Current Endoscopic/Laparoscopic Bariatric Procedures

2

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Abbreviations

ABS	Adjustable balloon system
ACC	American College of Cardiology
ACE	Articulating circular endoscopic
AE	Adverse event
AHA	American Heart Association
ANGPTL	Angiopoietin-like protein
ASGE	American Society for Gastrointestinal Endoscopy
ASMBS	American Society for Metabolic and Bariatric Surgery
ATIIP	Adjustable totally implanted intragastric prosthesis
BED	Binge-eating disorder
BIB	BioEnterics Intragastric Balloon
BMI	Body mass index

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BTA	Botulinum toxin A
CA	Completers' analysis
CCK	Cholecystokinin
CI	Confidence interval
CLGES	Closed-loop gastric electrical stimulation
CRP	C-reactive protein
DEXA	Dual-energy X-ray absorptiometry
DJBL	Duodenojejunal bypass liner
DJBS	Duodenojejunal bypass sleeve
DMR	Duodenal mucosal resurfacing
EBMIL	Excess BMI loss
EBMT	Endoscopic bariatric and metabolic therapy
EBT	Endoscopic bariatric therapy
EDNOS	Eating disorders not otherwise specified
EMA	European Medicines Agency
ESG	Endoscopic sleeve gastroplasty
EVG	Endoluminal vertical gastroplasty
EWL	Excess weight loss
FDA	Food and Drugs Administration
FGF	Fibroblast growth factor
GEGB	Garren-Edwards gastric bubble
GI	GastroIntestinal
GIP	Gastric inhibitory peptide or glucose-dependent insulinotropic polypeptide
GJBS	Gastroduodenojejunal bypass sleeve
GLP-1	Glucagon-like peptide-1
H. pylori	*Helicobacter pylori*
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HTG	High triglycerides
ICU	Intensive care unit
IFN-γ	Interferon-γ
IGB	Intragastric balloon
IL	Interleukin
IMAS	Incisionless magnetic anastomotic systems
IOP	Incisionless operating platform
ITT	Intention-to-treat
IU	International unit
LA(S)GB	Laparoscopic adjustable (silicone) gastric banding
LDL	Low-density lipoprotein
LS	Long segment
MAO	Monoamine oxidase
MCP-1	Monocyte chemoattractant protein-1
mITT	Modified intention-to-treat

mL	Millilitre
NAFLD	Non-alcoholic fatty liver disease
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute of Health
NTG	Normal Triglycerides
OSAS	Obstructive sleep apnoea syndrome
PEG	Percutaneous endoscopic gastrostomy
PIVI	Preservation and Incorporation of Valuable endoscopic Innovations
POSE	Primary obesity surgery endolumenal
PP	Pancreatic polypeptide
PP	Per-protocol
PPI	Proton pump inhibitor
PYY	Peptide YY
RCT	Randomised controlled trial
RYGB	Roux-en-Y gastric bypass
SAB	Semistationary antral balloon
SAE	Serious adverse event
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
SG	Sleeve gastrectomy
SGB	Silimed gastric balloon
SMC	Standard medical care
SS	Short segment
T2DM	Type 2 diabetes mellitus
TAPES	Transmural antero-posterior endoscopic suture
TBWL	Total body weight loss
TERIS	Transoral endoscopic restrictive implant system
TGF-1	Transforming growth factor-1
TGVR	Transoral gastric volume reduction
TNF-α	Tumour necrosis factor-α
TOGa	Transoral gastroplasty
TOS	The Obesity Society
TPS	Transpyloric shuttle
VBloc	Vagal blocking
WHO	World Health Organization

2.1 Introduction

Obesity is a chronic, lifelong, multifactorial and genetically related, life-threatening disease of excessive fat storage, which in addition to how the fat is distributed places the individual at risk of premature death and obesity-associated diseases. As discussed in Chap. 1 almost every organ system is affected by obesity, and the gastrointestinal tract is involved as well. This is the first reason why gastroenterologists

should take care of the obese patient and the desired weight loss together with drug therapy will, apart from the allusion in Chap. 1, be discussed more in detail in this chapter. In the second place, the gastrointestinal tract is involved in the regulation of the energy balance and many treatments will concentrate on the digestive tract and the gut-brain axis. Side effect of medication and endoscopic bariatric surgery comes here into play, which is discussed in this chapter. The third reason is the burgeoning interest in bariatric surgery. There is still a debate whether a gastroenterologist should be part of the multidisciplinary team and whether he/she should take part in the preoperative screening. This will be discussed in Chap. 4. The widespread use of bariatric surgery and the increasing number of patients being operated also means that a significant proportion of these patients will suffer from surgical complications that may be solved by minimally invasive endoscopic techniques. These have to be distinguished in early complications, discussed in Chap. 5, or midterm and late complications, discussed in Chap. 6.

Authoritative institutions such as the National Heart, Lung and Blood Institutes (National Institute of Health, NIH), the World Health Organization (WHO), the National Institute for Health and Clinical Excellence (NICE) and the American Heart Association, the American College of Cardiology and The Obesity Society (AHA/ACC/TOS) have documented that weight loss reduces many of the risk factors for increased death and obesity-related diseases [1–4]. Improvements after weight loss have been noticed for type 2 diabetes mellitus (T2DM), hypertension, dyslipidaemia, metabolic syndrome, osteoarthritis, cancer and sleep apnoea. As far as non-alcoholic fatty liver disease (NAFLD) is concerned outcomes are variable and there is insufficient evidence for an effect on major depression [5]. The initial goal of weight loss is to reduce body weight by approximately 5–10% from baseline. A reasonable timeline for a 10% reduction in body weight is 6 months. Although this weight loss may appear insignificant, it is associated with a fall in systolic blood pressure of 10 mmHg and in diastolic blood pressure of 20 mmHg [1]. Dyslipidaemia is corrected by a decrease of 10% in total cholesterol, 15% in LDL cholesterol and 30% in triglycerides and an increase of 8% in HDL cholesterol. A 5–10% weight loss is associated with improved glycaemic control and a weight loss of 15–20% is able to reverse the elevated mortality risk of diabetes and to cure diabetes. Ovarian function and quality of life are improved by a 5% weight loss. Resolution of sleep apnoea usually needs a greater weight loss of 15–20%. After 6 months of effective weight loss, treatment efforts to maintain the weight loss over a period of at least 1–2 years but preferentially lifelong should be instituted [1, 2].

Treatment algorithms are typically staged, with the first step consisting of intensive lifestyle intervention; the second step consists of drug treatment, and the final step involves surgery [1–4]. However, as obese patients may suffer from many comorbidities, one of the first actions should be to screen the medication list. Medications commonly prescribed for hypertension (β-blockers), diabetes (sulphonylurea derivatives, insulin), depression (paroxetine, amitriptyline), epilepsy (almost all anti-epileptic drugs), rheumatoid arthritis (corticosteroids) and psychiatric illnesses (neuroleptic drugs) may promote weight gain. For most of these disease, a weight neutral of weight-reducing alternative exists [5].

Based on evidence-based guidelines, the first approach should consist of lifestyle modification: a combination of an energy-restricted diet, physical exercise and behaviour modification [1–4]. With intensive lifestyle treatment, a majority of obese participants in clinical trials lose 7–10% of their initial weight at 1 year [6]. Also, many lifestyle intervention trials in obese people with impaired glucose tolerance show a moderate weight loss between 3% and 5% and an impressive reduction in the transition of impaired glucose tolerance into frank diabetes by 40–55% [7, 8]. However, results from these trials are far better than those attained in everyday clinical practice, where studies using low-intensity counselling have not demonstrated clinically meaningful weight losses [9, 10]. Energy restriction can be a fixed amount of daily energy intake, usually 1200–1500 kcal for women and 1500–1800 kcal for men, but many studies used a 500–750 kcal deficit or a 30% energy deficit, subtracted from the calculated daily energy intake or needs. There has been a lot of discussion whether macronutrient composition has an important contribution in the adherence to a diet and subsequent weight loss. Low-carbohydrate and low-glycaemic diets and the Mediterranean diet have a central role in this discussion [10]. Albeit this is not the place to discuss all dietary options and referral to a dedicated dietician with interest in the problem of obesity is highly appropriate, patients prefer the low-carb diets as they lose a lot of (water) weight in the beginning and they can check their compliance with the diet every day with keto sticks, indicating the presence of ketones in the urine, and do not have to wait for weeks to see an effect on the scales. The legendary study by Sacks et al. in 2009 is illustrative in this regard [11]. They randomly assigned 811 overweight adults to four diets with different macronutrient compositions and offered the participants also group and individual instructional sessions for 2 years. Satiety, hunger ratings, satisfaction with the diet and attendance at group sessions were similar for all diets as were the weight losses. Attendance at the sessions, however, was the only finding that was strongly associated with weight loss (0.2 kg per session attended) [11]. Regular contact with a multidisciplinary team has been shown to be critical in maximising patient outcomes. The American Heart Association, the American College of Cardiology and The Obesity Society (AHA/ACC/TOS) Task Force reviewed all clinical studies related to lifestyle interventions and concluded that a face-to-face contact of 16 times per year on average was a major determinant of body weight loss outcomes and included this recommendation in their guideline [4]. A systematic review of multicomponent weight management programmes (diet, exercise and behaviour therapy) in overweight and obese adults included 12 randomised controlled trials. Weight changes were small, a significant weight loss of 10–15% was rarely achieved and weight regain was common in those studies that measured it [12]. It is known that weight loss that is based on caloric restriction through dieting results in significant increase in appetite with an increase in orexigenic gut hormones such as ghrelin and a decrease in anorexigenic gut hormones such polypeptide YY (PYY) [13]. This suggests that the high rate of relapse among obese patients after restrictive diets has a strong physiological basis [10, 13].

The components of behaviour modification include self-monitoring, stimulus control, slowing the rate of eating, social support, cognitive restructuring, problem

solving and relapse prevention. Exercise has many benefits: it improves cardiorespiratory fitness, enhances weight loss, preserves lean muscle tissue during weight loss and is an important tool for weight maintenance which resulted in a recommendation of ≥150 min per week of moderate intensity in the AHA/ACC/TOS guideline [4]. More exercise is needed for weight loss maintenance: 200–300 min per week of moderate-intensity exercise [4].

When motivated patients have seriously attempted but failed to achieve weight loss, pharmacotherapy with approved medication may be recommended. To get approval, current efficacy benchmarks for weight loss relative to placebo are a mean weight loss ≥5% more than that of the placebo group or the proportion of drug-treated participants who lose ≥5% of initial weight is ≥35% and approximately double the proportion who lose ≥5% in the placebo group at 1 year [14]. Drugs should always be embedded in an intensive lifestyle programme. Pharmacotherapy is indicated in subjects with a body mass index (BMI) ≥30 kg/m^2 or a BMI ≥27 kg/m^2 in the presence of obesity-associated comorbidity [5]. Guidelines on the pharmacological management of obesity were published by the Endocrine Society in 2015 [5]. The Endocrine Society, the European Society of Endocrinology and The Obesity Society recommend in their guideline that if a patient's response to a weight loss medication is deemed effective (weight loss ≥5% of body weight at 3 months) and safe, the medication may be continued [5]. If deemed ineffective (weight loss <5% at 3 months) or if there are safety or tolerability issues, they recommend that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered. The available drugs approved by the Food and Drugs Administration (FDA) are mentioned in Table 2.1, orlistat being approved in 1999 by the Food and Drug Administration (FDA) for indefinite treatment of obesity [5]. In Europe, the European Medicines Agency (EMA) only approved orlistat. Gastroenterologist should be aware that orlistat acts on the digestive system by inhibiting gastric and pancreatic lipase, thereby interfering with the fat absorption. This results in a 30% fat malabsorption with complaints of oily spotting, flatulence with discharge, faecal urgency, oily evacuation, increased defecation and faecal incontinence. These complaints may be decreased by co-administration of fibre-containing supplements. In addition to promoting malabsorption of fat calories, the medication reinforces avoidance of high-fat (energy-dense) foods. These adverse effects may cause patients who do not reduce their fat intake to discontinue therapy. Despite its FDA approval for lifelong intake, fewer than 10% of patients take orlistat three times 120 mg daily for at least 1 year and less than 2% take the medication for 2 years [15, 16]. Yanovski and Yanovski systematically reviewed the literature on long-term drug treatment for obesity up to September 2013 [14]. When prescribed with lifestyle interventions, these drugs produce additional weight loss relative to placebo ranging from approximately 3% of initial weight for orlistat and lorcaserin to 9% for top-dose (15/92 mg) phentermine/topiramate–extended release at 1 year. The proportion of patients achieving clinically meaningful weight loss of ≥5% ranges from 37% to 47% for lorcaserin, 35% to 73% for orlistat and 67% to 70% for top-dose phentermine/topiramate–extended release [14]. All these three medications

Table 2.1 Drugs approved by the FDA for use in the USA; in Europe only orlistat is approved by the EMA

Drug name	Class of drugs/dosage	Advantages	Disadvantages
Phentermine	Noradrenergic, 30 mg OD[a]	Inexpensive Greater weight loss[b]	Side effect profile No long-term data[c]
Phentermine/ topiramate	Noradrenergic/GABA modulator, 7.5/46 mg OD[a] Start 3.75/46 mg, escalating to maximally 15/92 mg	Robust weight loss[b] Long-term data[c]	Expensive Teratogen
Lorcaserin	5HT2c receptor agonist, 10 mg BDD, start with 10 mg OD[a]	Side effect profile Long-term data[c]	Expensive
Orlistat by prescription	Pancreatic and gastric lipase inhibitor 120 mg TDD[a]	Nonsystemic Long-term data[c]	Less weight loss[b] Side effect profile
Orlistat over-the-counter	Pancreatic and gastric lipase inhibitor 60 mg TDD[a]	Inexpensive	Less weight loss[b] Side effect profile
Naltrexone/ bupropion	Opioid antagonist/ dopamine and norepinephrine reuptake inhibitor 8/90 mg 2 tablets BDD[a], start with 8/90 mg 1 tablet BDD[a]	Greater weight loss[b] Food addiction Long-term data[c]	Side effect profile Moderately expensive
Liraglutide	3 mg OD[a], start with 0.6 mg	Side effect profile Long-term data[c]	Expensive Injectable

[a]*OD* once daily; *BDD* twice daily; *TDD* thrice daily
[b]Less weight loss 2–3%; greater weight loss >3–5%; robust weight loss >5%
[c]Long term is 1–2 years; the noradrenergic drugs available in the USA were already in the market before the current efficacy benchmarks for weight loss relative to placebo were issued and they are thus only approved for short term, a 12-week use

produce greater improvements in many cardiometabolic risk factors than placebo. However, less than 2% of people who qualify for pharmacological therapy receive it, mainly because of assumed limited effectiveness and high costs [17].

A surgical approach is restricted to very obese subjects (BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with obesity-associated comorbidity). Yet, only approximately 1% of eligible individuals with morbid obesity in the USA receive bariatric surgery [18]. Barriers often mentioned are concern both of patients and referring physicians about the risk of surgical complications and mortality, the fear of reoperations, the perceived invasiveness and irreversible nature of the intervention, limited access and difficulty in obtaining insurance and financing treatment [18–21]. The limited capacity of the healthcare system and the inability of surgeons to meet the grand demand are factors that come into play when more than the current 1% of eligible patients will apply for surgery in the near future.

Notwithstanding these treatment options, there is an intermediate group of patients who do not respond to medical therapy but are not or not yet surgical candidates. Some patients refuse surgery because of its invasiveness and fear of complications. For this group, an endoscopic treatment might look attractive [22]. The same holds true for severely obese patients with a BMI ≥40 kg/m^2, being poor surgical candidates for elective surgery such as hip replacement or organ transplantation, and for patients with a BMI ≥50 kg/m^2 being bariatric surgical candidates, as a bridge to surgery, in whom the achievement of a moderate preoperative weight loss might reduce anaesthesia risks and surgical complications and might allow to better visualise the operative field. So, endoscopic therapy, often labelled endoscopic bariatric therapy (EBT), or more recently endoscopic bariatric and metabolic therapy (EBMT), has a role to play in the treatment of obesity either as an alternative or as an adjunct to medical treatment. This has been discussed at length in many recent superb overviews [23–35]. New therapies have to be more effective and durable than lifestyle interventions alone, less invasive and risky than bariatric surgery, and easily performed at lower costs, thereby allowing improved access and application to a larger segment of the population with moderate obesity. They should be a viable and safe alternative for patients who have been unsuccessful at weight loss with diet and exercise, and should be appropriate for patients who are not suitable for, or are unwilling to undergo, a more invasive surgical procedure [34]. Emerging endoscopic bariatric therapies potentially meet these criteria [35].

The different endoscopic modalities may vary in mechanisms of action: by space occupation, delayed gastric emptying, gastric restriction and decreased distensibility, impaired gastric accommodation, stimulation of antroduodenal receptors, or duodenal exclusion and malabsorption. Vagal signalling to the hypothalamus and hormonal influences may play a role as well. Only treatments will be discussed that are covered in peer-reviewed articles. Figure 2.1 graphically summarises the different endoscopic bariatric modalities. One should realise that these developments are very costly and several companies went bankrupt. Except for intragastric balloons, duodenojejunal bypass liner and aspiration therapy, most of the other endoscopic tools are still investigational or under further development or refinement. Most of the endoscopic modalities are not reimbursed. The FDA approval process represents another challenge that any new device must navigate before becoming available for patients outside of clinical trials. To give an example: the ReShape Duo balloon applied for approval since its starting in 2007 and received it only in 2015 [36].

