historical overview of bariatric endoscopy in the management of obesity; moreover to selectively review and evaluate the currently available endoscopic weight-loss techniques and devices, and third to identify new directions and future prospects in this rapidly advancing field. ***Key Messages:*** Bariatric endoscopy procedures efficiently replicate some of the anatomical features and the physiological effects of the traditional weight-loss surgical approaches, while at the same time being more applicable, entirely reversible, less-invasive, safer and more cost effective. Endoscopic modalities in the treatment of obesity can be categorized into the following: restrictive procedures, malabsorptive procedures, gastric function/emptying regulation, gastric aspiration, and so on. To conclude, it is of high importance to constantly evaluate the long-term efficacy and safety of new endoscopic weight-loss techniques and devices, based on evidence-based medicine principles.

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Introduction

Obesity, defined as a body mass index (BMI) ≥30 kg/m^2 accompanied by detrimental excessive fat accumulation, is a global public health issue interconnected with a multitude of adverse health outcomes, significantly impaired quality of life, and reduced life expectancy. Worldwide obesity has nearly tripled since 1975 and consequently represents a large economic burden on the healthcare system. In 2016, an estimated 650 million adults (13% of the world's adult population) were obese, and also the prevalence rate has a tendency of constant growth [1]. This can be observed from projections of Kelly et al. [2], who estimated that 19.7% of the world's population (1.12 billion individuals) will be obese by the year of 2030 if the secular trends continue unabated.

Unfortunately, although reduced calorie diet and increased physical activity are the cornerstones of obesity

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management, it still represents an enormous challenge for most of the patients to permanently change their lifestyle habits [3]. Over and above that, the efficacy of currently available anti-obesity pharmacological agents falls far short (estimate weight loss of 3–7% compared with placebo) of the actual medical needs [4, 5]. On the other hand, bariatric surgery is momentarily the most effective weight-loss method; however, there are some important pitfalls that need to be mentioned here. It is associated with significant morbidity rates (from 3 to 20%) and substantial costs, and also it is not available to patients with BMI <35 kg/m^2 even if clinically significant comorbidities exist [6–8]. Finally, bariatric endoscopy procedures performed entirely through gastrointestinal tract by using flexible endoscopy efficiently replicate some of the anatomical features and the physiological effects of the traditional weight-loss surgery, while at the same time being less invasive, more cost effective and reversible [9–11]. Thompson has categorized bariatric endoscopy procedures based on different points of intervention. Latter categories may include early intervention procedures (providing weight loss in early-stage obese patients who do not yet qualify for traditional surgery), bridge to surgery procedures (reducing the obesity-related operative risk), metabolic procedures (primarily effect on comorbid illness such as diabetes, with only a modest effect on weight), primary obesity procedures (endoscopic option for the traditional surgical population with outcomes similar to those of current surgeries but with substantially reduced periprocedural risk), and last but not least, revision procedures (address-failed bariatric surgical procedures) [10]. Moreover, it is also of high importance to highlight the endoscopic weight loss modalities used in clinical practice. Restrictive procedures act by decreasing the gastric volume by space-occupying devices and/or by suturing or stapling techniques, whereas malabsorptive procedures tend to create malabsorption by preventing the food contact with the duodenum and proximal jejunum. Another, less frequent but possible modalities are gastric function regulation (intragastric injections of botulinum toxin A [Botox], gastric electrical stimulation [GES], vagal nerve blocking) and gastric aspiration (Table 1) [11, 12].

The objective of this article is to provide a historical overview of bariatric endoscopy in the management of obesity, to selectively review and evaluate the currently available endoscopic weight loss techniques and devices, and to identify new directions and future prospects in this rapidly advancing field.

Table 1. Bariatric endoscopy procedures and associated weight loss modified from [12]

	Weight loss[1]
Restrictive endoscopic weight loss procedures	
Fluid-filled intragastric balloons	
Orbera/BIB	34–42% EWL at 6 months
Silimed gastric balloon	8 kg after 6 months
MedSil intragastric balloon	19% EWL at 6 months
Spatz adjustable balloon system	46% EWL at 12 months
ReShape dual intragastric balloon system	25% EWL at 6 months
Air/gas-filled intragastric balloons	
Heliosphere BAG balloon	18% EWL at 6 months
Obalon gastric balloon	5 kg after 12 weeks
Ullorex oral intragastric balloon	1.5 kg over 2 weeks
Other space-occupying devices	
SAB	6.5 kg after 4 months
TPS	25% EWL at 3 months
	41% EWL at 6 months
SatiSphere	18.4 kg after 3 months
Gelesis100	29% EWL after 24 weeks
Suturing/stapling procedures	
EndoCinch suturing system	40% EWL at 3 months
	58% EWL at 12 months
Restore suturing system	28% EWL at 12 months
Overstitch endoscopic suturing system	30% EWL at 6 months
	55% EWL at 12 months
TOGA	25–46% EWL at 6 months
	39% EWL at 12 months
TERIS	30% EWL at 6 months
POSE	45% EWL at 12 months
Endomina suturing system	29% EWL at 12 months
Malabsorptive endoscopic weight loss procedures	
DJBS	12–24% EWL at 3 months
	32% EWL at 6 months
Gastroduodenal-DJBS	40% EWL at 3 months
	54% EWL at 12 months
Other endoscopic weight loss procedures	
DMR	2.5 kg after 24 weeks
Incisionless magnetic anastomosis system	40% EWL at 12 months
Intragastric injections of botulinum toxin A	11 kg after 2 months
V-BLOC	17% EWL at 12 months
GES	5 kg after 6 months
Gastric aspiration therapy/aspireAssist	41% EWL at 6 months
	50% EWL at 12 months

[1] Values extrapolated from representative reviews and clinical trials of each intervention.

%EWL, percentage of excess weight loss; BIB, BioEnterics intragastric balloon; SAB, semi-stationary antral balloon; TPS, TransPyloric shuttle; TOGA, transoral gastroplasty; TERIS, trans-oral endoscopic restrictive implant system; POSE, primary obesity surgery endoluminal; DJBS, duodenal-jejunal bypass sleeve; Gastroduodenal-DJBS, gastroduodenal-jejunal bypass sleeve; DMR, duodenal mucosal resurfacing; V-BLOC, vagal blockade; GES, gastric electrical stimulation.

Past

The initial idea of using endoscopically placed intragastric balloons for the treatment of obesity originated from the DeBakey's comprehensive review on large intragastric masses of foreign material, also known as bezoars. Since DeBakey demonstrated that bezoars are often well tolerated for a significant period of time with very few symptoms except weight loss, Nieben and Harboe [14] (preliminary communication, 1982) came up with the idea to use free-floating intragastric balloons as artificial bezoars in the treatment of obesity [13]. However, due to the low resistance to damage from gastric acid, they only remained inflated for 7–21 days [14].

Two years later (in 1984), Percival published an article on the "balloon diet" for morbid obesity in which he presented his experience of using inflated mammary implants as gastric balloons. Latter were resistant to gastric content (usually last for about 10 weeks); however, due to semipermeability they had to be refilled on a regular basis [15].

In 1985, Garren-Edwards gastric bubble (GEGB; American Edwards Laboratories, Santa Ana, CA, USA) was approved by the Food and Drug Administration as a gastric balloon for the treatment of obesity in addition to diet, exercise and behavioral therapy. The GEGB was a polyurethane, cylindrical air-filled balloon (capacity 200–220 mL) with a hollow central channel and a self-sealing valve, designed as a temporary device that required endoscopic removal at 4 months. Until 1988, GEGB was used extensively across the world and >25,000 devices were inserted [16]. However, several studies have demonstrated that GEGB is not superior to standard obesity therapy, and what is more, is relatively frequently associated with severe complications, such as gastric mucosal erosions (26%), gastric ulcer (14%) and intestinal obstruction (2%) [17–21]. Consequently, the manufacture and sale of GEGB were discontinued in 1988 by American Edwards Laboratories. Furthermore, Garren L withdrew his product from the market in 1992 [16].

It should also be mentioned that 2 more intragastric balloons were developed and used in Europe during the 1980s – Taylor balloon and Ballobes bubble. Taylor balloon (Dunlop Limited, Leicestershire, England) was a silicone, pear-shaped saline-filled (capacity 500–600 mL) device, whereas Ballobes bubble (DOT ApS Company, Denmark) was a silicone oval-shaped balloon filled with 500 mL of air and 10 mL of diatrizoate. Both intragastric balloons had less serious and less frequent gastric side effects and deflations in comparison to GEGB; however, results regarding weight loss were unsatisfactory [16].

Current State of the Art

Restrictive Endoscopic Procedures
Fluid-Filled Intragastric Balloons

BioEnterics Intragastric Balloon (BIB; Allergan Inc., Irvine, CA, USA) became commercially available in 1991. Since then it is the most extensively studied and the most commonly used (primary weight loss or bridge to surgery) endoscopic procedure due to its efficacy and safety. BIB is an elastic silicone balloon that is inserted under endoscopic control into the stomach under light sedation, and subsequently filled with 400–700 mL of saline stained with methylene blue (used for follow-up in case of balloon perforation) via a catheter through a self-sealing valve, and left in place for up to 6 months. At the end of the treatment, the balloon is pierced and saline is emptied via a catheter and then endoscopically removed by special extractor tweezers. The most common adverse events (AEs) associated with the present method are nausea and vomiting, whereas gastric erosion, ulceration and early balloon deflation and subsequent migration are relatively rare. It is worth mentioning that few years ago BIB was marketed as Orbera (Apollo Endosurgery, Austin, TX, USA) and received the Food and Drug Administration approval on August 6, 2015 [12, 22, 23]. One of the largest BIB series ($n = 2,515$) was reported by Genco et al. [24]. The percentage of excess weight loss (%EWL), achieved after 6 months of treatment, was 33.9 ± 18.7 and it was accompanied by significant improvement or resolution of diabetes and arterial hypertension in a majority of study subjects. The overall complication rate was relatively low (2.8%); however, it is important to mention that 5 cases (0.2%) of gastric perforation, followed by 2 lethal events, have occurred [24]. Croatian single-center prospective study conducted on 171 consecutive obese patients (41.6 ± 7.5 kg/m^2) also obtained encouraging results. After 6 months of BIB treatment, the overall mean BMI reduction of 5.8 kg/m^2 and %EWL of 39.7 ± 23.6 were achieved [25]. Moreover, a critical review of intragastric balloon for weight loss, which included 7 studies (overall 409 obese patients) reporting the efficacy of the BIB/Orbera, determined the mean weight loss of 16 kg. The authors also reported that 80% of this weight loss result was achieved within the first 3 months of therapy [23]. Finally, it has to be mentioned that, according to results of Dastis et al. [26] (experience based on 100 evaluated cases), only a quarter of patients manage to maintain weight loss 2.5 years after BIB procedure.