2.2 Endoscopic Bariatric and Metabolic Therapies

Roughly, the endoscopic bariatric and metabolic interventions can be separated into

1. Early intervention in obese patients (BMI ≥30 kg/m^2) to provide weight loss.

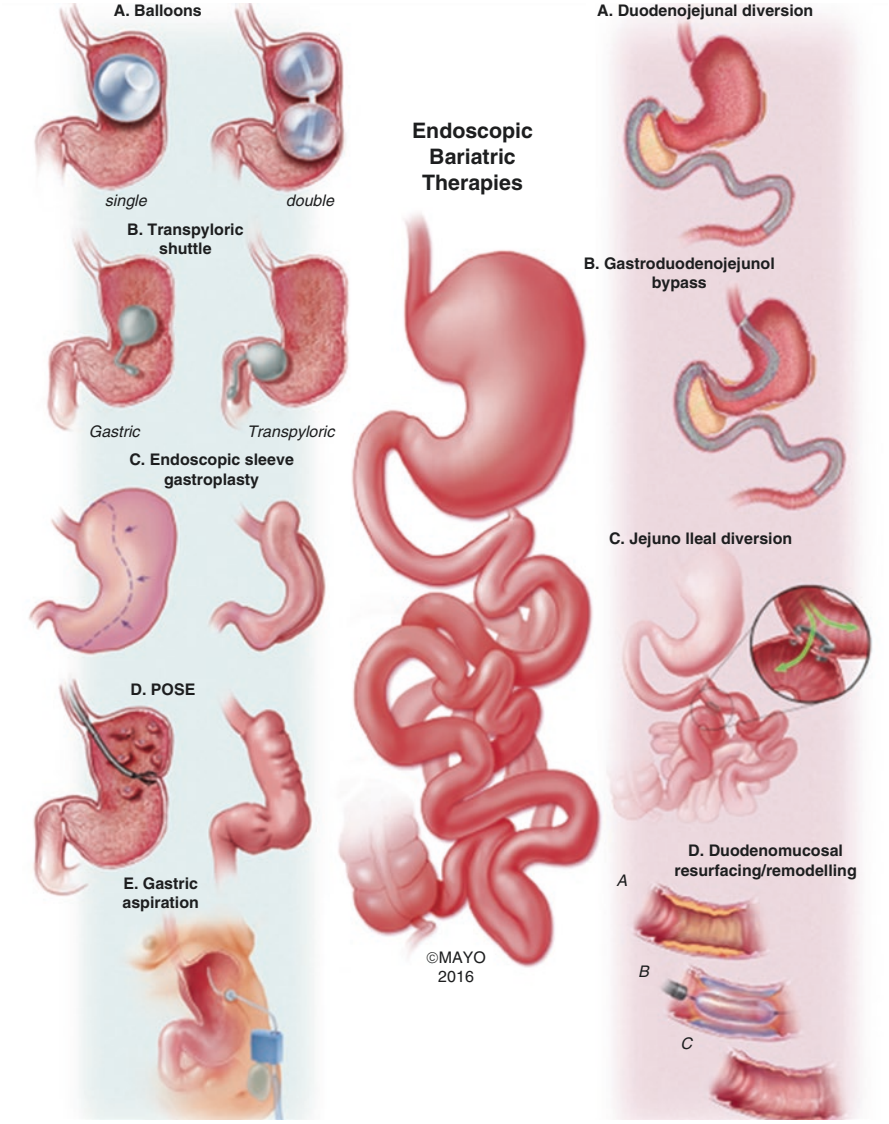


Fig. 2.1 Overview of currently used and approved endoscopic devices and devices that are under development or that apply for FDA approval. Devices are divided into those that work in the stomach (left-hand side) or those that affect the duodenum and small intestine (right-hand side) [35]. Reprinted from Gastroenterology 2017; 152: 716–729, Abu Dayyeh BK, Edmundowicz S, Thompson CC. Clinical practice update: expert review on endoscopic bariatric therapies with permission from Elsevier

2. Primary intervention in subjects eligible for surgery but who refuse surgery or have no access to surgery.
3. Secondary intervention as a bridge to elective surgery in those with BMI $\geq$40 kg/m^2 or as a bridge to bariatric surgery in those with BMI $\geq$50 kg/m^2.
4. Metabolic intervention, primarily addressing comorbid diseases such as diabetes with a modest effect on weight [37].

Contraindications have to be taken into account (Table 2.2) [22, 38, 39]. They can be related to weight loss in general or to the procedure more specifically. Each endoscopic treatment will have its own contraindications. The American Society for Gastrointestinal Endoscopy (ASGE) and the American Society for Metabolic and Bariatric Surgery (ASMBS) Task Force wrote a white paper in 2011 on endoscopic bariatric therapies in which they reviewed the requirements of such procedures as to weight loss, safety, efficacy, durability, reversibility, repeatability, costs and alteration of anatomy [39]. They recommended minimum threshold of weight loss and definitions of successful weight loss for the above-mentioned categories. In 2015, the ASGE Bariatric Endoscopy Task Force and ASGE Technology Committee reviewed the endoscopic bariatric therapies and in that same year a joint task force convened by the ASGE and the ASMBS published the thresholds in a Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) document [39–41].

Table 2.2 General weight loss and more procedure-specific contraindications for endoscopic bariatric treatment [38, 54]

	Endocrine or metabolic cause of obesity
General	Severe underlying disease or ASA $\geq$ III (renal or hepatic insufficiency, cardiovascular disease)
	Alcoholism or drug abuse
	(Desire of) pregnancy, lactating
	Not co-operative at endoscopy
	Lack of motivation or compliance, (inadequately treated) psychiatric disease, bulimia
	Malignancy in previous 5 years (except skin cancer)
Procedure specific	Oesophageal disorders (oesophagitis grade C or D, severe candida infection, varices, dysmotility, stenosis, webs, scleroderma, Zenker's diverticulum)
	Gastric disorders (peptic ulcer, hiatal hernia >3 cm, angiodysplasia, gastric varices, gastric dysmotility, gastroparesis)
	Severe coagulopathy or need of anticoagulants
	Use of NSAIDs, aspirin, corticosteroids, or immunosuppressants
	Inflammatory disease (Crohn's disease, active *Helicobacter pylori*)
	Previous abdominal or bariatric surgery
	Unwillingness to take PPIs
	Scuba diving and travel in unpressurised airplane cabins, as well as living at high altitudes: specific for gas-filled balloons [38]
	Allergy to the material in the system
	Serotonin syndrome or the use of drugs known to affect levels of serotonin in the body (if methylene blue is used in the balloon)

The PIVI criteria were as follows [41]:

- EBT intended as a primary obesity intervention in Class II/III obese individuals (body mass index (BMI) >35 kg/m^2) should achieve a mean minimum threshold of 25% excess weight loss (% EWL) measured at 12 months. Primary obesity interventions are stand-alone interventions in combination with lifestyle modification and/or behavioural therapy to induce weight loss and improvement in obesity-associated medical comorbidities.
- In addition to the above-mentioned absolute threshold of weight loss, the mean % EWL difference between a "primary" EBT and control group should be a minimum of 15% EWL and be statistically significant.
- Five percent of the total body weight loss (5% TBWL) should represent the absolute minimum threshold for any non-primary EBT (e.g. early intervention, bridge to surgery or metabolic therapy). Bridge-to-surgery obesity intervention is an intervention to promote weight loss, specifically to reduce the risk from a subsequent intervention, including bariatric and non-bariatric surgery, such as orthopaedic, cardiovascular and organ-transplant surgeries. Patients with a BMI >50 kg/m^2 present greater technical challenges and surgical risk than less obese, healthier patients; therefore, EBTs used for this indication should perform well in higher BMI groups.
- The risk associated with EBT should equate to a ≤5% incidence of serious adverse events.
- If a low-risk EBT proves to have a significant impact on one or more obesity-related comorbidities, the threshold for intervention may extend to Class I obese individuals (BMI 30–35 kg/m^2).

ASGE Bariatric Endoscopy Task Force and ASGE Technology Committee reviewed the different EBTs against these PIVI criteria and found an adequate number of studies for a meta-analysis on the Orbera intragastric balloon (IGB) and the EndoBarrier DuodenoJejunal Bypass Sleeve (DJBS), which are discussed in the respective subchapters [41]. Newer IGB had insufficient studies for an analysis such as the ReShape Duo IGB (two studies), the Spatz3 IGB (three studies), the Silimed IGB (three studies) and the Heliosphere IGB (five studies). Also the aspiration therapy and endoscopic gastroplasty techniques had insufficient data to be included in a meta-analysis.

The American Society for Metabolic and Bariatric Surgery (ASMBS), the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and, more recently, the American Society for Gastrointestinal Endoscopy (ASGE) and the ASMBS more specifically in the context of intragastric balloons have written position statements focused on these new procedures which are incorporated throughout this manuscript [42–46].

A very recent manuscript by Abu Dayyeh et al. had the intention to update the gastroenterologist on EBTs and to provide practice advices on how to implement them in clinical practice [35]. These Best Practice Advices are reiterated here literally because they are formulated very clear and succinct. The following advices are given:

Best Practice Advice 1	EBTs should be considered in patients with obesity who have been unsuccessful in losing or maintaining weight loss with lifestyle interventions.
Best Practice Advice 2	EBTs can be used in patients with severe obesity as a bridge to traditional bariatric surgery. They can also be used as a bridge to allow unrelated interventions that are unable to be performed because of weight limits (i.e. orthopaedic surgery, organ transplantation).
Best Practice Advice 3	Clinicians should use EBTs as part of a structured weight loss programme that includes dietary intervention, exercise therapy and behaviour modification, in both the active weight loss phase and the long-term maintenance phase.
Best Practice Advice 4	Clinicians should screen all potential EBT candidates with a comprehensive evaluation for medical conditions, comorbidities, and psychosocial or behavioural patterns that contribute to their condition before enrolling patients in a weight loss programme that includes EBTs.
Best Practice Advice 5	Clinicians incorporating EBTs into their clinical practice should follow up patients prospectively to capture the impact of the EBT programme on weight and weight-related comorbidities, and all related adverse outcomes. Poor responders should be identified and offered a detailed evaluation and alternative therapy.
Best Practice Advice 6	Clinicians embarking on incorporating EBTs into their clinical practice should have a comprehensive knowledge of the indications, contraindications, risks, benefits and outcomes of individual EBTs, as well as a practical knowledge of the risks and benefits of alternative therapies for obesity.
Best Practice Advice 7	Institutions should establish specific guidelines that are applied consistently across disciplines for granting privileges in EBTs that reflect the necessary knowledge and technical skill a clinician must achieve before being granted privileges to perform these procedures [35].

As will be discussed in Chap. 4, these advices will be easier to follow when a gastroenterologist is part of an obesity group or a bariatric team, because some of the mentioned tasks can be delegated to team members who are more experienced in certain tasks such as mentioned in Best Practice Advices three and four. Fanelli and Andrew noted that workforce readiness poses another inhibitor to adoption of EBTs, because who will do all the work [29]? Surgeons, who are experts in weight loss interventions of the present, will need to develop robust endoscopic expertise to provide these technologies in a safe and effective manner. Gastroenterologists, who are experts in endoscopic techniques, are often not involved in multidisciplinary weight loss programmes but may need to develop these relationships to responsibly care for the obese. Therefore, Fanelli and Andrew cautiously suggest that "the surgical endoscopist may very well be best positioned to aid patients in this new age of obesity intervention". However, not every country allows surgeons to perform endoscopy, certainly not in the Netherlands because of endoscopic quality measures and required volume of (emergency) endoscopies.

2.3 Gastric Endoscopic Bariatric and Metabolic Therapies

Gastric EBMTs include non-invasive devices that essentially leave the normal anatomy intact and are reversible such as space-occupying devices in the stomach (intragastric balloons) or a device that removes a portion of the

calories consumed after a meal (aspiration therapy), and more invasive devices that alter the gastric anatomy to reduce gastric volume and accommodation and to delay gastric emptying (suturing and stapling). Other treatments are presented at the end of the subchapter on gastric EBMTs as they are unproven, not further developed since the last publication, or have an unknown status at this moment.

2.3.1 Non-invasive Endoscopic Bariatric and Metabolic Therapies

2.3.1.1 Intragastric Balloon Treatment

Intragastric balloons have been used for over 35 years. Although being available for three decades, intragastric balloon treatment (IGB) is not covered by the existing evidence-based guidelines. This is partly the result of ineffective and hazardous balloons in the 1980s such as the FDA-approved Garren-Edwards Gastric Bubble (GEGB, American Edwards Laboratories, Santa Ana, CA, USA) [22]. The Garren Edwards Bubble is a 220 mL IGB made from polyurethane in the shape of a cylinder and filled with air. It had a central hollow channel to permit fluid passing down and to permit an easier free movement in the stomach. However, the GEGB had sharp ridges at the place where parts were sealed together. It was approved for use in the USA by the FDA in 1985, but was removed from commercial use in 1988 due to serious complications and lack of effective weight loss [36, 47]. Deflations occurred in 31% which needed surgical interventions in 2.3%. Gastric ulcers were seen in 26% and the balloon was not tolerated in 7% [48].

With the concerns of the design, construction and integrity of previous balloons in mind, experts participating in the workshop "Obesity and the gastric balloon" formulated the fundamental requirements for an optimal balloon design in 1987 [47]. Intragastric balloons should be smooth, seamless and constructed of long-lasting material with a low ulcerogenic and obstructive potential. They should have a radiopaque marker to allow appropriate follow-up in case of deflation. There was uncertainty about the ideal shape, fill volume and fill medium, but yet a preference was expressed to have the ability to be adjusted to a variety of sizes and be filled with fluid rather than air. None of the existing balloons conformed to these requirements (Table 2.3) and this resulted in the withdrawal of balloons from the American market [22]. Many years of research finally resulted in the development of a balloon (BioEnterics Intragastric Balloon, BIB™, currently named the Orbera balloon) that fulfilled the specified requirements. Over the last 15 years the balloon market is booming (Table 2.4) with the availability of many intragastric balloons around the world [22]. Only very recently three balloons are approved by the FDA for 6-month therapy for patients with a BMI 30–40 kg/m^2 with the requirement of supportive treatment for a total of 12 months: the Orbera balloon (formerly the BioEnterics Intragastric Balloon or BIB) since 2015, the ReShape Duo balloon with the requirement of the presence of ≥1 comorbidity besides the BMI values since 2015 and the Obalon balloon since 2016.

Table 2.3 Intragastric balloons removed from the market [22]

Balloon and country	Shape	Content and fill medium
Air filled		
Garren-Edwards (USA)	Cylindrical	200–220 mL Air
Wilson-Cook (USA)	Pear	300 mL Air, connected with fill tube to the nose
Ballobes (DK)	Oval	450–500 mL Air
Fluid filled		
Dow Corning (CAN)	Disc-like	200 mL Air + 200 mL Saline
Willmen (G)	Disc-like	275–400 mL Methylcellulose
Taylor (UK)	Pear	500–550 mL Water

USA United Stated of America, *DK* Denmark, *Can* Canada, *G* Germany, *UK* United Kingdom

Table 2.4 Intragastric balloon available at present [22]

Balloon and country	Shape	Content and fill medium
Fluid filled		
Orbera intragastric balloon (IGB, formerly BIB) (USA)	Spherical	400–800 mL Saline +10 mL MB
Semistationary antral balloon (SAB) (Br)	Oval	150–180 mL Saline, 30 cm duodenal stem at caudal end with 7 g metallic counterweight
Silimed gastric balloon (SGB) (Br)	Spherical	650 mL Saline + MB, introduced alongside endoscope with snare
Spatz Adjustable Balloon System (ABS) (USA)	Spherical	400–600 mL Saline + MB, adjustable by (re)fill tube, migration-preventing anchor
MedSill (Russia)	Spherical	400–700 mL Saline + MB
ReShape Duo (USA)	Spherical	900 mL Saline in two separate balloons, connected with each other; 375 mL per balloon for patients <1.64 m (64.5 in.) in stature
Fluid and air filled		
Endball (F)	Spherical	300 mL Saline and 300 mL Air, mounted on tip of endoscope
Air filled		
Heliosphere Bag (F)	Spherical	Double-bag polymer balloon covered with a silicone envelope, 650–750 mL Air
Adjustable totally implantable intragastric prosthesis/ Endogast (ATIIP) (F)	Oval	300 mL Air, adjustable by port
Orally ingested balloons		
Air filled		
Ullrorex (USA)	Spherical	300 mL Carbon dioxide
Obalon (USA)	Spherical	300 mL Gas mixture
Fluid filled		
Elipse (USA)	Spherical	550 mL Saline

USA United Stated of America, *DK* Denmark, *Can* Canada, *G* Germany, *UK* United Kingdom, *Br* Brasil, *F* France, *MB* Methylene Blue

Intragastric balloons are endoscopically placed or swallowed, endoscopically removed or excreted rectally after planned degradation, air or saline filled, single or dual, spherical or oval, adjustable or nonadjustable, silicone or polymer balloons that are resistant to breakdown by gastric secretions (Table 2.4, Fig. 2.1) [22]. Some balloons have anti-migration characteristics.

Single Ballloons

Orbera Balloon (Formerly Bioenterics Intragastric Balloon (BIB); Apollo Endosurgery, Austin, TX, USA)

The Orbera balloon (formerly the BioEnterics Intragastric balloon (BIB)) is the most commonly used balloon. It is a spherical large-volume (500–750 mL) silicone balloon, usually filled with 500 mL saline (Table 2.4, Fig. 2.2a). Some prefer to add 10 mL of methylene blue (10 mg/mL), which is systemically absorbed from the gastrointestinal tract and excreted by the kidneys. It acts as an indicator of balloon deflation as it colours the urine green. Methylene blue is an inhibitor of monoamine oxidase (MAO) and may thus potentiate other MAO inhibitors [49]. More dangerous with even a fatality is the serotonin syndrome that may develop when drugs affecting serotonin such as serotoninergic antidepressants are used [49–51]. The syndrome is well known in cardiology where methylene blue is administered intravenously during cardiac surgery, but also cases after systemic absorption without intravenous administration are described [49–51].

Prior to positioning, an endoscopy has to be performed to rule out abnormalities that preclude insertion (Table 2.2) [52]. After removal of the endoscope the placement assembly, that consists of a sheath with the collapsed balloon and a balloon fill tube, is inserted up to 10 cm beyond the distance from incisor teeth to the gastro-oesophageal junction. Then the endoscope is reinserted into the stomach, to observe the balloon-filling and -releasing steps. With a syringe, attached to the balloon fill tube, the balloon is filled with the recommended initial volume of 500 mL saline. After filling the balloon, gentle suction by withdrawing the plunger of the syringe creates a vacuum that seals the valve. The balloon is released by a short pull at the fill tube upon which fill tube and empty placement assembly are removed [52]. The balloon should be

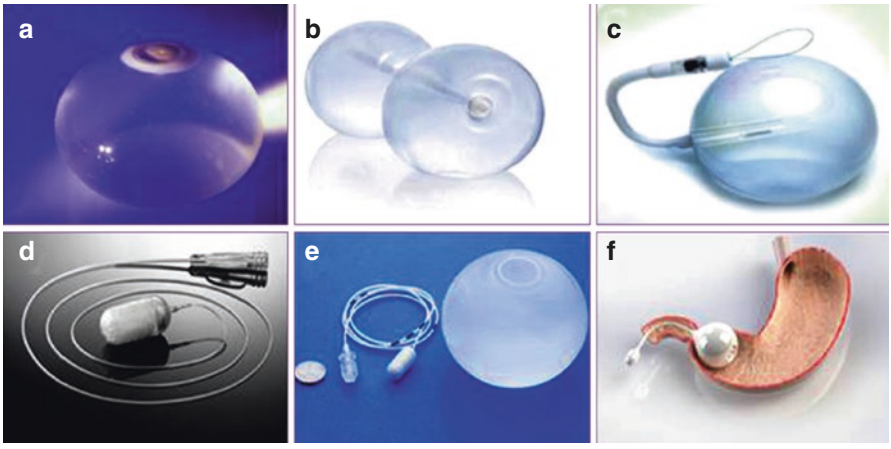


Fig. 2.2 Intragastric endoscopic balloon devices: (**a**) Orbera balloon; (**b**) ReShape Duo balloon; (**c**) Spatz adjustable balloon system; (**d**) Obalon swallowable balloon; (**e**) Elipse swallowable balloon; (**f**) transpyloric shuttle [66]. Reprinted from Clin Endosc 2017; 50: 42–66, Bazerbachi F, Vargas Valls EJ, Abu Dayyeh BK. Recent clinical results of endoscopic bariatric therapies as an obesity intervention (Open Access Article)

removed after a maximum of 6 months because beyond this period there is a higher risk of spontaneous balloon deflation. In case of balloon removal, a needle aspirator is available to puncture the balloon and to remove as much fluid as possible by suction before grasping the balloon with a snare or a two- or three-pronged grasper [52]. The endoscope and the grasped balloon are gently removed. Because of a risk of aspiration of solid food materials coated on top of the balloon, an important advice to patients is to only take clear liquids the day before balloon removal [52].

After insertion, nausea, vomiting, abdominal cramps and acid reflux are to be expected for 72 h and require aggressive treatment with anti-emetics, antispasmodics, analgesics, suppositories or acid suppressants [52]. Instructions for a 72-h post-insertion liquid diet have to be provided. Thereafter, antacids or acid-suppressing drugs are given upon request. However, most of the treating physicians prescribe proton pump inhibitors (PPIs) during the whole period of balloon treatment.

Most of the studies with the Orbera balloons were done in the era when they were named BIB. To avoid confusion, the name BIB has been replaced by the current name Orbera or the general abbreviation intragastric balloon (IGB) is used.

Efficacy and Safety

To assess efficacy and safety of the Orbera balloon three systematic reviews and one meta-analysis are available [53–56]. A Cochrane review included many studies with older balloon designs that were withdrawn from the market because of unsafety [53]. This review concluded that despite the evidence for some additional benefit of the intragastric balloon in the loss of weight, its costs should be considered against a programme of eating and behavioural modification. Two reviews and one meta-analysis discussed newly designed balloons, mainly the Orbera balloon [54–56]. Imaz et al. pooled 15 articles (3608 patients) to estimate Orbera effectiveness [56]. The estimates for weight lost at balloon removal after 6 months were 14.7 kg, 12.2% total body weight loss (TBWL), and 5.7 kg/m^2 (BMI units) or 32.1% excess weight loss (EWL). A meta-analysis of two randomised controlled trials (RCTs) which compared balloon with placebo – one in favour of the balloon and one showing no difference – estimated that patients with balloon group lost more weight than the placebo group; differences in weight loss were 6.7 kg, 1.5% TBWL, 3.2 kg/m^2 or 17.6% EWL [52, 57]. The two systematic reviews included a third RCT which showed no difference but which did not have efficacy evaluation as a primary aim [58]. Safety was assessed in 13 articles with 3442 patients on early balloon removal and 12 studies with 3429 patients on complications [56]. Early balloon removal occurred in 4.2% of cases. Nearly half of the early removals were voluntary in 1.8%, followed by abdominal pain in 0.9% and obstruction of the digestive tract in 0.6%. An overall complication rate was not given because each patient could suffer from more complications [56]. Early deflation occurred in 0.1%, gastric ulceration in 0.1%, gastric perforation in 0.2% and gastrointestinal (GI) tract obstruction in 0.6%. There were two deaths from gastric perforation, both in patients with prior gastric surgery [56]. The two systematic reviews found gastric perforations in a total of nine patients, five of whom had previous gastric surgery, an absolute contraindication for balloon positioning (Table 2.2) [54, 55]. The most feared complications are

oesophageal and gastric perforation and small-bowel obstruction due to deflated balloons. Recently, Abou Hussein et al. reported three gastric perforations, two with the Spatz balloon and one with the Orbera balloon that were treated minimally invasive with combined endoscopy and laparoscopy [59]. They reviewed the literature and found 18 cases since 2003, three of them being lethal and six occurring after gastric surgery. One case of cardiac arrest after BIB placement has been described, which was thought to be secondary to vagal nerve activation caused by stretching of the gastric wall [60]. Oesophagitis has been analysed by Rossi et al. who reported oesophagitis to be present at insertion in 15% and slightly increasing up to 18% with IGB treatment [61]. Therefore, an advice to use PPIs was given. Mathus-Vliegen et al. performed pH measurements and manometry in balloon-treated patients who did not receive PPIs [62, 63]. They studied in a double-blind study two times a 13-week consecutive period. Group 1 had first a sham placement followed by verum balloon and group 2 had twice a verum balloon. The Orbera balloon was filled with 500 mL saline. Impaired lower oesophageal sphincter (LOS) function and increased gastro-oesophageal reflux were observed in one-quarter of the untreated obese subjects [63]. In group 1, weight loss ameliorated manometry and pH values, but subsequent balloon positioning tended to counteract these beneficial changes. In group 2 patients with balloon treatment from the start, the adverse effects on manometry and pH measurements by the first balloon seemed to wear off with prolonged balloon treatment [62, 63]. They ascribed the increased gastro-oesophageal reflux and oesophagitis to increased rates of LOS relaxations by the presence of a balloon with a potential involvement of cholecystokinin A receptors in their triggering [64, 65].

The ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessed the ASGE PIVI thresholds for the Orbera balloon [41]. They reviewed the literature published between January 1988 and December 2014 and found 82 manuscripts for Orbera intragastric balloons. Three RCTs reported the % EWL over a sham or control group at balloon removal, and 17 studies reported % EWL at 12 months, which is 6 months after balloon removal. Fifty-five studies reported the percentage of total body weight loss (% TBWL) at 6 months, three reported % TBWL at 12 months, and two reported % TBWL at 36 months. Sixty-eight studies were used to calculate adverse events and early removal rates.

Based on a meta-analysis of 17 studies including 1638 patients, the % EWL with the Orbera IGB at 12 months was 25.4 and TBWL was 11.3%; this finding was associated with a high degree of heterogeneity. Three RCTs compared % EWL in patients who received the Orbera IGB (n = 131) with a sham or control group (n = 95). The mean difference in % EWL in patients who received the Orbera IGB over controls was 26.9% (95% CI, 15.6–38.2; $P < 0.001$); also this finding was associated with a high degree of heterogeneity. So, the Orbera balloon fulfilled the PIVI criteria for primary treatment of Class II/III obese individuals (BMI >35 kg/m^2) [41]. As to the criteria for non-primary/bridge therapy, the pooled % TBWL after Orbera implantation was 12.3% at 3 months, 13.2% at 6 months and 11.3% at 12 months after implantation [41]. Another criterion for the Orbera balloon to be used as non-primary obesity therapy is the need to perform sufficiently well in patients with a BMI >40 kg/m^2. A metaregression of the efficacy of the Orbera

balloon over a wide range of BMIs showed its efficacy over the whole range and also in high-BMI subjects, thereby fulfilling both criteria for non-primary therapy [41]. A manual review of 68 studies rated the adverse events after placement of the Orbera balloon (Fig. 2.3). Because of accommodation of the stomach to the balloon, abdominal distension and pain, or nausea were frequent side effects, occurring in 33.7% and 29%, respectively. Gastro-oesophageal reflux disease was noticed in 18.3% and erosions in 12.0% of subjects. Early balloon removal occurred in 7.5% [41]. However, early and more aggressive use of proton pump inhibitors, antispasmodic drugs and anti-emetics in the peri- and post-procedural period may allow for a higher rate of balloon conservation [66]. Serious side effects such as balloon migration and gastric perforation were rare, with an incidence of 1.4% and 0.1%, respectively. Four out of eight (50%) gastric perforations occurred in patients who had undergone previous gastric surgeries, a from-the-outset well-known absolute contraindication (Table 2.2). Small-bowel obstruction occurred in 0.3%. Four deaths (0.08%) associated with the Orbera IGB were related to gastric perforation or pulmonary aspiration [41]. So, besides conforming to the criteria for the use as primary and non-primary treatment, the Orbera balloon also fulfilled the safety criteria.

Unfortunately, the committee did not consider the impact on one or more obesity-related comorbidities despite the fact that the safety risk of Orbera was below the threshold value of 5%. So no verdict was given upon the extension to use the Orbera balloon in class I obese individuals (BMI 30–35 kg/m^2).

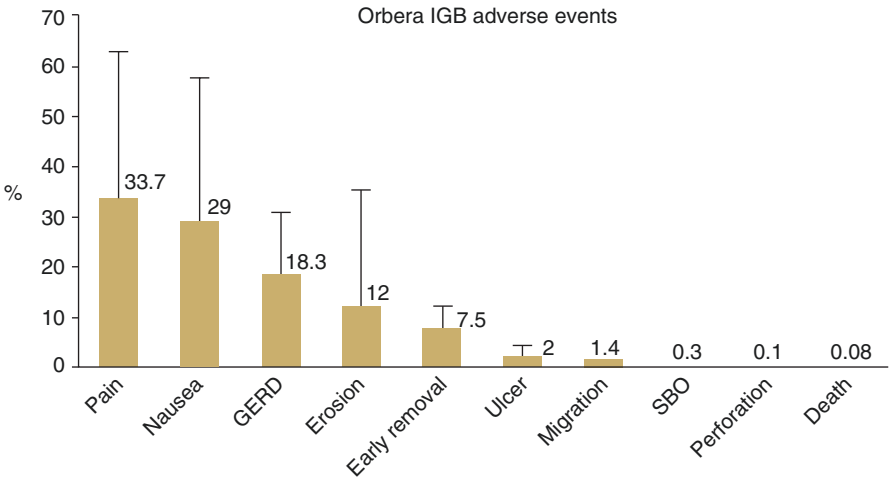


Fig. 2.3 Adverse events with the Orbera balloon as retrieved by a manual review of 68 studies [41]. Reprinted from Gastrointest Endosc 2015; 82: 425–438, ASGE Bariatric Endoscopy Task Force and ASGE Technology Committee. Abu Dayyeh BK, Kumar N, Edmundowicz SA, Jonnalagadda S, Larsen M, Sullivan S, et al. ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies with permission from Elsevier

However, class I obese subjects were included in the approval of the FDA, who approved the Orbera balloon for primary treatment of obesity (BMI 30–40 kg/m^2) in August 2015, thereby, however, excluding the use as non-primary therapy for those with a BMI >40 kg/m^2, making this an off-label use of the device [67]. Also, the FDA did not approve the device for use in successive implantations.

The pivotal US trial for Orbera, a "Randomized, Multicentre Study to Evaluate the Safety and Effectiveness of the BIB IGB System as an Adjunct to a Behavioural Modification Program, in Comparison with a Behavioural Modification Program Alone in the Weight Management of Obese Subjects", known as IB-005, included 225 patients (BMI 30–40 kg/m^2) in a multicentre, prospective, randomised, non-blinded trial [68]. All participants were engaged in a 12-month behavioural modification programme, while 125 patients were randomly assigned to also have the Orbera placed for the first 6 months. At 6 months, weight loss was −3.3% of total body weight (−3.2 kg) in the lifestyle modification arm versus −10.2% (−9.9 kg) in the balloon plus lifestyle intervention arm ($P < 0.001$); at 9 months (3 months after balloon removal), weight loss was −3.4% (−3.2 kg) versus −9.1% (−8.8 kg, $P \leq 0.001$); and at 12 months, −3.1% (−2.9 kg) versus −7.6% (−7.4 kg, $P \leq 0.001$). There were two co-primary endpoints: the achievement of a ≥25% EWL and the achievement of at least 15% EWL over the mean of the control group. Both primary endpoints were achieved. IGB-treated subjects had a mean % EWL of 26.5% where the target was 25% EWL and the lifestyle-treated subjects 9.7%, and 45.6% (36.7–54.8, $P < 0.001$) of IGB-treated subjects achieved at least 15% EWL over the mean of the control group. A ≥10% total body weight loss at the time of device removal (6 months) was obtained by 46% of the IGB and 12% of the control group ($P < 0.001$). At 9 months, 3 months after balloon removal, 41% of IGB and 14% of the control group ($P < 0.001$), and at 12 months, 6 months after device removal, 32% of IGB subjects and 16% of the control group achieved ≥10% total body weight loss ($P = 0.003$). The majority of balloon subjects experienced adverse events of nausea (86.9%), vomiting (75.6%) and abdominal pain (57.5%). The balloon removal rate in 30 (18.8%) was fairly high; eight had their device removed before 6 months because of an adverse event, seven for miscellaneous reasons and 15 on subject request [68]. The rate of serious adverse events (SAEs) in the Orbera US pivotal trial was 10% ($n = 16$), with the vast majority due to hospital admissions for nausea, vomiting, abdominal pain or early device removal, anticipated as a result of the gastric accommodation to the balloon. This is twice as high as the PIVI threshold of ≤5% SAEs [41]. There were no ulcerations and no balloon deflations. Other SAEs included one case of gastric outlet obstruction with diffuse gastritis, one case of gastric perforation with sepsis, one case of aspiration pneumonia, two cases of mucosal oesophageal tears (managed endoscopically) and one case of laryngospasm. All SAEs resolved without sequelae, and there was no mortality. Baseline predictors of % TBWL loss at 12 months revealed to be the % TBWL at 3 months [68]. There were no significant improvements in comorbidities at 9 months compared with the lifestyle group. So, the FDA trial affirmed the results of the PIVI threshold criteria and allowed the Orbera for use as primary treatment in adults with a BMI of 30–40 kg/m^2 for the duration of 6 months [68]. The FDA requires a

comprehensive 12-month weight management programme to be employed with Orbera placement.

Predictors of Weight Loss

Several studies investigated factors predicting a greater weight loss, and apart from the already mentioned % TBWL at 3 months the weight loss in the first month, initial BMI, female gender, adherence to the dietary programme, allocation to balloon treatment and guess, correctly or not, of having a balloon in the double-blind studies, and changes in gastric emptying induced by the balloon predicted a greater weight loss [52, 68–70]. There was no influence of balloon fill volume or balloon location [52]. The influence of fill volume was again studied in a very recent meta-analysis of 44 studies, including 5549 patients [71]. A meta-regression showed no statistically significant association between filling volume and % TBWL at 6 months. When the BMI was investigated in BMI strata, only BMI 40–50 kg/m^2 demonstrated a small significant correlation between fill volume and weight loss. There was a statistically significant, but clinically irrelevant, increase of 0.5% TBWL per 100 mL balloon fill volume ($P = 0.03$). The authors explained the lack of fill volume effect by their observation of the relationship between change in size and change in volume; the diameter of a 400 mL balloon is 9.14 cm, while a 700 mL balloon is only 20% wider at 11.0 cm [71]. Yet, they found an important effect of balloon volume <600 mL versus higher volumes and therefore recommended a 600 mL fill volume; the rate of oesophagitis of 2.4% and the rate of migration of 0.5% were both less with balloons >600 mL versus 9.4% and 2.3%, respectively, with balloons <600 mL [71].

Binge-eating is not always a contraindication but at least it is a predictor of poor results [72].