There are several other commercially available fluid-filled intragastric balloons, such as Silimed gastric bal-

loon (Silimed, Rio de Janeiro, Brazil), MedSil (Medsil, Moscow, Russia), the Spatz adjustable balloon system (Spatz FGIA, Inc., Great Neck, NY, USA) and ReShape dual intragastric balloon system (ReShape Medical, San Clemente, CA, USA). Silimed is a silicone gastric balloon with a self-sealing valve that becomes spherical when filled with saline solution (470–850 mL). It is especially characterized by the technical improvements in the placement and removal process when comparing with other intragastric balloons [27]. MedSil is a saline-filled balloon, made out of hypoallergenic silicone, with a capacity of 400–700 mL. According to manufacturer's recommendations, lubricant is needed in order to achieve easier detachment of the balloon from the filling tube [28]. The Spatz adjustable balloon system is a saline-filled balloon with an extractable inflation tube for volume adjustment after initial insertion. Hence, fluid can be removed if prolonged nausea, excessive vomiting or pain/discomfort occur, or added if appetite increases or weight loss reaches a plateau. It is approved for a 1-year use, which is 6 months longer when compared to other intragastric balloons [9, 12]. The ReShape duo balloon consists of 2 closely attached, independently saline-filled balloons with a fill volume of 450 mL each. The dual design is being used in order to achieve better conformation to the natural curvature of the stomach, and subsequently improved tolerability and weight-loss efficacy [12].

To deduce, the limited data shows relatively similar efficacy and safety of the previously mentioned fluid-filled balloons to the BIB/Orbera; however, they are less frequently used in everyday practice.

Air/Gas-Filled Intragastric Balloons
In addition to fluid-filled intragastric balloons, several air/gas filled intragastric balloons have been developed: Heliosphere BAG balloon (Helioscopie Medical Implants, Vienne, France), the Obalon gastric balloon (Obalon Therapeutics Inc., Carlsbad, CA, USA), and Ullorex oral intragastric balloon (Phagia Technologies, Inc., Fort Lauderdale, FL, USA). Generally speaking, air/gas-filled balloons have better tolerance after implantation (nausea and vomiting are slightly less frequent) but result in less weight loss in comparison to fluid-filled ones.

The Heliosphere BAG balloon is a double-bag polymer balloon covered with a silicone envelope approved for 6-month implantation. Since filled with air, it is significantly lighter (approximately 30 g) in comparison to fluid-filled balloons (500–700 g). The effect of Heliosphere BAG balloon on weight loss appears to be very similar to other balloons, although several instrumental and technical issues (high rate of system failure at positioning, high rate of spontaneous deflation, absence of a marker such as methylene blue allowing appropriate follow-up in case of balloon rupture, large size of the balloon that causes patient discomfort) still need to be solved [29, 30].

The Obalon gastric balloon is a thin-walled, gas-filled, swallowable gelatin capsule containing the deflated balloon. Once the capsule reaches the stomach, fluoroscopy is used to ensure that the capsule is prepared to be inflated (to a maximal size of 250 mL) via micro-catheter. Depending on patient's weight loss progress, up to 3 balloons can be placed over a 12-week period (afterwards the removal is performed by upper GI endoscopy). Mion et al. [31] conducted a pilot study on 17 overweight/obese subjects to evaluate the Obalon's safety and the impact on weight loss. The study showed no significant side effects induced by up to 3 balloons inflated. Additionally, weight loss was significant at weeks 4, 8, and 12 [31].

The Ullorex intragastric balloon consists of a large capsule that is injected with citric acid and subsequently ingested. After 4 min, the injected acid reacts with the sodium-bicarbonate and the gas product of this reaction (carbon-dioxide) slowly inflates the intragastric balloon to a volume of 300 cm^3. The Ullorex intragastric balloon has a plug that is slowly being degraded by gastric acid over 25–30 days, thereby allowing the balloon to deflate and pass through the digestive tract in feces. Hence, the latter intragastric balloon completely replaces the need for endoscopic placement, as well as the removal process. Martin et al. [32] tested Ullorex intragastric balloon on 12 patients, 2 of which received placebo capsules. Participants who received balloons achieved a mean weight loss of 1.5 kg over a 2-week period [32]. Further trials, following the reengineering of the plug in order to prevent premature deflation of the balloon and provide long-term treatment, are needed to draw the conclusions.

Semi-Stationary Antral Balloon
The semi-stationary antral balloon (SAB; JP Industria Farmaceutica, Ribeirao Preto, Brazil) is a pear-shaped silicone gastric balloon, with a 30-cm long duodenal stem and a 7-g metallic counter-weight at its distal end, designed to be placed in the gastric antrum for inducing early prandial satiety by the intermittent occlusion of the pyloric opening, prolonging gastric emptying and stimulating antral and duodenal satiety receptors. Lopasso et al. [33] conducted a pilot study on 26 patients who failed to lose weight despite dietary interventions (BMI 34.3 kg/m^2), in order to examine the safety, tolerance, and effi-

cacy of SAB. Median weight reduction was 6.5 kg. Four cases of SAB malfunction were reported in the latter study (in one patient, the balloon leaked spontaneously but remained in the stomach, whereas in 3 patients, the balloon migrated distally).