Improvement of Comorbidities

Weight loss with the BIB resulted in improvement of metabolic abnormalities in serum levels of glucose, insulin, LDL cholesterol, total cholesterol and triglycerides [52]. Other studies demonstrated improvement in liver dysfunction and liver steatosis, insulin sensitivity, diabetes and serum HbA1c, metabolic syndrome, fertility, plasma total antioxidant capacity and obstructive sleep apnoea syndrome and a significant improvement of the quality of life [52, 58, 73–79]. In one centre in Spain, 714 consecutive patients treated with an Orbera IGB in 2005–2007 had a mean BMI loss of 6.5 kg/m^2 after 6 months [80]. The overall complication rate was 4.1%. Comorbidities were resolved in 64 (40%) of the 162 patients with one or more diagnosed comorbidities before start of the treatment [80]. Genco et al. demonstrated in 2515 Italian patients with a BMI of 44.8 kg/m^2 an % EWL of 33.9% or a BMI decrease of 4.9 kg/m^2 with only 0.08% failed balloon insertions [81]. Preoperative comorbidities were present in 56.4% of patients and these resolved in 44.3% of cases and improved in a further 44.8%. Resolution or improvement occurred in 87.2% of the 488 patients suffering from diabetes, in 93.7% in patients with hypertension, 100% in patients with respiratory disorders and 87% in patients with osteoarthritis. Dyslipidaemia resolved or improved in 51.9% [81].

Course of Body Weight and Prevalence of Comorbidities After Balloon Removal

One of the major drawbacks is the limited duration of therapy for only 6 months and weight regain after balloon removal. In the meta-analysis by Imaz et al. two studies provided data on maintenance of weight loss after 1 year of treatment [56]. The 143 patients included in these studies lost a mean of 15.9 kg at balloon removal; 133 patients were followed 1 year after balloon removal and had recovered 6.3 kg, representing 39.6% of the weight lost at removal. Hervé et al. detailed that still 56% had ≥20% EWL at 1 year and Mathus-Vliegen and Tytgat reported that 47% of patients still had ≥10% weight loss 1 year after removal of the balloons after a 1-year active balloon treatment episode, suggesting that some proportion of the weight loss can be maintained for 24 months [52, 82].

Dastis et al. followed a cohort of 100 patients who had received an IGB for 6 months over a period of 2.5 years without a structural weight maintenance programme after balloon removal [83]. Ninety-eight patients completed final follow-up at a mean of 4.8 years. With the IGB they lost 12.6 kg or 38.3% EWL and 63 had a ≥10% body weight loss. After 1 and 2 years of follow-up they had regained 4.2 kg and 2.3 kg or 37% of the lost weight, and ≥10% weight loss was present in 57% and 38%, respectively. After a mean of 4.8 years, 28% had lost ≥10% weight at final follow-up, 35 patients had undergone bariatric surgery and 34 had no significant weight change from baseline. Kotzampassi et al. followed 474 patients after a 6-month balloon positioning [84]. Average BMI before therapy was 43.7 kg/m^2. Success was defined as ≥20% EWL; 83% attained this successful weight loss with an average loss of 23.9 kg and a BMI loss of 8.3 kg/m^2. Out of 395 successful subjects 53%, 27% and 23% maintained a ≥20% EWL after 12, 24 and 60 months, respectively. After 5 years, an % EWL of 17% and a TBWL of 9 kg were observed [84].

The ORBERA pivotal study showed a 7.6% TBWL 26 weeks after balloon removal (12 months after balloon placement) and the AGSE meta-analysis a 11.7% TBWL 18 months after IGB placement [41, 68]. A review to assess the kinetics of weight loss during and after Orbera balloon therapy and the timing of serious adverse events included seven studies that reported weight losses at 3 and 6 months, with two studies reporting body weights monthly [85]. In seven studies, the average weight loss after 3 and 6 months of Orbera balloon therapy was 12.9 kg and 16.0 kg, respectively, indicating that 80% of the weight loss achieved in 6 months of Orbera balloon therapy occurs within the first 3 months. Two studies (253 patients) reported the timing of adverse events related to malfunction and leaking of the Orbera balloon. In one study 49 of the 51 balloons leaked beyond the recommended removal date of 6 months, whereas two occurred before that date [86]. Only two caused a partial large-bowel obstruction and were removed, once by using colonoscopy and once by laparoscopy. The other study reported 15 balloons that leaked: seven occurred in the first 4 months of Orbera balloon therapy, whereas eight occurred after 4 months of therapy [87]. All balloons passed per vias naturales. Nine studies with 547 patients reported weight losses 6 and 12 months after removal and demonstrated a sustained weight loss of 95% and 52%, respectively, of the weight lost during IGB treatment [85]. Similarly, 3 cohorts with 572 patients reported weight

losses at 12 months after balloon removal and 43–68% of the weight loss was sustained [84, 88, 89].

Besides the weight loss obtained and maintained thereafter, the effects on obesity-associated comorbidity and its sustainment are even more important.

Crea et al. followed 143 patients for 1 year after balloon removal [88]. They had lost 6.6 BMI points, 14.1% of total body weight and 29.3% of excess weight at balloon removal. After 12 months these figures were 4.2 kg/m^2, 11.2% TBWL and 26.1% EWL. The prevalence of diabetes, hypercholesterolaemia, hypertriglyceridaemia and hypertension decreased during balloon treatment from 32.6%, 33.4%, 37.7% and 44.9% to 20.9%, 16.7%, 14.5% and 30.4%, respectively, but increased very modestly in the balloon-free year to 21.3%, 18.9%, 17.4% and 34.8%, respectively (Fig. 2.4). The metabolic syndrome kept on declining from 34.8% to 14.5% over the 1.5 years, and the 11.6% maintenance of at least 10% body weight loss was associated with these improvements which agrees with the guideline advices, mentioned before, of obtaining and maintaining a 10% body weight loss [1, 5, 88]. A 3-year follow-up of 261 overweight patients with a BMI of 27–30 kg/m^2 (mean 28.6 kg/m^2) with at least one comorbidity, which could be evaluated from the original group of 349 subjects treated in a multicentre European study, showed that the reported excess weight loss of 55.6% at 6 months was fairly good maintained with a 29.1% EWL at 3 years [90]. Mean %BMI loss was 11.5% and 6.1% at 6 months and 3-year follow-up, respectively. Forty (15%) patients had post-IGB surgery; 172 (66%) patients followed a dietician's plan after removal of the intragastric balloon. The rate of hypertension decreased from 29% at the start to 16% after 3 years, diabetes from 15 to 10%, hyperlipidaemia from 32 to 21% and osteoarthritis from 25 to 13% at 3 years [90]. Even

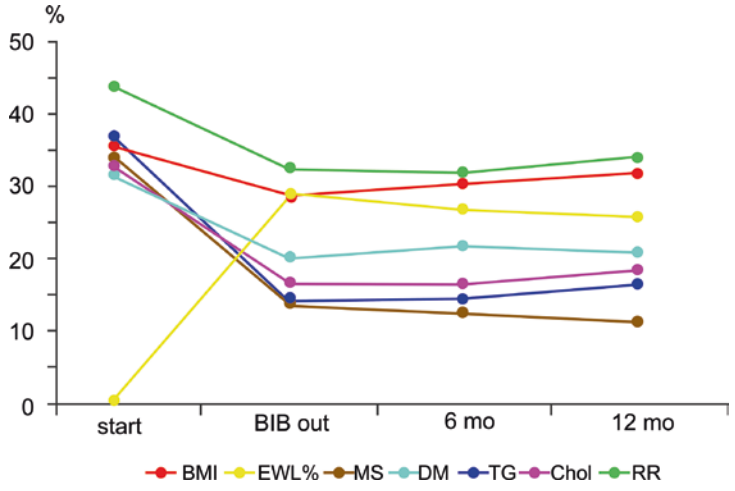


Fig. 2.4 Results obtained 1 year after balloon removal and persistence of effects on body weight and obesity-associated comorbidities [88]. *BMI* body mass index, *EWL* excess weight loss, *MS* metabolic syndrome, *DM* type 2 diabetes mellitus, *TG* hypertriglyceridaemia, *Chol* hypercholesterolaemia, *RR* hypertension

more impressive and clinically very relevant are their 6-year follow-up data of 83 patients who asked for a second or even third or fourth balloon [91]. The "weight cycling" or "yo-yo dieting", a pattern of alternating phases of dieting and relapse, has been the subject of several studies suggesting that increased risks of morbidity and mortality may be associated with fluctuations in weight, although contested by others [92–96]. It is certainly a matter of public concern. Despite their "weight cycling" or "yo-yo dieting", the percentage of comorbidities that resolved or improved at follow-up was 73% for diabetes, 65% for hypertension and 89% for the obstructive sleep apnoea syndrome (OSAS) [91]. No worsened comorbidities were present after 6 years. A significant difference was recorded in the presence of comorbidities at baseline (80% of the patients) and follow-up after 72 months (30%; $P = 0.02$). So, as the authors stated: "Yo-yo dieting may be better than not dieting at all" [91].

Special Subgroups

Special subgroups are important to consider as the FDA approved the Orbera IGB for subjects with a BMI between 30 and 40 kg/m^2 and the PIVI review indicated that the Orbera IGB met both the criteria for primary as well as non-primary treatment [41, 67]. This subgroup analysis is also important as it gives information on patients, usually excluded from studies because of contraindications.

Super-Obese (BMI ≥50 kg/m^2) and Super-Super-Obese (BMI ≥60 kg/m^2) Subjects

Laparoscopic surgery in extremely obese patients is technically complex due to technical limitations of instrument length and reduced ability to reach the angle of His [97]. Large fatty omental tissue is often an obstacle in visualising the stomach and technical difficulties are due to markedly thickened abdominal walls hindering fine laparoscopic movements and control of laparoscopic instruments. Huge ponderous fatty livers are not well retracted by laparoscopic retractors and may result in poor exposure and increased susceptibility to injury. It is honest to say that some surgeons consider such statements exaggerated. The IGB may be used to bridge the time until surgery and to reduce the surgical complications as has been shown by modest proportions of preoperative weight boss (10–20% EWL or 5% weight loss) [98, 99]. Patients with a BMI >60 kg/m^2 obtained a 20–30% EWL with a preoperative balloon [100]. Busetto et al. performed a case-control study ($N = 43/43$) and showed a lower conversion rate, shorter operative time and hospital stay, and a lower rate of band-related and port-related complications after laparoscopic gastric banding after a preoperative 26.1% EWL in balloon-treated patients [101]. In the first phase of weight loss a preferential reduction of visceral fat and a reduction of liver volume are seen, explaining these beneficial results. Frutos et al. showed a 31.8% reduction in liver volume after 6 weeks of IGB therapy [102]. The reduction in liver volume facilitated subsequent laparoscopic gastric bypass [102]. The metabolic effects of 6 months of Orbera balloon placement and a 1000–1200 kcal diet were examined in detail in a prospective trial including 130 patients (average BMI 43.1 kg/m^2) [76]. Premature balloon removal was required in ten patients due to intolerance, abdominal pain or vomiting. The average weight loss of 13.1 kg was associated with a decrease of hyperglycaemia from 50% to 12%, and

hypertriglyceridaemia from 58% to 19%. In patients with a decrease in BMI of greater than 3.5 kg/m^2 a significant and important decrease in the prevalence of severe hepatic steatosis from 52% to 4% was observed [76]. A larger study in 60 consecutive super-super-obese subjects with an average BMI of 66.5 kg/m^2 studied the utility of a balloon as a bridge to gastric bypass [103]. The balloon was placed in 23 patients and remained for a mean of 155 days, while 37 patients went to surgery without prior balloon therapy. The balloon group achieved BMI loss of 5.5 kg/m^2 at the time of the gastric bypass. This resulted in a 55-min shorter operation time and in fewer major adverse events (defined as conversion to laparotomy, ICU stay longer than 2 days and total hospital stay longer 2 weeks): two events versus thirteen events in patients who did not have balloon placement [103]. The effect of BIB on obstructive sleep apnoea has been specifically studied because it poses challenges to the anaesthesiologist during the perioperative period and a nearly complete resolution of sleep apnoea was reported in 17 very obese men (BMI 55.8 kg/m^2) [104]. Spyropoulos et al. treated 26 high-risk super-super-obese patients with a BMI of 65.3 kg/m^2 and at least three comorbidities, who were refused for surgery [105]. One death was related to cardiac arrest after aspiration related to the positioning of the balloon. They lost 22.4% excess weight after 6 months and improved their diabetes and hypertension in 81% and 83%, respectively. From the group of 25 patients 20 became fit enough for bariatric surgery and underwent their operation the day after balloon removal [105]. A systematic review by Yorke et al. which captured studies that reflected the use of IGB only for bariatric specific weight loss, showed a 15.7 kg, 5.9 kg/m^2 and 36.2% EWL before surgery but did not comment on outcomes of subsequent surgery [106].

Coffin et al. disagreed with the salutary influence of balloon-induced weight loss on subsequent bariatric surgery [107]. They performed a prospective randomised multicentre study to compare the impact of a preoperative 6-month intragastric balloon treatment with standard medical care (SMC) in super-obese patients before undergoing laparoscopic gastric bypass [107]. The primary endpoint was the proportion of patients requiring a stay at the intensive care for >24 h and secondary endpoints were weight change, operation time, duration of hospital stay and perioperative complications. The authors calculated a need of randomisation of 314 patients (157 in each group). Due to insufficient enrolment the study had to be interrupted after the inclusion of only 115 patients (BMI 54.3 kg/m^2), of whom 55 had a balloon placement. The proportion of patients who stayed in ICU >24 h was similar in both groups, mean operation time was similar and both groups had a similar hospitalisation stay. At 6 months before the operation, the weight loss in BMI units was significantly greater in the IGB group (2.8 kg/m^2) than in the SMC group (0.4 kg/m^2), and the weight loss occurred mainly in the first 3 months. However, in the end, already at 6 months post-operatively the weight loss was not different anymore. Three severe complications occurred during IGB removal. Five patients had one or more surgical complications, all in the IGB group. Although conclusions may be not well founded because of insufficient numbers, the authors concluded that it is true that IGB insertion before gastric bypass induced weight loss but it did not improve the perioperative outcomes or affect post-operative weight loss.

Some surgeons also warn against balloon therapy prior to surgery. Jones et al. reported a complicated case with stenosis on the second post-operative day after a sleeve gastrectomy, in whom balloon dilation to 18 mm failed to relieve the stenosis and necessitated stent therapy on day 4 [108]. This super-obese patient was treated preoperatively with an intragastric balloon and because the authors had observed that intragastric balloons induced a thickening of the stomach their policy was to wait for an interval of minimally 2 weeks after balloon removal to allow the stomach tissues to decrease in thickness before the operation. This patient refused to wait and therefore the balloon was removed under the same anaesthesia as needed for the sleeve gastrectomy. The first firing with the green staple cartridge failed to close the stomach wall. The procedure was completed using hand-sewn sutures, with a midline laparotomy. They believe that failure of the staple line results from the excessive thickness of the antral stomach where most surgeons would use a green cartridge to initiate the sleeve [108]. The thickness of the stomach wall in this area corresponded to the lower end of the greater curvature of the stomach where the intragastric balloon was seen at endoscopy [108]. Although surgeons often express their fears of either a thickened or a decompensated gastric wall after balloon therapy, a search in the literature did not result in any report on this matter. Two studies examined the removal of balloons in the same setting as surgery [109, 110]. De Goederen–van der Mey et al. removed the balloon at the operation room and proceeded thereafter with a gastric band positioning by laparoscopy without difficulties [109]. Khan et al. investigated 40 consecutive super-super-obese subjects with a BMI 69.3 kg/m^2 which decreased to 62.3 kg/m^2 after 6-month balloon therapy [110]. In an attempt to reduce the number of interventions for these high-risk patients, they decided to offer simultaneous single-stage balloon removal and laparoscopic sleeve gastrectomy to all super-super-obese patients. The only contraindication to proceeding to surgery was the presence of active gastric ulceration. Simultaneous balloon removal and sleeve gastrectomy were achieved in 39 cases; one patient refused surgery. There was no operative mortality, there were no leaks and their new policy appeared safe [110].

IGB as a First Step Towards Bariatric Surgery

The potential role of the IGBs as a psychological bridge to surgery is a matter of debate [73, 89]. Angrisani et al. reported the almost total regain of excess weight 1 year after Orbera balloon removal in patients who had refused any other kind of treatment [89]. On the contrary, IGB therapy facilitated the acceptance of bariatric surgery in 32% of 140 patients who had initially refused surgery but accepted balloon therapy [73]. Bariatric surgery was most frequent in the group that had successfully lost weight with the IGB but then started to regain weight (64%). It was mixed in the group (33%) who had not lost weight and very low (7%) in those who had maintained a successful weight loss during follow-up [73]. Also, Genco et al. demonstrated that in a group of 83 patients who refused surgery and who were offered active guidance with repeat balloon positioning when indicated, 18 patients (22%) requested bariatric surgery after a mean interval of 47.7 months (range 12–72) [91]. They underwent laparoscopic gastric banding (2), laparoscopic gastric bypass (6) and laparoscopic sleeve gastrectomy (10).

Testing of Patient's Eligibility for a Restrictive Surgical Operation: The "BIB Test"

Another potential use is to predict how well a patient will respond to a purely restrictive bariatric procedure; those that lose a significant amount of weight with the Orbera balloon (BioEnterics Intragastric Balloon (BIB), therefore the usual term "BIB test") would, in theory, respond better to surgical procedures that involve gastric volume reduction instead of intestinal bypass [111]. Some surgeons use the balloon as a predictive instrument to single out subjects who would not benefit from gastric restrictive surgery (sweet eaters, snackers, grazers, compulsive eaters and binge-eaters). A BIB test is positive when >10 kg weight is lost with the Orbera balloon. Loffredo et al. tested whether patients with a positive BIB test appeared eligible for a restrictive procedure or when the BIB test is negative a malabsorption procedure had to be considered [87]. Indeed, following a previously positive BIB procedure a significant further weight loss for more than 6 months after laparoscopic gastric banding (LAGB) was reported. De Goederen-van der Meij et al. tested this prospectively in 40 patients who underwent Orbera IGB therapy for 6 months followed by laparoscopic adjustable gastric banding [109]. Successful treatments were defined as ≥10% baseline weight loss with the balloon and a further weight loss of ≥15% with surgery. They found that the BIB test had a mixed predictive value for further weight loss with gastric banding (positive and negative predictive values of 56% and 73%, respectively). The final weight loss was higher in patients with successful versus unsuccessful IGB therapy (12.4 vs. 9.0 kg/m^2 at 18 months, respectively, $P < 0.05$). Genco et al. divided 1357 patients in a successful IGB group A (≥25% EWL, $n = 699$) and in a less successful IGB group B (<25% EWL, $n = 658$) [112]. During subsequent surgery there were significant differences between group A and B: group B had longer mean operation time, more complications, more often difficult anatomy, more perioperative bleedings, more conversion and lengthier hospital stay. After 1, 3 and 5 years the differences in BMI and % EWL observed at the time of balloon removal persisted, and patients with good results after intragastric balloon treatment gain an advantage in terms of BMI and % EWL in the short and medium terms [112].