TransPyloric Shuttle

The Transpyloric Shuttle (BAROnova Inc., Goleta, CA, USA) is an endoscopically placed device composed out of silicone that consists of a large spherical bulb (prevents migration from the stomach) interconnected to a smaller cylindrical bulb (passes freely across the pylorus during peristalsis) by a flexible catheter. Intermittent obstruction is being created which then delays gastric emptying and enables a reduction in food intake by inducing early and prolonged satiety [9, 34]. Marinos et al. [35] enrolled 20 subjects (2 groups of 10 patients scheduled to have the device for 3 or 6 months) in their clinical trial in order to evaluate the efficacy and safety of Transpyloric Shuttle. Early device removal occurred in 2 patients due to symptomatic gastric ulcerations, which were determined on a scheduled endoscopic evaluation. The mean percentage of excessive weight loss was 25.1 and 41.0 at 3 and 6 months respectively. Transpyloric Shuttle seems as a potentially promising technology that provides a non-surgical ambulatory method for weight loss; however, further studies are required before arriving at the final judgment [35].

SatiSphere

The SatiSphere (EndoSphere, Inc., Columbus, OH, USA) is a new endoscopically implantable device designed to prolong and increase the contact between the ingested food and afferent neurons lining the duodenum in order to trigger the release of hormones that regulate appetite and satiety. SatiSphere device consists of a 1-mm nitinol wire with pigtail ends and several mesh spheres mounted along its course, released in the duodenum and gastric antrum to conform to the configuration of duodenum and thus self-anchor. Sauer et al. [36] have conducted a randomized (2:1) controlled study in order to test the efficacy, safety and metabolic effects of SatiSphere insertion. Overall, the trial included 21 patients treated with SatiSphere for 3 months and 10 controls. The migration rate of the device was relatively high (10 out of 21 patients) and resulted in necessitating emergency surgery and subsequent termination of trial in 2 cases. Achieved %EWL at 3 months was 18.4, 12.2, and 4.4 in study completers, intention-to-treat analysis group and controls respectively. Moreover, it was observed that SatiSphere de-

layed glucose absorption and insulin secretion and altered kinetics in GLP-1 levels. To deduce, despite short-term efficacy regarding weight loss, due to common device migrations the modification is highly required [36].

Gelesis100

Gelesis100 (Gelesis, Boston, MA, USA) is a non-systemic, superabsorbent hydrogel used in the development of potential treatment of overweight or obesity. It is made from 2 naturally derived building blocks, modified cellulose cross-linked with citric acid, that create a three-dimensional matrix. Orally administered in capsules with water before a meal, Gelesis100 particles rapidly absorb water in the stomach and homogenously mix with ingested foods. When hydrated, Gelesis100 occupies about one-fourth of the average stomach volume. Rather than forming one large mass, it creates 1,000 of small individual gel pieces with the elasticity of solid ingested foods without caloric value. Gelesis100 maintains its three-dimensional structure and mechanical properties during transit through the small intestine. Once it reaches the large intestine, the hydrogel is partially broken down by enzymes and loses its three-dimensional structure along with most of its absorption capacity. The released water is reabsorbed in the large intestine, and the remaining cellulosic material is expelled in the feces. Gelesis100 is considered a medical device because it achieves its primary intended purpose through mechanical modes of action consistent with mechanobiology constructs.

The Gelesis loss of weight study was a 24-week, multicenter, randomized, doubleblind, placebo-controlled study, which included 436 patients (mean BMI 34 kg/m^2). Gelesis100 treatment caused greater weight loss over placebo (6.4 vs. 4.4%, $p = 0.0007$), while 59% of Gelesis100-treated patients achieved weight loss of ≥5%, and 27% achieved ≥10 vs. 42 and 15% in the placebo group respectively. Other than an increase in overall gastrointestinal AEs, most of which were assessed as mild, there was no difference in the incidence and severity of AEs between the Gelesis100 and placebo groups. In both treatment groups, most AEs were mild or moderate in intensity. No serious AEs were observed in the Gelesis100 group [37].

EndoCinch Suturing System

The EndoCinch Suturing System (C.R. Bard, Murray Hill, NJ, USA) was the first device that has been used for endoluminal vertical gastroplasty. After suctioning stomach tissue into the capsule that is attached to the end of endoscope, sutures are deployed in a continuous and

cross-linked fashion from the proximal fundus to the distal body of the stomach to create a narrow tube-like passage [12]. Fogel et al. [38] published their single-center clinical experience of using EndoCinch for endoluminal vertical gastroplasty in 64 patients (BMI 39.9 kg/m^2). No serious AEs were reported. During the follow-up period, 14 patients underwent repeated endoscopy in order to check the suture line and only 2 of them required additional intervention. Mean %EWL was 21.1, 39.6, and 58.1 at 1, 3, and 12 months respectively. However, further studies are needed to draw final conclusions regarding the maintenance of the observed weight loss and stability of the placed sutures.

Restore Suturing System

Restore Suturing System (Bard/Davol, Warwick, RI, USA) and suture fastening system are operated through the working channel of the endoscope; hence, multiple gastric plications can be completed. Its safety and weight-loss efficacy have been evaluated in the Transoral gastric volume reduction as an intervention for weight management trial. Overall, 18 patients were enrolled in the latter trial, whereas 14 of them completed the 12 month of follow-up with the average %EWL of 27.7. Brethauer et al. [39] reported no device- or procedure-related serious AEs. Serious disadvantages observed in the Transoral gastric volume reduction as an intervention for weight management trial was the partial or complete release of aplications in 13 out of 14 patients due to inability of the device to create a continuous suture pattern owing to suture tension [39].

Overstitch Endoscopic Suturing System

The Overstitch Endoscopic Suturing System (Apollo Endosurgery, Austin, TX, USA) is a newer endoscopic suturing device for transoral gastroplasty that allows physicians to place full-thickness sutures through a flexible double-channel endoscope. A technical feasibility of the system for endoscopic gastric volume reduction was initially demonstrated in a study by Abu Dayyeh et al. [40]. Moreover, in a prospective single-center 1 year follow-up study by Lopez-Nava et al. [41], conducted on 25 obese subjects (BMI 38.5 kg/m^2), no major intra-procedural, early, or delayed AEs were reported. Twenty two subjects completed the overall 1-year follow-up period and their mean %EWL was 54.6 [41].

In the largest series of patients undergoing endoscopic sleeve gastroplasty (ESG) to date, Alqahtani et al. [42] reported outcomes in 1,000 consecutive patients (BMI 33.3 ± 4.5 kg/m^2). The mean percentage of total weight loss at 6, 12, and 18 months was 13.7 ± 6.8%, 15.0 ± 7.7%, and 14.8 ± 8.5% respectively. With regard to postoperative complaints, 924 patients (92.4%) complained of nausea or abdominal pain that was controlled with medications during the first week after the procedure. Twenty-four patients were readmitted: 8 for severe abdominal pain, of whom 3 had ESG reversal; 7 for postprocedure bleeding, 2 of whom received blood transfusion; 4 for perigastric collection with pleural effusion, 3 of whom underwent percutaneous drainage; and 5 for postprocedure fever with no sequelae [42].

Recently published meta-analytic study comprising 1,607 cases, reported that the serious AE rate was 1.1%, with a total of 18 events, including 7 fluid collections, 6 cases of hemorrhage requiring blood transfusion and/or endoscopic treatment, 3 cases of refractory symptoms requiring endoscopic ESG reversal, 1 pneumoperitoneum and pneumothorax requiring percutaneous drainage, and 1 pulmonary embolism [43, 44].

Transoral Gastroplasty

The transoral gastroplasty system (TOGA; Satiety Inc., Palo Alto, CA, USA) is a set of flexible, endoscopically guided staplers (introduced over a guide wire) that enable the creation of a restrictive pouch along the lesser curvature of the stomach, which then results in early satiety and limited overall food intake. Devière et al. [45] have conducted the first multicenter study evaluating safety, feasibility and weight loss of TOGA system. Overall, 21 obese patients were included (BMI 43.3 kg/m^2). Device introduction was completed safely in all patients. Vomiting, pain, nausea, and transient dysphagia were the only AEs reported. Average %EWL at 1, 3, and 6 months was 16.2, 22.6, and 24.4 respectively. It is worth mentioning that gaps in the staple line were present in 13 out of 21 patients at a 6-month follow-up endoscopy [45]. Latter observations were subsequently improved by closer apposition of the staple lines and perioperative administration of diclofenac and methylprednisolone. Following this technical improvement, the second pilot study of the TOGA system was conducted. Device introduction was completed safely in all patients and there were no serious AEs reported. Mean %EWL at 1, 3, and 6 months was 19.2, 33.7, and 46.0 respectively [46]. Moreover, Familiari et al. [47] in their prospective, multicenter, single-arm trial conducted on 53 patients, reported the %EWL of 29.3, 36.8, and 38.7 at 3, 6, and 12 months respectively. Overall, 2 serious complications were reported during the trial (respiratory insufficiency and an asymptomatic pneumoperitoneum), whereas epigastric pain, nausea, and vomiting were the

most common adverse effects. Unfortunately, the rate of staple line dehiscence still remained high (50%), despite previously mentioned technical improvements [47].

Trans-Oral Endoscopic Restrictive Implant System

Trans-oral endoscopic restrictive implant system (TERIS; Barosense, Inc., Menlo Park, CA, USA) is an endoscopic procedure for the treatment of obesity that is based on a placement of a restrictor with a 10 mm central channel for food passage at the gastric cardia, thereby creating a restrictive pouch. It is worth mentioning that the device is designed to be permanently implanted; however modification or removal is possible if required [38, 48]. Verlaan et al. [49] have demonstrated the results of their study, which was conducted on 18 patients (BMI 42.1 kg/m^2) in order to determine the 6-month efficacy and safety of TERIS for the treatment of obesity. When it comes to the procedure's safety, 3 serious AEs have occurred (2 pneumoperitoneum and 1 perforation); however, resolution was successfully achieved (spontaneously or with medication) in all cases. In 62.5% of subjects, the anchors remained intact for 6 months and the %EWL after 6 months was 30.1. However, due to poor durability of the system, TERIS cannot be recommended as a standalone endoscopic bariatric therapy. Finally, the company decided to discontinue the TERIS system and to further develop the successful parts of it (e.g., articulating circular endoscopic stapler) [49].

Primary Obesity Surgery Endoluminal

Primary obesity surgery endoluminal (POSE) procedure reduces the stomach size by using the Incisionless operating platform (USGI Medical, San Clemente, CA, USA) that has 4 working channels that can accommodate a slim endoscope and 3 specialized instruments (g-Prox EZ Endoscopic Grasper, g-Lix Tissue Grasper, and g-Cath EZ Suture Anchor Delivery Catheter). One-year weight loss and safety outcomes for 147 patients (BMI 38.0 ± 4.8 kg/m^2) who underwent POSE were reported by López-Nava et al. [50] in 2015. At 1 year, mean %EWL, of 116 patients who were available for follow-up, was 44.9 ± 24.4. According to their observations, POSE also turned out to be a safe and well tolerated weight loss procedure [50].