Consecutive Balloons

The restricted duration of therapy, i.e. 6 months, the main limitation of the treatment, might be overcome by successive balloons. Dumonceau et al. studied 118 patients treated with an IGB in a prospective non-randomised study over a period of 5 years [113]. Nineteen patients (16%) asked for a repeat IGB to prolong their first treatment ($n = 8$) or after a balloon-free interval of 16.4 months ($n = 11$) in which they regained 13.6 kg on average. The repeat balloon fill was 100 mL greater than the initial fill. Compared with subjects with a single treatment ($n = 99$), those with repeat treatment ($n = 19$) had greater weight loss in kilograms at 1 year (12.0 kg vs. 6.0 kg) and in excess weight loss (40.9% vs. 20.8% EWL; $P < 0.008$), but the difference became less than 2 kg starting at 3 years and the effect of a second balloon placement dissipated by the third year of follow-up [113]. They lost less weight with the second balloon (9.0 kg vs. 14.6 kg, or 18.2% EWL vs. 49.3% EWL) when compared with the first balloon, and had a trend towards more complications.

Dumonceau et al. found this strategy of repeating balloon therapy disappointing, as 3 years after removal of the first balloon weight loss curves and proportions of subjects with ≥10% baseline weight loss were almost identical for subjects treated with a single or repeat balloon [113]. Lopez-Nava et al. studied 714 patients who underwent IGB placement: 112 had a second IGB placement after an interval of 1 month [80]. A second balloon could be positioned without difficulties and after a second balloon patients continued to lose weight though not at the same rate as with the first balloon, an average BMI loss of 2.5 kg/m^2 with the second balloon in addition to BMI loss of 6.5 kg/m^2 with the first balloon. Genco et al. randomised patients to two groups: IGB for 6 months followed by diet therapy for 7 months (group A, $n = 50$) and IGB for 6 months followed by a second balloon after 1 month, for again 6 months (group B, $n = 50$) [114]. The 1-month period between the two balloons was to allow the stomach to restore to pre-IGB placement conditions and to reset the normal motility of the stomach before repeating therapy to provide further weight loss. In that intermediate month, both groups gained 0.9 BMI units in weight. After removal of the first balloon weight loss parameters were not different: % EWL 43.5 and 45.2 and BMI 34.2 and 34.8 kg/m^2, respectively, for group A and group B [114]. At the end of the13-month study, weight loss parameters were significantly more beneficial in patients who underwent consecutive balloons in group B: BMI 30.9 kg/m^2 and % EWL 51.9% versus 35.9 kg/m^2 and 25.1% in group A [114]. A second balloon achieved good results with continuing weight loss. A similar investigation by the same group was done in 50 patients with eating disorders not otherwise specified (EDNOS) [115]. At the end of 6-month balloon treatment, the BMI in both groups decreased with 8 kg/m^2. The eating scores did not differ at the outset and decreased to a similar extent in groups A and B. At the end of 13 months BMI was significantly more reduced in group B by 11.9 kg/m^2 versus 7.5 kg/m^2 in group A [115]. Also, the consecutive balloon positioning in group B significantly reduced scores for grazing, emotional eating, after-dinner grazing and sweet eating when compared with group A. Two consecutive balloons demonstrated significant advantage over a single procedure in terms of influencing EDNOS [115]. One of the longest term studies was performed in the Netherlands in 2005 [52]. Forty-three patients were enrolled in 2-year study. Patients in group 1 had an Orbera balloon placed for an initial 3 months followed by replacement at 3-month intervals for three more occurrences (12 months total and four balloons). Group 2 had an initial sham procedure followed by balloon placement every 3 months for three occurrences (12 months total and three balloons). Both groups were subsequently followed up for a second year to assess weight loss maintenance. Although more than 40% of patients achieved greater than 20% total body weight loss in group 1 (four balloons) at 1 year, this was similar to group 2 (three balloons). At 2 years, 60% of the weight loss was maintained [52]. The IGB does seem to have a legacy effect for up to a year with some persistent weight loss (perhaps due to changed dietary habits and behaviour), so repeated therapy may become the most common paradigm for this device to maintain a long-term effect.

A very long-term study with follow-up of 6 years was published by Genco et al. [91]. Eighty-three patients with a BMI >40 kg/m^2, good candidates for surgery but

refusing it, were enrolled in a clinical treatment protocol allowing multiple intragastric balloon placements. The protocol was such that a second balloon was placed when the patients had regained ≥50% of the weight loss achieved with the previous balloon. After the first balloon removal, patients were encouraged to maintain the weight by physical exercise, diet and, if needed, psychological support. A dietician was involved who gave a specific low-calorie diet to all. With their first balloon patients decreased in weight from a BMI of 43.7 to a BMI of 35.9 kg/m^2. Every patient asked for a second balloon placement after a mean of 12 months (range 1–55); 18 patients (22%) had a third device placed and 1 (1.2%) patient had a fourth device placed. Although they initially refused surgery, after a mean interval of 47.7 months (range 12–72), 18 patients (22%) requested and underwent bariatric surgery. Only three patients were lost to follow-up (4.1%). After the first balloon treatment, their BMI went up from 35.9 kg/m^2 to 37.9 kg/m^2, and at the end of second IGB treatment, mean BMI was again down to 34.8 kg/m^2. At 76-month follow-up, mean BMI was 37.6 kg/m^2. Apart from the earlier mentioned significant improvement in comorbidity despite this weight cycling or yo-yo dieting, they also experienced a far better quality of life [91]. Obesity is a chronic disease and the authors showed that physicians must be prepared to provide long-term guidance and treatment and the authors must be congratulated for doing so. It would have been nice to have a cost-benefit analysis of such an approach.

Miscellaneous Indications

There are some subgroups that should have been excluded based on the exclusion criteria but were examined to justify these criteria.

(a) Eating disorders: Apart from the above-mentioned study in eating disorders by Genco et al. [91], Puglisi et al. investigated the effect of treatment in patients presenting with binge-eating disorders (BED) [72]. The degree of BMI reduction was significantly less in BED patients (3.3 vs. 5.7 kg/m^2), the BED group requested more often early balloon removal and complications and failure were statistically higher than in the non-BED group, suggesting that the presence of binge-eating disorder is a negative predictive factor for treatment success.

(b) Depressed patients: Often, depressed patients are excluded from pharmaceutical trials and sometimes also do not pass the psychological screening before bariatric surgery. Many antidepressants are associated with weight gain [5]. Therefore, the study by Deliopoupou et al. was urgently needed [116]. A hundred consecutive female patients, characterised as depressed (65 patients) or non-depressed (35 patients) using the Beck Depression Inventory score, were treated with Orbera balloons. The weight loss was similar between groups (39.3% EWL in depressed patients vs. 36.1% EWL in non-depressed patients) and the Beck Depression Inventory score improved from 20.3 to 7.9 during balloon therapy. Resolution of depression occurred in 70.8% of the depressed patients, with a decrease in the prevalence of severe depression (from 27.7% to 1.5%), so demonstrating significant mental health benefits and refuting the customary exclusion of depressed patients.

(c) Overweight subjects (BMI 27–30 kg/m^2) with at least one comorbidity: A retrospective study in 261 subjects showed a decrease in BMI from 28.6 to 25.4 kg/m^2 after 6 months, which after 3 years was still lower than at the start (BMI 27.0 kg/m^2) [90]. Psychological disorders decreased from 54 to 13% at 6 months. The proportions of patients with diabetes, hypertension, dyslipidaemia and osteoarthritis were all reduced to one-third and one-half. The finding that many patients maintained the weight loss achieved by the 6-month balloon treatment in the medium term (3 years) suggests that intragastric balloon therapy can be used, in combination with other treatments, as part of a strategy for preventing the progression of overweight to obesity. It may well be that disordered alimentary behaviours and comorbidities are not as deeply rooted in overweight patients as in obese patients and that these may have greater potential for reversal.

Combined Treatments

Though sibutramine (a centrally acting serotonin-norepinephrine reuptake inhibitor) has been withdrawn from the market due to increased risk for cardiovascular events, the addition of sibutramine has been shown to augment the weight loss effects of IGB, providing a rationale for additive benefits of pharmacotherapy in conjunction with IGBs [117, 118]. Dargent et al. investigated the four-quadrant injection of hyaluronic acid, an absorbable filling agent similar to collagen, which is genetically bioengineered, non-allergenic and currently widely used in cosmetic surgery, at the gastro-oesophageal junction as an adjunct treatment before or after balloon placement and compared this with a balloon-only group [119]. A combined treatment was significantly more effective than single-balloon treatment (at 18 months a BMI loss of 2.8 BMI units vs. 1 BMI units, $P < 0.05$). The treatment that started with hyaluronic acid was inferior to the two groups that started with balloons (balloon-only group or balloon followed by hyaluronic acid after 6 months). Injection of hyaluronic acid after an intragastric balloon, which seemed to be the preferential order, was hampered by food stasis on top of the balloon and at the gastro-oesophageal junction and resulted in a liver abscess in one patient. Dargent et al. did not recommend to add hyaluronic acid to the treatment with balloons [119].

Comparison with Surgery

Orbera balloons have been compared with controls, receiving either no therapy or sham treatment or some form of lifestyle intervention with a diet, exercise, behavioural therapy or a combination of these. It might be interesting to see how they perform when comparing with surgery. There are two retrospective studies comparing IGBs with sleeve gastrectomy and one prospective study [120–122]. Peker et al. compared prospectively 1 year of IGBs (so two connected periods of 6-month balloon treatment, $n = 16$) with 1 year of laparoscopic adjustable gastric banding (LAGB, $n = 16$) [120]. Although the % EWL (39.3% vs. 32.3%) and % excess BMI loss (% EBMIL) (47.1% vs. 36.3%) after the first 6 months were more

encouraging in the IGB patients compared with LAGB patients, it was not statistically significant. But at the 12-month period, when the IGB treatment is completed, the % EWL (57%) and % EBMIL (70%) were significantly higher in favour of the IGB group ($P = 0.023$, and $P = 0.011$, respectively). They reported no complications in either group over the 12-month treatment period [120]. The authors suggested that two consecutive IGB applications may be offered to obese patients who do not feel ready for surgery. After 18 months, when the continuous effect of LAGB on food intake restriction continued and the IGB group did not have any restricting device, the % EWL and % EBMIL parameters were similar for LAGB and IGB [120]. So, consecutive IGB applications are feasible and apparently more efficient for weight loss, at least in their hands, in comparison to the LAGB at the 12-month period.

The two retrospective studies compared sleeve gastrectomy with IGB. Milone et al. compared their own 20 patients with a sleeve gastrectomy (SG) in the USA with 57 patients as a historical group who had their balloons placed in Germany and Italy [121]. There were no complications for patients undergoing the SG. For patients undergoing IGB, four patients (7%) had the balloon removed due to intolerance. Body weight loss was significantly better for the sleeve group with 45.5 versus 22.3 kg, 35% versus 24% EWL and change in BMI with 16 versus 8 BMI units. Weight loss decreased comorbidities in 90% of patients after both procedures. Milone et al. suggested that sleeve gastrectomy may be a superior procedure compared with IGB as a first stage for super-obesity [121]. In their clinic, treatment for super-obese subjects ≥60 kg/m^2 consists of an initial sleeve gastrectomy, followed 6–12 months later by a definitive biliopancreatic diversion with duodenal switch, and this study did not change their practice. Genco et al. compared data from their own department and performed a case-control study with two IGB cases for one sleeve gastrectomy case [122]. Mortality, intra- and post-operative complications in SG group, and complications during endoscopy and in the 6 months thereafter in IGB group were absent. BMI at baseline was 54.1 kg/m^2 and 54.8 kg/m^2 in IGB and SG patients, respectively (NS). At 6-month follow-up, mean BMI was 46.2 kg/m^2 and 45.3 kg/m^2 in the BIB and SG patients, respectively (NS). After 12 months, IGB patients were 6 months without a balloon and had to comply with a strict diet regimen and regained weight, while SG patients continued to lose weight. Despite this, at 12-month follow-up, the mean BMI was still not significantly different with 48.1 kg/m^2 and 43.1 kg/m^2 in BIB and SG groups [122]. So, BMI values were not different and also there were no significant differences between the groups as far as comorbidities are considered. Both groups had a similar failure rate: 2/40 SG and 4/80 IGB patients did not achieve a weight loss ≥10% TBWL. In contrast to Milone, Genco et al. concluded that laparoscopic sleeve gastrectomy and intragastric balloon are both valid options for producing weight loss as a first-step procedure in super-obese subjects [122].

Other Intragastric Balloon Types

Spatz Adjustable Balloon System (ABS) (Spatz FGIA Inc., Great Neck, NY, USA)

The Spatz Adjustable Balloon System (ABS) is a spherical silicone balloon filled with 400–800 mL saline with an anchor to prevent migration and a filling tube

(Table 2.4, Fig. 2.2c). One of its key advantages is the ability to adjust the balloon volume, tailoring it to the tolerance of the patient with a decrease in volume in case of intolerance, and to the weight loss with an increase in volume in case of regain of appetite or halting of weight loss. For placement the sheath containing the balloon is fixed with a releasable rubber tape on the tip of the endoscope which ruptures upon balloon inflation. Also removal is by endoscopy. The balloon is adjustable by extracting outwards the fill tube by endoscopy. It is allowed to stay for 12 months. Weight losses are comparable to or slightly better than with the Orbera balloon, although RCTs are missing. In a case-control study, twice as many Orbera IGB subjects who received two balloons to cover the 12-month period were compared with subjects having the ABS for 12 months [123]. At the end of the study weight loss parameters were similar (EWL 55.6% vs. 56.7%, respectively, for Orbera and Spatz balloons). Complications were more frequent in the ABS group in 7 out of 40 (14.5%) of whom 6 needed balloon removal [123]. These complications consisted of migration (4), anchor system rupture (1), deflation (1) and an asymptomatic ulcer (1). In the Orbera IGB there were two complications of intolerance (2/80, 2.5%) [123]. The two open studies which reported on 91 subjects showed a 45.0–48.8% EWL at 52 weeks [124, 125]. Adjustments for intolerance were needed in 17.6% and for weight gain or stabilisation in 67%. Intolerance and physical problems were encountered in 10 (11%) and balloon- or tube-related problems in 11 (12.1%) patients; a total of 5 (5.5%) needed surgery. These previous generations of Spatz adjustable balloons had significant weight losses of up to 20% TBWL over 12 months, but had complications related to the design of the device. The Spatz 3 is the most recent generation of the balloon, which overcomes many of the shortcomings of the previous designs. It is currently being used in a pivotal multicentre randomised trial in the USA to support its regulatory approval in the country.

Silimed Gastric Balloon (SGB) (Silimed, Rio de Janeiro, Brazil)

This spherical silicone balloon is advanced by scope traction, rolled up inside a thin silicone sheath, anchored to the top of the endoscope with a snare. It is filled with saline 650 mL, contrast dye 20 mL and methylene blue 10 mL (Table 2.4). For removal the balloon is punctured by a specially developed catheter containing the needle and used also to empty the balloon. The balloon is grasped by a polypectomy snare and pulled and held in an overtube and withdrawn as an entire system. Carvalho et al. performed 2 studies in a total of 71 patients [126, 127]. Weight losses were 8–10 kg or 3.1–3.9 BMI points. Thirteen patients (18.3%) did not tolerate the balloon and there were four deflated balloons (5.6%).

MedSil Intragastric Balloon (MedSil, Moscow, Russia)

The MedSil Intragastric balloon is very similar to the Orbera balloon with a similar introduction sheath and filled with saline between 400 and 700 mL (Table 2.4). A small study with 22 patients reported an 18.4 kg and 5.5 BMI units weight loss, the % EWL was 26.3% and the % EBMI loss was 26.3% [128]. Fasting glucose did not change but HbA1c was significantly reduced. The authors also measured a whole battery of adipokines and found decrease in leptin levels and no change in levels of

adiponectin, angiopoietin-like protein 3 (ANGPTL-3), angiopoietin-like protein 4 (ANGPTL-4) and fibroblast growth factor 19 (FGF19). Fibroblast growth factor 21 (FGF21) decreased significantly after 6 months. Ghrelin was significantly increased after 3 and 6 months. They measured the body composition by DEXA after 6 months and found a decrease in fat mass of 11.3 kg but also a fairly high decrease in fat-free mass of 5.3 kg [128]. There were no complications at placement or removal of the balloon and no complications during balloon stay except from transient gastrointestinal complaints in the beginning.

Intragastric Balloon Types with Unknown Status

Some intragastric balloons are under reconstruction or reconsideration or did not provide further studies, so their status was considered as unknown. Attempts at contacting the companies were fruitless.

Heliosphere Bag (Helioscopie Medical Implants Company, Vienne, France)

The Heliosphere Bag consists of a double-bag polymer balloon covered with a silicone envelop which is inflated with 840–960 cm^3 of air which gives the final volume of 650–700 cm^3 of air as air is compressed (Table 2.4). Two RCTs compared the Heliosphere Bag with the Orbera IGB and both studies showed a better tolerance of the Heliosphere Bag due to differences in balloon weight (500–800 g for the Orbera IGB filled with fluid, 30 g for the Heliosphere Bag) [129, 130]. Weight loss was similar for both balloon types. However, one of the studies was stopped prematurely for safety reasons [129]. A non-randomised study compared Heliosphere Bag in 13 patients (BMI 45.0 kg/m^2) with the Orbera balloon in 19 patients (BMI 45.6 kg/m^2) who failed after 6 months of medical and dietary weight loss therapy [131]. The Orbera balloon was more effective, with weight loss of 19.0 kg versus 13.0 kg with the Heliosphere Bag (38% EWL vs. 21% EWL, $P = 0.01$). One patient with the Orbera balloon required removal for persistent nausea and vomiting at 1 month. One patient died (3.1%) of cardiac arrest due to aspiration at day 13 after Orbera balloon placement. In the largest published study, which included 82 consecutive patients with a median follow-up of 182 days, 70% of patients with the Heliosphere Bag achieved more than 10% body weight loss [132].

Six studies with reports on 189 Heliosphere Bag-treated patients showed a system failure at positioning in 7.4%, a high rate of spontaneous deflation in 11.1% and a difficult extraction of the balloon in 35.4% with difficulties to pass the cardia and upper oesophageal sphincter because of the large size, rigidity and low pliability that needed surgery in two and rigid oesophagoscopy in three [129, 130, 132–135]. The balloon was discontinued because of high system failure at positioning, high rate of spontaneous deflation and difficult extraction. Upon contact with the company, the company mentioned a new balloon product, distributed ad promoted in 52 countries, without further providing details or scientific studies.

Semistationary Antral Balloon (SAB) (JP Industria Farmaceutica S.A., Ribeirao Preto, Sao Paulo, Brazil)

This is a pear-shaped silicone balloon with a conical pole oriented to the pylorus and here fixed to a 30 cm silicone duodenal stem and a 7 g counterweight at the tip

designed for anchoring the balloon in the antrum (Table 2.4). The balloon is filled with 150–180 mL saline. The mechanism of action is somewhat different from the other balloons and hypothesised to act through intermittent occlusion of the pyloric opening, prolonged gastric emptying and stimulation of the antroduodenal satiety receptors. Twenty-six patients received the device for 4 months and lost 6.5 kg [136]. In four the balloons deflated spontaneously, were expelled rectally in two and retrieved endoscopically in the stomach in one and once it had to be removed surgically. The design looks very similar to the transpyloric shuttle discussed later.

Adjustable Totally Implanted Intragastric Prosthesis ATIIP–Endogast (Districlass Medical S.A., France)

The ATIIP-Endogast balloon is an air-filled balloon of polyurethane material, filled with 210-330 mL of air and by a percutaneous endoscopic gastrostomy procedure, followed by a surgical procedure for the placement of subcutaneous stainless steel chamber that is connected with the balloon, avoids its dislocation and enables adjustment of balloon volume by accessing the chamber by needle puncture similar as being done with the adjustable gastric band in LAGB procedures (Table 2.4). Besides the contraindications mentioned in Table 2.2, the contraindications for gastrostomy placement are operative. The mechanism of action is different; it is positioned proximally in the gastric fundus-corpus area. This proximal gastric positioning is aimed at affecting various control processes such as gastric accommodation, electrical activity and neurohormonal mechanisms to enhance satiety. The only publication dates back to 2007. A multicentre study in 57 patients showed a good tolerance without vomiting [137]. The main complications were early local infection related to PEG placement in seven (12.2%), one with a severe subcutaneous infection which required removal of the prosthesis, and late port erosions in three (5.2%). A symptomatic pneumoperitoneum occurred in three, treated conservatively. Weight losses were 7.4 BMI points (22.3% EWL) at 3 months in 40 patients and 12.2 BMI points (39.2% EWL) at 12 months in 20 patients.

Dual Balloons

The ReShape Duo Balloon (ReShape Medical, San Clemente, CA, USA)

The Integrated Dual Balloon System or ReShape Duo balloon consists of two silicone spheres attached to each other (Table 2.4, Fig. 2.2b). The system is inserted over a guidewire introduced by endoscopy. They are separately filled with saline and independently sealed. The ReShape Duo is designed to maximise space occupation in the stomach and is filled with an evenly distributed volume of 900 mL of saline, 450 mL in each balloon, with the advice to fill with less saline (375 mL) in females less than 1.64 m (64.5 in.) in height. The proximal balloon sits high in the fundus which might contribute to early satiety. The dual balloon design provides significant protection against deflation-related complications. If one balloon deflates the second balloon will maintain the device in the stomach. Another hypothesis is that because the shape of the dual balloon is better adapted to the gastric silhouette, impaction should be avoided and tolerability be improved. The first prospective trial of the ReShape Duo included 30 patients in a 2:1 randomisation ratio at three centres (21 ReShape Duo vs. 9 controls) [138]. Both groups received diet and exercise

counselling. Four of the 21 ReShape Duo patients were admitted for nausea, and two patients were found to have gastritis at the time of balloon removal. Percentage of excess weight loss (% EWL) at device removal (6 months) was 32% in the treatment group compared with 18% in the controls. After 48 weeks, almost 6 months after balloon removal, 30% of the ReShape Duo patients remained at 25% EWL versus 25% of the control patients [138]. Lopez-Nava et al. performed a similar study in Spain in 60 patients with a BMI of 38.8 kg/m^2 [139]. After 6 months, a decrease in BMI with 6.1 units, in total weight of 16.6 kg, and a 15.4% TBWL and 47.1% EWL were obtained without any difference in weight loss between different grades of obesity, age or sex. Morbidly obese patients demonstrated a greater total body weight loss, and women and less obese subjects obtained higher excess weight losses. There was one early removal for patient intolerance, one early deflation without migration and one gastric perforation. Fourteen patients had small, clinically insignificant ulcers or erosions noted at the time of removal but the study was conducted with the first design device, before modification of the balloon [139].

The pivotal study in the USA, the REDUCE study ("A Prospective, Randomized Multicentre Study to Evaluate the Safety and Efficacy of the ReShape Duo Intragastric Balloon System in Obese Subjects"), included a total of 326 patients, randomly assigned to a treatment (n = 187) or sham endoscopy group (n = 139) [140]. Both groups were followed up for an additional 6 months after balloon removal to determine weight loss maintenance. The sham group was given the option of device placement during this second 6-month follow-up period. The primary endpoints in this study were the achievement of at least 25% EWL by the treatment group and a significant difference in % EWL versus diet and lifestyle modification. Both of these primary endpoints were met, as the treatment group achieved a significantly higher % EWL of 25.1% and the sham group 11.3%. The % TBWL was 7.6% in the balloon and 3.6% in the sham group. The mean % EWL dropped to18.8% 24 weeks after balloon removal. Statistically significant improvements of comorbid conditions were also seen in the intervention group, including decreases in HbA1c, systolic blood pressure and serum lipids which persisted in the additional 6 months after removal. There was a 15% rate of early removal for device intolerance including nausea and abdominal pain [140]. Although 6% of patients experienced a deflation, there were no balloon migrations due to the presence of two independent balloons. An initial frequent finding was gastric ulceration, which was observed in 39.6% of balloon patients, even in the presence of mandatory PPI therapy. In only one patient this was clinically relevant because of a bleeding ulcer at the gastro-oesophageal junction requiring transfusion. After modifications in the balloon design the ulcer frequency declined to 10.3% and ulcer size diminished from 1.6 to 0.8 cm. Severe adverse events, apart from the bleeding ulcer, were one oesophageal mucosal tear treated with clips, one oesophageal perforation treated conservatively with antibiotics, and one post-retrieval aspiration pneumonitis. The device placement was successful in 99.4% and the retrieval of the balloon in 100% with short procedure times [140]. The ReShape Duo is FDA – approved for adults with BMI of 30–40 kg/m^2 and one or more obesity-related comorbidities and for the duration of 6 months [141].

Orally Ingested Intragastric Balloons

In the search for minimally invasive placement and removal of intragastric balloons there was an intensive search for balloons that could be ingested orally without the need of endoscopy. Endoscopy and conscious sedation or anaesthesia used for placement and removal can lead to adverse events in an overweight or obese individual and significantly add to the cost. Moreover, endoscopic removal of balloons can be unsafe and patients incur risks of aspiration pneumonitis or mechanical damage of the stomach or oesophagus. Finally, endoscopic balloons that have not been removed from individuals who were lost to follow-up have been reported to migrate into the intestines and to cause bowel obstruction. Even though the available balloons can be inserted under fluoroscopy, they still need an endoscopy for removal and the challenge here is to also eliminate the removal endoscopy. One potential concern regarding a swallowed balloon is the absence of a screening endoscopy prior to balloon placement and the lack of ascertainment of mucosal damage by the balloon upon balloon removal. Therefore, the study by Mathus-Vliegen in 303 patients in an attempt to answer the question "Is Endoscopy Really Necessary for Placing Intragastric Balloons?" is clinically relevant [142]. She demonstrated that a careful history can identify patients who may have contraindications for balloon therapy and that balloons can be placed safely under fluoroscopy after taking a careful history without screening endoscopy. As far as the most important exclusion criterion, i.e. hiatal hernia, is concerned, X-ray with contrast was actually more effective in identifying small anatomical abnormalities such as hiatal hernia. Moreover, screening endoscopy was not useful in predicting balloon intolerance or potential complications [142].

Obalon Intragastric Balloon (Obalon Therapeutics, Carlsbad, CA)

The Obalon intragastric balloon is a 250 mL, gas-filled balloon (Table 2.4, Fig. 2.2d). The balloon is compressed, folded and fitted in a large porcine gelatine capsule that has to be swallowed and that is attached to a slender tube that allows filling of the balloon after fluoroscopy has verified that the capsule has entered the stomach. The gelatine dissolves, freeing the balloon. The catheter is connected to a dispenser that contains a can filled with nitrogen-sulphur hexafluoride gas mixture to inflate the balloon controlled by a pressure gauge. The balloon contains a self-sealing valve that closes upon detachment and removal of the tube. If the balloon is tolerated, a second balloon can be swallowed at 4 weeks and a third balloon at 8 weeks. Upper endoscopy is still needed to puncture and remove the balloon(s). It should be noticed that unique contraindications for the gas-filled balloons are scuba diving and travel in unpressurised airplane cabins [38]. The Obalon website mentions that one should not live 1200 m (4000 feet) higher or 760 m (2500 feet) lower than the physician placing the balloons.

Seventeen subjects (BMI between 27 and 35 kg/m^2) ingested a first balloon, 16 a second balloon and 10 a third balloon; 98% of balloons were swallowed successfully [143]. Weight loss after 12 weeks was 5 kg, 36.2% EW and 2.5 BMI units. All balloons were removed successfully by endoscopy at 12 weeks.

In a US pivotal multicentre randomised blinded clinical trial (SMART trial: "Six Month Adjunctive Weight Reduction Therapy"), including 387 subjects who all underwent moderate-intensity lifestyle modification (n = 185 in the Obalon capsule arm, n = 181 in the sham capsule arm), two co-primary endpoints were defined: the difference in mean percent total body weight loss (% TBWL) between the treatment group and control group, and a responder rate, defined as ≥5% TBWL, achieved in ≥35% of participants [144, 145]. The TBWL was 6.81% and 3.59% in the treatment and control groups, respectively, at 6 months from first balloon insertion (three balloons inserted at 0, 3, 9 or 12 weeks) accounting for a difference of 3.23% TBWL (P = 0.0338) [33, 38, 144]. The responder rate was 64.3% and 32.0% in the treatment and control groups, respectively, so both co-primary endpoints were met. Significant improvements in systolic blood pressure, fasting glucose, LDL cholesterol and triglycerides occurred in the treatment group but not the control group. No unanticipated device events occurred. Adverse events, mostly due to accommodation of the stomach such as abdominal cramps and nausea, occurred in 89.9% of subjects and 99.7% of these complaints were rated as mild or moderate. One case of gastric ulcer was seen as ulcer in a patient concomitantly taking non-steroidal anti-inflammatory drugs against study protocol [144]. The Obalon system was approved by the FDA in September 2016 for BMI 30–40 kg/m^2 [145]. Note that the Obalon is indicated in Europe for use at a lower BMI than other IGBs (at 27 kg/m^2 as opposed to 30 kg/m^2) [38].

Elipse Swallowable Balloon (Allurion Technologies Inc., Natick, MA, USA)

The Elipse is a swallowable fluid-filled balloon (Table 2.4, Fig. 2.2e). This is not truly an *endoscopic* bariatric therapy device as it does not require endoscopy for placement or removal but endoscopic facilities should be available in case of unforeseen problems or an early request of removal. The balloon is covered in a biodegradable vegetal capsule and is fixed to a slender flexible tube. Once the balloon is swallowed, its placement is confirmed via X-ray or ultrasound and then inflated with 550 mL of fluid, and while the self-sealing valves close the catheter is removed through the mouth. This device is designed to decompress spontaneously after a planned period of 4 months. During gastric residence, a resorbable material inside the balloon degrades. The resorbable material must completely degrade before a release valve opens and allows the balloon to empty instantaneously and to pass out through the stool. Eight Elipse devices used in a proof-of-concept pilot study were swallowed without the need for endoscopy and all passed uneventfully [146]. Twice an endoscopy was needed: once to puncture the balloon with a needle and forceps because of intolerance and once to puncture a balloon that appeared to be partially collapsed on ultrasound after 11 days. Both were left in the stomach and passed spontaneously per rectum. A recent prospective, open-label, observational study in 2 European centres with 34 patients (mean BMI 34.8 kg/m^2) reported a 10% TBWL and a 3.9 kg/m^2 reduction in BMI units at 4 months in the 25 patients (BMI 34.4 kg/m^2) who completed the study [124]. Reductions in HbA1c, systolic and diastolic blood pressure were statistically significant. In these patients, the mean residence time of the balloons was 117 days. Of the 34 patients included, 6 received an

experimental balloon, and of the remaining 28 patients 3 required endoscopy, 2 patients requested endoscopic deflation owing to intolerance and in 1 patient the capsule did not enter the stomach and remained at the lower oesophageal sphincter. All 34 balloons passed in the stool (88%) or through emesis (12%) [124]. No serious adverse events occurred and expected balloon-related gastrointestinal adverse events, mainly rated as mild, occurred in 86%, such as nausea (54%), vomiting (64%) and abdominal pain (25%). Other complaints consisted of constipation (18%), diarrhoea (14%) and gastro-oesophageal reflux (11%) despite twice-daily 20 mg omeprazole. Importantly, a combination of ondansetron and the NK1 antagonist aprepitant dramatically decreased the side effects associated with balloon therapy [124]. A pivotal randomised multicentre trial to support regulatory approval is currently being planned in the USA.

Orally Ingested Balloon with Unknown Status

Ullorex Oral Intragastric Balloon (Obalon Therapeutics Inc., Carlsbad, CA)

Already in 2007 preliminary results with an orally ingested balloon were published but since then no further studies could be retrieved. The idea is very similar to that of the Elipse balloon. The Ullorex is a large capsule that is injected with citric acid and swallowed within 4 min. A carbon dioxide generator in the balloon uses the injected citric acid to release CO2, which after a 4-min delay slowly inflates a 300 cm^3 round balloon. Two capsules can be swallowed to achieve a volume of 600 mL. The balloon has a plug that is degraded by stomach acid over 25–30 days. This causes the balloon to deflate spontaneously and pass harmless in the stools. A feasibility study was performed in 12 obese subjects, who swallowed up to three balloons at a time [147]. Participants who received the balloon lost 1.5 kg more weight than sham-treated subjects over 2 weeks. It is unclear what prevents the capsule from passing through the pylorus into the small bowel before full inflation, and there are concerns about unintended expansion within the oesophagus if the capsule should become lodged [27, 29, 147].

Mechanisms of Action of Intragastric Balloons

Almost every investigation on the mechanism of action of intragastric balloons has been performed with the Orbera balloon. Intragastric balloons are hypothesised to mediate satiety peripherally, by being a physical impediment of food intake, by reducing the gastric capacity and by delaying gastric emptying, and centrally by activating gastric stretch receptors that transmit signals via afferent vagal nerves, solitary tract and paraventricular nuclei, to the ventromedial and lateral hypothalamus [148]. Short-term satiety is primarily affected by gastric distension and gastric volume. Short-term food intake is affected by the weight and volume of the food rather than its energy content [149]. This volume-regulated satiety is thought to result primarily from gastric distension. Mechanical gastric balloon distension to a volume greater than 400 mL during meals significantly reduces oral intake [150, 151].