In a multicenter randomized controlled trial in the United States, 221 patients received the POSE procedure combined with low-intensity lifestyle interventions for a period of 12 months [29]. They achieved a TBWL of 4.95 ± 7.04% in comparison to 1.38 ± 5.58% in the sham group (n = 111). Procedure-related serious AEs were 4.7% (1.9% vomiting, 1.6% nausea, and 0.4% pain), which often occurred within the first week post-procedure and required extended hospital stay. In addition, one subject experienced an extra gastric bleeding and another one a liver abscess that required percutaneous drainage [51].

Endomina Suturing System

The Endomina triangulation platform (Endo Tools Therapeutics SA – ETT, Gosselies, Belgium) is a novel single-use suturing device that is assembled in the stomach using an endoscope and allows physicians to perform large plications with transmural sutures and serosa to-serosa apposition. Huberty et al. [52] have recently reported the first prospective multicenter study evaluating the safety and efficacy of the Endomina technique on 51 patients (BMI 35.1 ± 3 kg/m^2). The mean procedure duration was 97 min. EWL and total body weight loss at 1 year were 29 and 7.4% respectively. When follow-up upper endoscopy was performed in 30 patients, 88% of sutures were still in place. AEs during the procedure consisted of small self-contained bleedings, which did not compromise the completion of the suture and did not require any specific hemostasis. AEs within 1 month of the procedure consisted of mild abdominal discomfort in the majority of patients, which disappeared within 5 days in all cases without specific therapy. No other adverse or severe AEs related to the procedure occurred within the 1-year follow-up [52].

ESG was born as a minimally invasive and cost-effective endoscopic alternative option to laparoscopic sleeve gastrectomy (LSG). While acknowledging the similarities between ESG and LSG, it is important not to equate these weight-loss procedures with each other. Each has its own indication, weight loss mechanism, and AE profile. Multiple studies documented neurohumoral and metabolic changes after LSG [53–55]. While both procedures alter gastric emptying and lower ghrelin levels, the weight loss and metabolic changes that are observed after LSG are more pronounced [56].

Bariatric endoscopy is heading toward a distinction among its application criteria and the ones considered the surgery application criteria: surgery should be considered the gold standard intervention for severe obesity, while bariatric endoscopy should progressively face the possibility to be the gold standard therapeutic strategy for mild-moderate obesity. Therefore, ESG may have a role in the treatment of obese persons who do not undergo bariatric surgery, including those with mild-moderate obesity, and those who require a bridge to surgery, including superobese individuals.

Malabsorptive Endoscopic Procedures
Duodenal-Jejunal Bypass Sleeve

Duodenal-jejunal bypass sleeve (DJBS), marketed as the EndoBarrier Gastrointestinal Liner (GI Dynamics Inc., Lexington, MN, USA), is a flexible, endoscopically implanted, and removable 60-cm long sleeve, open at both ends, that is anchored in the duodenal bulb and extended into the proximal jejunum [57]. The anchor system is a self-expanding stent that allows the barbs to fixate within the gastrointestinal tract, hence decreasing the risk of migration. The sleeve stays in the place from 3 to 12 months and allows undigested food to pass to the distal jejunum while at the same time preventing contact with the duodenum, biliary, and pancreatic secretion. Since this action not only delays ingestion but also intervenes with the body's metabolic functions, including the alteration of incretin pathways, it has a potential both in terms of weight loss and control of obesity-related comorbidities (e.g., type 2 diabetes) [12, 58, 59].

Rohde et al. [60] conducted a systematic review and meta-analysis to evaluate the effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes and the procedure's safety. Overall, 5 randomized controlled trials (235 subjects) and 10 observational studies (211 subjects) were included. Meta-analysis showed that the DJBS was associated with significant EWL of 12.6% compared with diet modification; however, the mean differences in hemoglobin A1c (HbA1c) and fasting plasma glucose, among subjects with type 2 diabetes, did not reach statistical significance. When it comes to procedure's safety, AEs consisted mainly of abdominal pain/discomfort, nausea, and vomiting [60].

Gastroduodenal-DJBS

Gastroduodenal-DJBS (GDJBS; ValenTx Endo Bypass System, Inc., Hopkins, MN, USA) is another bariatric endoscopic malabsorptive procedure. The device needs to be anchored at the gastroesophageal junction by endoscopic and laparoscopic techniques and extended through the stomach about 120 cm into the small intestine. Consequently, an endoluminal gastroduodenojejunal bypass is created, and hence food passes directly from the esophagus into the small bowel avoiding absorption of nutrients in the stomach, duodenum, and jejunum [61, 62].

In a prospective, single-center trial by Sandler et al. [61], the GDJBS was successfully delivered in 22 out of the 24 patients (92%) and finally retrieved endoscopically from all 22 in whom it was implanted. Out of the latter, 17 patients maintained GDJBS and completed the full 12-week trial (postoperative dysphagia was the primary reason for earlier explantation) and achieved %EWL of 39.7 [61]. After the initial accomplishments, the same group of authors conducted another prospective, single-center 12-month trial on 13 obese patients. One patient was excluded, at the time of endoscopic evaluation due to inflammation at the gastroesophageal junction, and 2 additional patients required early explantation (within the first 4 weeks) of the device due to intolerance. Finally, 6 out of remaining 10 patients had fully attached and functional devices during the follow-up period, and consequently achieved mean %EWL of 54 at the completion of the study. Also, in the latter subgroup, obesity-related comorbidities (diabetes, hypertension, dyslipidemia) showed improvement during the trial [63].