Changes in gut peptides and hormones such as cholecystokinin (CCK), pancreatic polypeptide (PP) and ghrelin, affecting appetite control and gastric emptying,

work in concert herewith [152, 153]. In two randomised sham-controlled studies, there was no difference between sham control and active subjects with an IGB on fasting or postprandial ghrelin concentrations [58, 153]. Interestingly, despite substantial weight losses during 26 weeks of balloon treatment, ghrelin levels did not show the expected rise seen after prolonged fasting and weight loss [153]. Authors, however, do not agree on fasting ghrelin levels which have been reported to remain unchanged to decrease or fail to increase despite weight loss or ghrelin suppression by meals was not always investigated [58, 153–155]. Konopko-Zubrzycka et al. studied ghrelin, leptin and adiponectin after IGB and found a significant decrease in body weight of 17.1 kg (12.3% TBWL) in IGB patients, compared with only 3.5 kg (2.3% TBWL) in the control group treated with diet and physical exercise [155]. The IGB group showed a significant increase in ghrelin after 1 and 6 months that returned to baseline values 3 months after balloon removal. They also noticed a significant decrease in leptin, related to the weight loss. Unexplained is the fact that adiponectin levels did not change in the IGB group [155]. Other gut hormones such as CCK and PP have been barely investigated. In a sham-controlled design Mathus-Vliegen and de Groot examined fasting and postprandial CCK and PP levels in two groups: one sham group who started with a 13-week sham period and then received their first balloon for 13 weeks and an IGB group who started with a 13-week IGB and continued with a second 13-week IGB therapy [152]. In the sham group, basal CCK levels decreased, explained by the effect of dieting, but meal-stimulated responses remained unchanged after 13 weeks of sham treatment. In the IGB group, basal and meal-stimulated CCK levels decreased after 13 weeks of balloon treatment. By the end of the second 13-week period, when the sham group had their first balloon treatment, they duplicated the initial 13-week results of the IGB group, whereas the IGB group continued their balloon treatment and reduced meal-stimulated CCK release. These findings are compatible with a delayed gastric emptying, which was not measured in this study. The authors alluded to their clinical findings of delayed gastric emptying by stressing the significant retention of food in the stomach on top of the balloon seen endoscopically upon balloon removal [152]. Both groups showed reduced meal-stimulated pancreatic polypeptide (PP) secretions at the start, after 13 weeks of sham or balloon treatment and after a second period of IGB in everyone. Improvements in glucose tolerance and insulin sensitivity partly explained the PP results. Changes in diet composition and visual analogue scores of satiety were similar [152].

Although the literature on gastric emptying over the years has been very inconsistent, more consistent findings have emerged recently [154, 156, 157]. A small prospective study by Su et al. demonstrated by scintigraphy that gastric emptying half-times for solids and liquids were significantly longer after IGB placement, with a significant positive correlation between gastric emptying times and body weight loss [158]. A randomised controlled trial of the Orbera intragastric balloon in 27 subjects who all received lifestyle modification therapy (LMT) with 13 receiving a balloon and 14 having sham endoscopy studied gastric emptying at baseline, after 8 and 16 weeks while the balloon was still present and at 27 and 39 weeks when the balloon was out for 1 and 13 weeks [69]. A highly significant increase in retained gastric contents 2 h after a ^{99}Technetium-labelled meal ingestion was observed in

the IGB group compared with the control group at 8 weeks (61.4% and 25.7% retained, respectively, $P = 0.0003$) and 16 weeks (62.1% and 18.7% retained, respectively, $P < 0.001$) [69]. After balloon removal gastric emptying returned to the pretreatment baseline levels. No difference was seen in retained gastric contents in the IGB group compared with the control group at baseline or 1 and 13 weeks post-IGB removal, supporting an independent role of IGB on gastric motility. Moreover, weight loss was correlated with the change in gastric retention. Subjects in the IGB group (6 out 13) with 50% or more increase in gastric retention at 8 weeks after IGB insertion had significantly higher % TBWL compared with subjects (7 out of 13) with <50% increase in gastric retention [69]. Moreover, the amount of gastric retention correlated with weight loss, not only at balloon removal but also in the period after balloon removal, suggesting that some of the physiologic changes, which resulted in delayed gastric emptying during intragastric balloon treatment, continue to exert some effect even after the device is removed. This might also explain the weight maintenance and very gradual weight regain in contrast to the immediate weight gain that is seen after cessation of obesity medications in the previously mentioned studies over up to 6 years [5]. In a larger multicentre study, published in abstract form [70] and for some parts in articles [69, 159], 118 subjects had paired scintigraphic gastric emptying studies before and after endoscopic bariatric therapy (EBT) including 15 undergoing a sham endoscopic procedure, 14 lifestyle modification only, 45 gastric injections of botulinum toxin A (BTA), 15 saline-filled intragastric balloon (IGB), 25 duodenal-jejunal bypass sleeve (DJBS) and 4 endoscopic sleeve gastroplasty (ESG) [70]. Sham procedures and lifestyle modification therapy were not associated with delay in gastric emptying (median % increase in gastric retention at 2 h of −1%) compared to a 9% increased retention after BTA injection, 24% after DJBS, 30.5% after ESG and 47% after IGB. Interestingly, rapid baseline gastric emptying and degree of slowing in gastric emptying after EBTs were associated with % TBWL at 6 months on univariate and multivariate analysis after adjusting for age, sex, BMI, diabetes and intervention [70]. Subjects in the EBT group in the highest gastric emptying quantile lost four times more weight than non-EBT-treated controls. Both baseline gastric emptying and change in gastric emptying after EBT significantly predicted achieving ≥15% TBWL at 6 months [70]. One may conclude from this study that in tailoring the EBT method to the characteristics of the patient, pretreatment measurement of gastric emptying might be of help to assign an IGB to patients with rapid gastric emptying at the start.

Balloons may stay for 6 months; only the Spatz adjustable balloon system is allowed for a 12-month period. Interestingly, studies suggest that the first month's weight loss is predictive for successful weight loss, defined as ≥10% weight loss after 6, 12 and 18 months [160]. At 3 months the majority of the weight loss achieved after 6 months is obtained, while satiety levels are maximally at 1–3 months and delayed gastric emptying tends to return back to accelerated pretrial values after 3 months [52, 58, 157]. Also the review by Gaur et al. demonstrated that 80% of the weight loss at 6 months was achieved already at 3 months [85]. The fact that most weight is lost in the first 3–4 months with a plateauing thereafter has been supposed

to relate to an adaptation effect of the stomach to the balloon. After 30 years of balloon treatment it is still not clear if gastric adaptation occurs [151, 161, 162].

Remarks for Use of Balloons in Clinical Practice

As mentioned earlier, the FDA approved the Orbera, ReShape Duo and Obalon balloons for a 6-month period being imbedded in a 12-month comprehensive weight management programme [67, 141, 145]. The ASMBS mentioned in their position statement, endorsed by SAGES, that the efficacy of an intragastric balloon intervention has at least two components: (1) the behavioural (diet and lifestyle) effect and (2) the balloon effect [46]. The ASMBS and SAGES support the use of balloons regarding the evidence level 1 data on the clinical utility, efficacy and safety of intragastric balloon therapy for obesity. They also emphasised the temporary treatment of 6 months and the 12-month multidisciplinary approach around balloon therapy [46]. The context of the workplace and working programme determine the outcome and therefore a comparison of the US pivotal studies with the three-decade experience in European and some South American centres is appropriate. An average result can be obtained from meta-analyses.

Comparison of US Studies with Non-US Studies

The weight loss seen in the three US pivotal trials is lower than what is seen in clinical practice outside of the USA by as much as 50% [33]. For Orbera balloons, the active group in the US pivotal study achieved a 10.2% TBWL and 79.2% achieved a ≥5% TBWL or ≥25% EWL [68]. In the Imaz meta-analysis the TBWL was 12.3% and the % EWL was 32.1% [56]. The meta-analysis by Abu Dayyeh et al. with mostly European and South American studies reported these same figures at 12 months, so 6 months after balloon removal: a TBWL of 11.3% and an % EWL of 25.4. The three RCTs that were analysed showed a 26.9% greater EWL in the active group [41]. In the US pivotal ReShape Duo trial the active group showed a 6.8% TBWL and 48.8% achieved a ≥5% TBWL or ≥25% EWL [140]. One pilot study in 21 patients with the ReShape Duo balloon showed a 32% EWL [138]. A clinical case series of 60 patients with the ReShape Duo balloon demonstrated a 15.4% TBWL and a 47.1% EWL at IGB removal [139].

Another conspicuous finding is the very different rate of early removal of balloons. Early retrieval of balloons in the Orbera US study was 18.9% with 50% on own request [68]. In the ReShape Duo US trial there were 15.0% early retrievals [140]. Vomiting occurred in 86.9% and 86.7% of Orbera and ReShape Duo balloons, respectively, and nausea was reported by a respective 75.6% and 61.0% and abdominal pain in 57.5% and 54.5%, respectively [68, 140]. Data from the Imaz meta-analysis showed an early removal in 4.2%, 43% on own request [56]. In Abu Dayyeh's meta-analysis the early removal was 7.5%, nausea was present in 29% and abdominal pain was present in 33.7% [41]. Lopez-Nava et al. reported a 1.7% early removal [139]. So, also here there is a large difference between pivotal US studies and the year-long experience from elsewhere.

There are almost no data on the air-filled Obalon balloon, but comparison of other air-filled with fluid-filled balloons reported a much better tolerance of the air-filled balloon [129, 130, 163, 164]. Also, in the US pivotal Obalon study, the

air-filled balloon was much better tolerated with vomiting in 17.3% and nausea in 56.0%, but still abdominal pain was present in 72.6% of cases [144]. Early removal was 9.6% for the Obalon device, yet higher than the Imaz and Abu Dayyeh meta-analysis data [41, 56, 144]. It is important to recognise that the investigators in these US trials had no or limited experience with managing patients with IGBs and certainly did not realise the impact of – especially fluid filled – IGBs in the first 3 days on well-being and may therefore have been less aggressive in the treatment of these symptomatic patients. This assumption is verified by the lower numbers in the meta-analyses of clinical trials performed by more experienced practitioners.

More information on the everyday practice is given by the study of Mathus-Vliegen et al. who noticed that much of the data collected on balloons has been in the context of clinical trials in academic medical centres or in large obesity centres, or as a bridge to bariatric surgery in obesity bariatric centres [165]. Moreover, virtually no reports have been published on patients who are treated exclusively outside the academic or hospital settings, and outside the setting of a clinical trial. They recognised the challenge of balloon placement in an everyday practice by gastroenterologists or surgeons with less experience than their academic colleagues or bariatric surgeons, and to take up the gage of realising a similar degree of efficacy and safety as has been published in the scientific literature. They had access to efficacy and safety data in a private practice setting, where compliance with dietary advice, physical exercise, behavioural modification and frequency of follow-up visits were left to the wishes of the patient [165]. A total of 815 consecutive patients were included (131 males, mean body weight 111.7 kg, mean BMI 38.1 kg/m^2). In 672 patients the mean weight loss at 6 months was 20.9 kg, and the BMI decreased by 7.2 BMI units. Of these, over 50% (372 patients) were only seen once at balloon placement and after 6 months for balloon removal. These patients, despite not receiving any dietary support or counselling, achieved a weight loss of 19.4 kg (6.6 BMI units). A total of 326 patients attended for weight consultation at 3 months and had lost 15.8 kg and 5.4 BMI units, again bearing out the statement of the largest weight loss in the first 3 months. Three months after balloon removal, 65 patients remained 6.6 BMI units (18.8 kg) lower than at baseline level. Successful weight loss after 6 months as defined by internists (≥10% total body weight loss) was achieved by 571 patients (85.0%). Successful weight loss as defined by surgeons (≥50% EWL) was achieved by 299 patients (44.5%). A total of 53 patients (6.5%) requested balloon removal during the first month. Nine balloons (1.1%) were removed for medical reasons [165]. There were four serious adverse events (0.5%): two cases of severe dehydration and two cases of balloon deflation who required surgery. The high rate of self-requesting balloon removal, 6.5% in the current study, compared with only 1.8% in the meta-analysis of Imaz suggests that patients may not have been well informed about the initial side effects of balloon therapy and the need for adequate medication to overcome symptoms [56, 165]. Every patient (n = 815) showed up for balloon removal, 807 on the agreed 6-month appointments and eight patients who returned after 9 months. Inspection of the stomach revealed abnormalities in 69 patients (8.5%), with clinical irrelevant abnormalities in 57, severe asymptomatic oesophagitis was present in 12 patients (1.5%) [165].

Meta-analysis

Two meta-analyses examined the outcomes of Orbera balloons and have been discussed earlier [41, 56]. Both included RCTs and open studies. A Cochrane review which included many studies with older balloon designs such as the Garren Edwards Gastric Bubble (GEGB) that were withdrawn from the market because of unsafety had a very negative tenor [53]. Three very recent meta-analyses only included RCTs and two of them included some of the older studies with the Garren Edwards Gastric Bubble that set the world of balloon treatments in stir and commotion [166–168]. One meta-analysis only reviewed studies with balloons filled with >400 mL, and thereby automatically excluded the older balloon versions [168]. This meta-analysis included 9 studies with 669 patients using either the Orbera, ReShape Duo or air-filled balloons. The meta-analysis favoured the IGB group with a 1.4 kg/m^2, 3.6 kg and 14% EWL greater weight loss compared with the sham/diet group. There were no differences between air-filled and fluid-filled balloons. Zheng et al. excluded all crossover trials and thereby excluded a great deal of available studies [166]. They included the older balloon versions and reported the results separately for those having less than 6 months and 6 months of balloon treatment. Those with less than 6-month therapy showed 1.5 kg and 1.2 kg/m^2 greater losses with balloons over controls, but when carefully looking at their data these results came all from the older balloons that are not available anymore. The 6-month results, so with larger size balloons and either air filled or fluid filled, reported a 8.9 kg, 3.1 kg/m^2 and 21.0% greater weight loss compared with controls [166]. Saber et al. also included the crossover trials and as these crossed over after 3 months they had to divide their data into overall, 3 months and >3 months' data. Older balloon studies were included as well [167]. Twenty studies involving 1195 patients were analysed. Also, their data were in favour of IGBs as they showed greater weight losses over controls of 1.59 and 1.34 kg/m^2 for overall and 3-month BMI loss, respectively; 14.3% and 11.2% for overall and >3-month percentage of excess weight loss, respectively; 4.6 and 4.8 kg for overall and 3-month weight loss, respectively; and 2.8%, 1.6% and 4.1% TBWL for overall, 3-month and >3-month, respectively. Interestingly, they demonstrated that fluid-filled balloons were significantly more effective than air-filled balloons [167]. Complaints of flatulence, abdominal pain, abdominal distension and general discomfort were significantly more prevalent after IGBs. They also found gastric ulcers in 12.5% versus 1.2% in controls ($P < 0.001$) but although they did not find a different risk of ulcers in air-filled and fluid-filled balloons, the unfavourable data on gastric ulcers and the better performance of fluid-filled balloons have to be viewed in the context of their decision to consider all balloons, also the old ones that proved to be ineffective and dangerous, the reason why they were taken from the market. Albeit Saber's meta-analysis is very recent from 2017, there is still room for a new meta-analysis of only the new and currently available balloons.

In view of the fact that balloon-induced weight loss occurs predominantly in the first 3–4 months, a new treatment modus may be developed by the availability of the new orally ingested and rectally excreted balloons. The limited durability of prior balloon treatments and FDA approval for 6 months only can now be extended if a

single balloon is followed by the use of multiple balloons. Repeated therapy may become the most common paradigm for this device to obtain and maintain long-term effects and this will be facilitated by balloons that do not require endoscopy for placement or removal. Whether this has to be done with a period of adaptation of the stomach during a balloon-free period in between to rest the stomach and reset its normal motility before repeating therapy should be investigated further.

2.3.1.2 Miscellaneous Endoscopic Techniques

AspireAssist Gastric Aspiration (Aspire Bariatrics, King of Prussia, PA, USA)
Endoscopic aspiration therapy involves the placement of a percutaneous endoscopic gastrostomy (PEG) tube via the pull technique for PEG placement (Figs. 2.1 and 2.5). The A-tube of the AspireAssist system is a gastrostomy tube, which has a 15 cm fenestrated intragastric portion to allow aspiration of gastric contents. After maturation of the gastrostomy tract after approximately 10–14 days, the proximal end of the A-tube is cut within 1 cm of skin level and attached to a Skin-Port. For aspiration the connector of the AspireAssist siphon is connected to the Skin-Port, herewith opening the Skin-Port valve. The AspireAssist siphon consists of a water reservoir for gastric infusion and a drain for stomach contents to drain into the lavatory, which are opened and closed by flipping a lever. The aspiration process involves infusing water into the stomach from a reservoir of 600 mL and then reversing the flow by flipping the lever and flushing food particles out of the stomach through the A-tube into the lavatory. This process is repeated (typically 3–8 infusions) until food particles are no longer seen in the aspirate. The aspiration process usually takes 10–15 min to perform and is done about 20 min after each of three main meals daily. Usually, ≈30% of the ingested meal can be aspirated. To