Other Endoscopic Weight-Loss Procedures
Duodenal Mucosal Resurfacing

Duodenal mucosal resurfacing (DMR) is a novel, minimally invasive endoscopic procedure that involves circumferential hydrothermal ablation of the duodenal mucosa using the Revita DMR system (Fractyl Laboratories, Inc., Lexington, KY, USA). This catheter-based procedure applies heated water to the duodenal surface deploying a special 2-cm long balloon under direct visualization. DMR is not associated with significant weight loss, but it has been shown to improve glycemic control in people with type 2 diabetes mellitus irrespective of BMI changes. It is hypothesized that DMR results in the destruction of diseased duodenal mucosa and subsequent regeneration after ablation [64].

A first proof of principle study in humans was carried out in 39 patients with type 2 diabetes (BMI 30.8 ± 3.5 kg/m^2; HbA1c 9.6 ± 1.4%). There was a reduction of HbA1c by 1.2% at 6 months despite modest weight loss of 3% TBWL. AEs included post-procedural abdominal pain in 20% of patients and duodenal stenosis in 3 patients that was treated with endoscopic balloon dilation [65].

The recently published multicentre, open-label study has further evaluated safety and efficacy of DMR in 48 patients with type 2 diabetes (HbA1c 7.5–10.0%) on stable oral glucose-lowering medication. Twenty-four weeks post procedure HbA1c has significantly decreased (–0.9 ± 0.2%), while weight was only modestly reduced (–2.5 ± 0.6 kg). Effects were sustained at 12 months. At least one AE related to DMR was reported by 52% of participants; however, majority of them were mild [66].

The Incisionless Magnetic System

The incisionless magnetic anastomosis system (IMAS; GI Windows, West Bridgewater, MA, USA) is used for

the formation of a dual-path enteral bypass permitting ingested nutrients and digestive fluids to go along the native anatomy and the jejuno-ileal anastomosis. Simultaneous placement of self-assembling magnets in the proximal jejunum and in the ileum causes necrosis in the tissue between them with remodeling of the surrounding tissue, eventually leading to the creation of an anastomosis. This partial jejunal diversion is thus unlike a jejuno-ileal bypass, a bariatric surgical procedure that creates a blind defunctionalized segment of small intestine, which may result in a number of serious AEs. Nevertheless, its metabolic effects are favorable due to gut hormone modulation similar to those seen with biliary pancreatic diversion with duodenal switch or ileal transposition surgery.

In the first pilot study designed to evaluate the technical feasibility and safety of IMAS to create a partial jejunal diversion, 10 patients with obesity and type 2 diabetes, prediabetes, or no diabetes were enrolled.

The IMAS was delivered through the working channel of a colonoscope, with laparoscopic supervision to confirm proper magnet coupling, and verify limb lengths. The total procedure time was 115 min. The average total weight loss was 14.6 and 40.2% EWL at 12 months. A significant reduction in HbA1c level was observed in all diabetic (−1.9%) and prediabetic (−1.0%) patients, while reducing or eliminating the use of diabetes medications. No serious AEs occurred, but most patients had transient nausea and diarrhea that resolved without sequela.

It appears that Endomina suturing system is superior to other procedures used to perform the endoscopic gastroplasty in terms of efficacy and safety profile [67].

Intragastric Injections of Botulinum Toxin A

Intragastric injections of Botox into the gastric wall inhibits the release of acethylcoline at the neuromuscular junction and subsequently causes the local paralysis of the injected muscle. The final result of the previously mentioned is the inhibition of antral motility and slowing down of gastric emptying. Additionally, Botox also blocks the ghrelin secretion from the gastric fundus. The effectiveness of intragastric injections of Botox for the treatment of obesity has recently been presented by Bang et al. [68] in their meta-analysis and meta-regression. Multiple injections (>10) were associated with weight loss, whereas a large amount of Botox (500 IU) was not [68]. However, in spite of latter results regarding weight loss, due to high costs and limited effect duration (3–6 months), the application of Botox for the treatment of obesity is still debatable.

Vagal Blockade

Vagal blockade (V-BLOC) therapy delivers intermittent, high frequency, low energy electrical signals through laparoscopically implanted leads on the front and rear vagal trunk in the proximity of gastroesophageal junction. Consequent vagal nerve transmission blockade is associated with reduced feeling of hunger and earlier feeling of satiety. Sarr et al. [69] in their randomized, double-blind, prospective, multicenter trial of the V-BLOC to induce weight loss in morbid obesity (EMPOWER) implanted the vagal blocking system in 294 subjects (treated group: $n = 192$, control group: $n = 102$). After 12 months, %EWL was 17 for the treated and 16 for the control group. Approximately 3% of patients experienced device-related AEs [69]. Further randomized trials are needed to draw the final conclusions regarding the long-term efficacy of V-BLOC in the management of obesity.

Gastric Electrical Stimulation

GES is primarily used in patients with gastroparesis; however, its potential role in bariatric medicine has also been investigated. The implant procedure is predominantly via laparoscopy, while endoscopy is used to control the implantation. Laparoscopic implantable systems include the implantable gastric stimulation (Medtronic, Transneuronix, Inc., Mount Arlington, NJ, USA) and Tantalus/Diamond System meal-activated device (Meta-Cure USA Inc., Orangeburg, NY, USA) that are based on gastric contractility modulation that (when eating starts) delivers electrical signals synchronized to the intrinsic antral slow waves resulting in food intake reduction, gastric emptying delay, decrease in appetite-stimulating, and increase in appetite-inhibiting gut hormones [12]. Sanmiguel et al. [70] enrolled 14 obese subjects with type 2 diabeteson oral antidiabetes therapy in his study with laparoscopically implanted Tantalus System. GES was well tolerated by all subjects, and 11 subjects completed the overall 6-month treatment period. Those patients significantly reduced their weight (107.7 ± 21.1 vs. 102.4 ± 20.5 kg, $p < 0.01$), improved their HbA1c (8.5 ± 0.7 vs. 7.6 ± 1%, $p < 0.01$), blood pressure and lipid parameters [70]. Despite relatively encouraging results, many questions still remain about this modality of therapy and its long-term results regarding weight loss.

Gastric Aspiration

Gastric aspiration is a relatively new technique that involves endoscopic placement of a gastrostomy tube (A-tube) and the AspireAssist siphon assembly (Aspire Bar-

Štimac/Klobučar Majanović/Belančić

iatrics, King of Prussia, PA, USA) to aspirate gastric content 20 min after meal consumption, which allows patients to remove about 30% of the ingested food from the stomach before the calories are absorbed into the body. The patient empties a portion of stomach contents into the toilet after each meal through the tube by connecting a small, handheld device to the Skin-Port [12]. Sullivan et al. [71] performed a pilot study on 18 subjects who were randomly assigned (2:1) to groups that underwent 1-year long aspiration therapy in combination with lifestyle modifications ($n = 11$) or lifestyle therapy only ($n = 7$). Ten out of 11 subjects from the aspiration therapy group and 4 out of 7 subjects from the lifestyle therapy only group completed the first year of the study. At that time, the %EWL was significantly higher in the aspiration therapy group (49.0 vs. 14.9%, $p < 0.04$). Moreover, the latter weight loss was maintained for an additional year for patients who continued with the gastric aspiration therapy. No serious adverse effects or episodes of binge eating due to gastric aspiration therapy have occurred in the present study [71]. Encouraging results were also obtained in a study Forssell and Norén [72] who evaluated the gastric aspiration therapy on 25 obese subjects. In the 22 subjects who completed 6 months of therapy, the mean %EWL was 40.8, and what is more, no serious AE were reported [72].

On the Horizon

The rising demand for less-invasive therapeutic options has attracted both physicians and engineers to cooperate closely. Successful example of the latter is the development of the ingestible wireless weight management capsule. In 2010, Kencana et al. [73] developed a prototype of an intragastric balloon in the form of an ingestible wireless capsule with a diameter of 57 mm and length of 157 mm. Once the capsule is ingested and reaches the patient's stomach, an on-board electric actuator needs to be activated remotely via wireless command in order to trigger the inflation of the attached intragastric balloon. On the other hand, at the end of the obesity treatment period, remote should be used to send the wireless signal for the deflation process to start [73]. Moreover, Yan et al. [74] proposed a prototype of a smaller (30×80 mm) weight loss capsule. The mechanism of action is similar, however, once remotely activated, the on-board linear motor releases the contained acetic acid in order to mix it with sodium bicarbonate in the balloon. Additionally, the carbon dioxide released during this chemical reac-

tion, then inflates the intragastric balloon to a maximal size (110 mL) within 2 min [74]. Since on-board electronic mechanisms result in a larger size (harder to swallow) capsule, and due to debatable question regarding safety of their batteries power requirements, the development of the magnetic soft ingestible capsule-inflated intragastric balloon by Do et al. [75] in 2016, was definitely a new significant step forward. It is of high importance to highlight that only magnetic field is used for opening of the inflation/deflation valve [75]. However, due to lack of the relevant studies, final conclusions regarding the efficacy and safety of ingestible weight management capsules still cannot be drawn. Conducting relevant studies on the present topic, as well as new and exciting innovations are definitely going to emerge in the years to come. Hence, there is a certain possibility that the landscape of bariatric endoscopy will be completely changed relatively soon.

Conclusion

Obesity is a chronic systemic disease that first of all requires a multidisciplinary approach in prevention, treatment, and follow-up. The choice of the right treatment must be individualized and adapted to the severity of obesity and the comorbidity complex affecting the patient. To date, not enough studies with valid designs, double-blind randomized controlled trials and meta-analyzes focusing on the outcomes of bariatric interventions are available. Defined guidelines to follow in order to choose the best individualized treatment are still lacking and represent a key unmet need.

Bariatric endoscopy interventions may offer a useful armamentarium in the obesity management, since their effectiveness regarding weight loss is accompanied by a favorable safety profile and being less-invasive, reversible and more cost-effective in comparison with traditional surgical procedures. However, since this is an area of rapid development, it is of high importance to constantly evaluate the long-term efficacy and safety of new endoscopic weight loss techniques and devices, based on evidence-based medicine principles, in order to critically select the most quality ones and introduce them in everyday clinical practice.

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Author Contributions

D.Š., S.K.M., and A.B. contributed equally to this work. A.B. contributed to literature search and produced the first draft version of this manuscript. D.Š., S.K.M., and A.B. study concept and design. S.K.M. and A.B. acquisition of data. A.B., S.K.M., and D.Š. analysis and interpretation. D.Š. study supervision.

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