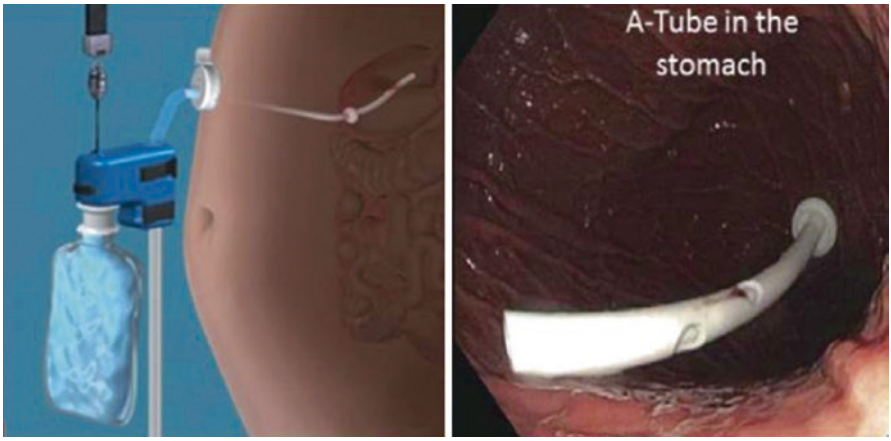


Fig. 2.5 AspireAssist system with A-tube in the stomach and the AspireAssist siphoning system plugged onto to the Skin-Port, herewith opening the Skin-Port valve. Reprinted from Clin Endosc 2017; 50: 42–66, Bazerbachi F, Vargas Valls EJ, Abu Dayyeh BK. Recent clinical results of endoscopic bariatric therapies as an obesity intervention (Open Access Article)

safeguard long-term unsupervised and overzealous use the connector has a counter-mechanism which allows 115 times the opening of the Skin-Port valve; thereafter it can no longer open the Skin-Port valve and the patient has to visit the physician to obtain a new connector. Exclusion criteria, additionally to those mentioned in Table 2.2, consisted of eating disorders, major depression and usual contraindications for a PEG procedure. In a pilot trial, Sullivan et al. randomised 18 obese subjects to 1 year of aspiration therapy plus lifestyle (n = 11) or lifestyle only (n = 7) [169]. Ten of the 11 and 4 of the 7 completed the first year. Weight losses after the first year were 18.6% TBWL and 49% EWL in the aspiration group (initial BMI 42.0 kg/m^2) and 5.9% TBWL and 14.9% EWL in the lifestyle group (initial BMI 39.3 kg/m^2) ($P < 0.05$). Seven of the ten completed another year and maintained their weight loss with 20.1% TBWL and a 54.6% EWL [169]. No adverse effect on eating behaviours or compensation for aspirated calories was seen. Initially abdominal pain at the aspiration tube site was frequently reported, which improved after the device was redesigned. Once a hypokalaemia and three peristomal infections occurred despite a 7-day course of antibiotics. Five tubes became blocked. Four patients had their tubes removed and one had a persistent gastrocutaneous fistula. In a subsequent study, 25 patients with a BMI of 39.8 kg/m^2 were enrolled after a 4-week run-in period of a very-low-calorie diet (VLCD) in a 6-month aspiration treatment period by Forssell and Norén [170]. In the per protocol analysis (22 patients), weight loss at 6 months after aspiration therapy was 16.5 kg including the VLCD period and 8.0 kg without VLCD-induced weight loss. Total excess weight loss was 40.8% with 14.8% TBWL, which is very much in line with Sullivan's data [169, 170]. There was a trend towards improved fasting glucose and haemoglobin A1c, and significant improvement in fasting glucose in the seven patients with type 2 diabetes mellitus [170]. Three of five patients taking medication for diabetes were able to discontinue it. Early adverse events included post-procedure abdominal pain, intra-abdominal fluid collection and skin breakdown around the stoma; a later skin infection required treatment with antibiotics. Moderate abdominal pain was reported by 52% of patients in the first week, and severe pain by 12% [170]. In each study, three patients discontinued therapy: because of relocation, pain and personal life issues in Sullivan's study, and because of inability or unwillingness to spend 45 min per day on aspiration therapy in the study by Forssell and Norén [169, 170]. To meet criticism of creating eating disorders, both studies offered lifestyle therapy or cognitive behavioural therapy. The claim of inducing adverse eating behaviours could not be substantiated by Sullivan et al. [169]. Patients also did not compensate for the energy lost by aspiration. In the US pilot trial, bomb calorimetry of gastric aspirate from aspiration therapy after a meal was compared with an identical unconsumed meal and it revealed that 25–30% of calories were removed with each aspiration session [169]. This only accounted for 80% of the weight loss achieved in the subjects undergoing aspiration therapy if they aspirated 25–30% of all consumed calories, which they apparently did not as they did not aspirate snacks and frequently aspirated only twice a day. This means that another explanation likely accounts for a part of the weight loss, and indeed, patients self-reported a decrease in food intake as they have to change their eating

behaviour considerably. They must take more time to thoroughly chew food and drink sufficient water with meals to ensure that food will be successfully aspirated and will not clog the tube, which may lead to smaller portions of food consumed [169]. So, by itself the AspireAssist promotes key elements of behaviour modification therapy.

The US pivotal multicentre study ("Pivotal Aspiration Therapy with Adjusted Lifestyle", the PATHWAY trial) randomised subjects in a 2:1 ratio to AspireAssist with lifestyle counselling, or lifestyle counselling alone [171]. The main eligibility criteria were age 21–65 years and a body mass index of 35.0–55.0 kg/m^2. A total of 207 participants were randomised, 137 to AspireAssist (BMI 42.2 kg/m^2) and 70 to lifestyle counselling alone (BMI 40.9 kg/m^2). Of these, 111 in the AspireAssist group and 60 in the lifestyle counselling group were enrolled and 82 AspireAssist (74% of those enrolled) and 31 lifestyle counselling participants (52% of those enrolled) completed the entire 52-week study. A modified intention-to-treat (mITT) and a completer's analysis (CA) were performed. Successful endoscopic placement of the A-tube was achieved in 97% of attempts. The co-primary endpoints were mean percent excess weight loss which had to be at least 10% higher in the AspireAssist group and the proportion of participants who achieved at least a 25% excess weight loss, which had to be at least 50% higher in the AspireAssist group. Both primary endpoints were reached as the % EWL in the AspireAssist group (31.5% in mITT and 37.2% in CA) was 22% greater than the % EWL achieved in the lifestyle counselling-only group (9.8% in mITT and 13.0% in CA). Moreover, 58.6% of the AspireAssist group (68.3% in CA) lost at least 25% of their excess body weight, which was more than the 50% pre-specified criterion. This was the case for 22.0% of the mITT and 25.8% of the CA analysis in the lifestyle counselling-only group. At 52 weeks, based on an mITT analysis, mean percent body weight loss at 52 weeks was 12.1% (14.2% for completers only) in the AspireAssist group and 3.5% (4.9% for completers only) in the lifestyle counselling group [171]. Early responsiveness with the AspireAssist, defined as 5% or more body weight loss at week 14, was predictive of weight loss at week 52. Ninety percent of the study-related adverse events were associated with the gastrostomy tube and half of them occurred in the first week after placement. Five (3.6%) severe adverse events were reported: one case of mild peritonitis, twice severe abdominal pain, one prepyloric ulcer related to the A-tube and once an A-tube malfunctioning. Four instances of hypokalaemia were noticed. There were no differences in comorbidities between the groups, and eating patterns remained undisturbed and there was no evidence of a compensatory increase in food intake. Of the 29 subjects who had their A-tubes removed before the end of the 52-week study, one had a persistent fistula that was clipped successfully [171]. An additional small European trial of 11 subjects (average BMI 66.5 kg/m^2 and body weight 196.1 kg) demonstrated a 21.4% TBWL included on purpose super-superobese subjects to investigate aspiration therapy as a bridge-to-surgery. After 1 year a weight loss of 41.1 kg, 21.4% TBWL and 33.9% EWL were obtained in these 11 patients [172]. After 2 years in 6 subjects these figures were 45.0 kg, 23.3% TBWL and 38.8% EWL. Three minor skin infections were seen which were treated with antibiotics [172].

In June 2016, the device was approved by the FDA for long-term implantation in patients with a BMI between 35 and 55 kg/m^2 [173].

TransPyloric Shuttle (BAROnova, Goleta, CA, USA)

The TransPyloric Shuttle (TPS) consists of a large silicone spherical bulb attached to a smaller cylindrical bulb by a flexible tether (Figs. 2.1, 2.2f, and 2.6a–c). The smaller cylindrical sphere is small enough to enter the duodenal bulb with peristalsis, and pulls the larger spherical bulb into the pylorus where it occludes the pylorus intermittently to reduce gastric emptying. The TPS is preloaded in its delivery system in a coil configuration. The device delivery system is inserted through an overtube into the stomach. Under fluoroscopic view, the coil is deployed, and the TPS is constructed and locked into its treatment profile for gastric residence. Removal is by endoscopy using the same type of gastric overtube (Fig. 2.6b, c). Once the overtube is in position, an endoscope is used to locate the TPS and with a standard endoscopic rat tooth forceps the lock-release mechanism to deconstruct the device is actuated and after retrieval of the locking device the device can be unfolded by a polypectomy snare into the overtube and removed. Two groups of ten patients (BMI of 36 kg/m^2) were treated, ten patients for 3 and ten for 6 months [174]. Three-month patients had mean % EWL of 25.1%, mean % excess BMI loss of 33.1% and mean TBWL of 8.9%. Six-month patients had mean % EWL of 41.0%, mean % excess BMI loss of 50.0% and mean TBWL of 14.5%. Both the 3- and 6-month patients had statistically significant improvements in the overall quality-of-life score. Mild complaints in the first 30 days were pharyngeal/laryngeal irritation due to the overtube, a sore throat, nausea, vomiting and abdominal pain. Endoscopic observations of mucosal erosion and/or granulated tissue were noted in 15/20 patients. A gastric ulcer, defined as ≥5 mm in diameter, was noted in ten patients and ulcers were all located in the antrum. Eight of ten ulcers were asymptomatic endoscopic findings and resolved by medication such as proton pump inhibitors and sucralfate, but in two patients persistent ulcers with acute-onset epigastric pain and epigastric pain and vomiting led to early device removal [174]. Symptoms resolved immediately after device removal. A surface feature on the device appeared to be associated with the development of ulceration. This prompted changes in the design to the current generation of the TPS. A US pivotal study (ENDOBESITY II) is in progress.

Botulinum Toxin A (BTA) Injection (Botox; Allergan, Irvine, CA, USA)

Botulinum toxin A (BTA) is produced by *Clostridium botulinum*. It inhibits acetylcholine release at the neuromuscular junction and selectively inhibits the activity of cholinergic nerves, and smooth and striated muscles. When injected in the antrum it delays gastric emptying and induces satiety by means of a pharmacologically induced gastroparesis. When injected in the fundus, BTA was hypothesised to decrease gastric accommodation and ghrelin secretion and to induce an early sensation of satiety and fullness [175]. The first meta-analysis of six studies, three open studies and three RCTs, in 2008 evaluated the effect of intragastric injection of BTA by endoscopy on obesity [176]. These six studies yielded conflicting results and part

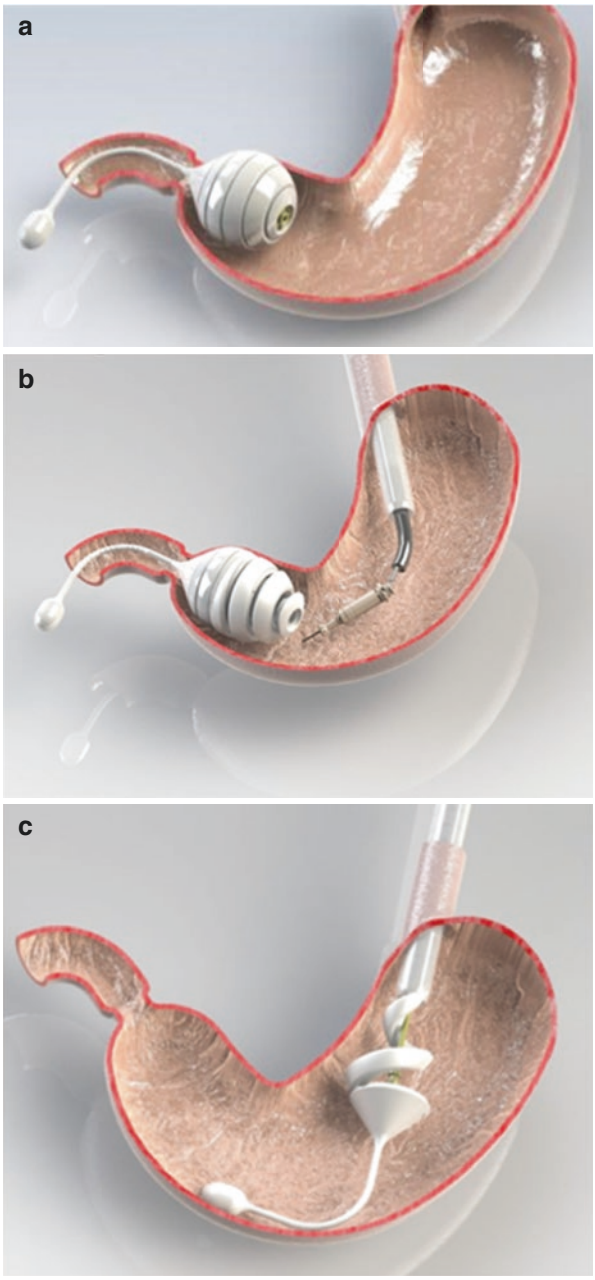


Fig. 2.6 Transpyloric shuttle: (**a**) Position of the large silicone spherical bulb in the stomach which is attached to a smaller cylindrical bulb in the duodenum; (**b**, **c**) deconstruction of the device by activating the lock-release mechanism and unfolding of the device after retrieval of the locking device [174]. Reprinted from Surg Obes Relat Dis 2014; 10: 929–935, Marinos G, Eliades C, Muthusamy R, 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 with permission from Elsevier

of the inconsistency was due to differences in patient selection, injected BTA doses (100–300 IU), method of application (number and depth of injections) and area of application (antrum, antrum combined with fundus). Of these six studies, five reported negative and one positive results. The positive study used eight injections in both the antrum and fundus. Recently, in 2015, a new meta-analysis of eight studies (4 RCTs, 4 open, 115 patients, 79 treated vs. 36 placebo) encountered the same methodological problems but adapted the method of statistical analysis [177]. They found a significant effect on weight both between and within subjects. Sensitivity analysis learned that a wider area of injection (fundus and body vs. antrum only) and multiple injections (>10) but not the dose of BTA (> or <500 IU) were associated with weight loss [177]. Multiple injections showed significant efficacy, and the reason for this efficacy seems to be the enhanced intramuscular diffusion of toxin. Botulinum toxin A is known to spread by diffusion to an area as large as 3 cm from the injection site. The meta-analysis only reports effect sizes and does not report the percentage of weight lost, which is relevant for the treating physician [177]. Furthermore, the method is expensive (100 IU cost 300 euro) and the duration of the effect is limited to 3–6 months. Not included in the meta-analysis is a recent study reported in a letter where 118 patients were treated with follow-up in 75% [178]. Treatment consisted of 100 IU BTA per area of antrum, body and fundus and each 100 IU BTA was given in five spaced injections. Patients lost 14 kg after 4 months and regained 2 kg at 6 months. Mainly complaints of vomiting (12.5%) and diarrhoea (3.4%) occurred [178]. So, the application of BTX-A injections remains very controversial. To demonstrate the effects on gastric emptying 45 BTA injection patients were compared with patients with sham procedures (n = 15) and lifestyle modification therapy (n = 14) with no delay in gastric emptying (median % increase in gastric retention at 2 h of −1%) and BTA-treated patients showed a 9% increase in gastric retention, a rather small effect [70].

Techniques with Unknown Status

SatiSphere (Endosphere, Columbus, OH, USA)

The SatiSphere is an endoscopically implantable device designed to delay transit time of nutrients through the duodenum which may alter satiety hormone levels and glucose metabolism [179]. It consists of a 1 mm preformed memory nitinol wire with several polyethylene terephthalate mesh spheres mounted along its course. It is released in the duodenum and made to stay in place by pigtail endings in the antrum and down to the ligament of Treitz, mimicking the anatomy of the duodenal C-loop configuration. A trial of 31 patients with an average BMI of 41.3 kg/m^2 compared 21 SatiSphere patients with 10 controls, with a scheduled device removal after 3 months. Device migration was reported in 10 of 21 implanted patients and emergency surgery was necessary in two patients which led to the termination of the trial due to safety concerns. Weight loss after 3 months was 4.6 kg in the ITT analysis and 6.7 kg in the group completing the therapy (n = 12) versus 2.2 kg in controls. The EWL was 18.4% compared with 4.4% in the control group. The differences in weight loss with controls were only significantly higher for the completers. SatiSphere was associated with delayed glucose absorption, delayed insulin secretion and altered GLP-1 kinetics [179]. It is unknown whether the European study is still ongoing.

Full Sense Device (Baker, Foote, Kemmeter, Walburn LLC, Grand Rapids, MI, USA)
The Full Sense Device is a modified fully covered metal stent with a cylindrical oesophageal component and a gastric disc component connected by struts that is placed across the gastro-oesophageal junction and that is removed endoscopically. By residing in the cardia, it induces satiety and feelings of fullness. There are only some data on the Internet but no peer-reviewed data or abstracts have been published to date.

2.3.2 Invasive Endoscopic Bariatric and Metabolic Therapies

In contrast to the previously discussed endoscopic options to treat obesity, which are mostly at the disposal of and practicable by endoscopist but have the disadvantage of limited durability, the gastric volume reduction devices require high endoscopic skills and much time and some are still in its infancy of development. The methods are more invasive and not reversible and in the analogy of surgery also named endoscopic bariatric and metabolic therapy (EBMT) [180]. As these procedures use stitches and sutures or staples which cannot be removed, they should always have to consider the feasibility of bariatric surgery if needed in the near future. The endoscopic procedures may mimic bariatric surgical interventions such as the vertical banded gastroplasty, gastric band, gastric plication and sleeve gastrectomy (Table 2.5) [180]. As is the case with bariatric surgery, the principles underlying the mechanisms of action are being unravelled. Some of these EBMTs fell into disfavour, but in view of the insights obtained and lessons learned from these methods they will be reported as well. There are two main methods of making plications: by suturing and by stapling.

Table 2.5 Endoscopic bariatric and metabolic therapy and their surgical analogues [180]

Endoscopic bariatric and metabolic therapy	Surgical analogues
Stomach	
Endoluminal vertical gastroplasty (EVG)	Vertical banded gastroplasty (VBG)
Transoral gastric volume reduction (TGVR)	Laparoscopic gastric plication
Primary Obesity Surgery Endolumenal (POSE)	Laparoscopic gastric plication
Endoscopic sleeve gastroplasty (ESG)	Laparoscopic gastric plication
TransOral Gastroplasty (TOGa)	Vertical banded gastroplasty (VGB)
Transoral endoscopic restrictive implant system (TERIS)	Laparoscopic gastric banding (LAGB)
Articulating circular endoscopy (ACE) stapler	Laparoscopic gastric plication
Small intestine	
Duodenojejunal bypass sleeve (DJBS)	Roux-en-Y gastric bypass (RYGB)
ValenTx bypass sleeve	Roux-en-Y gastric bypass (RYGB)
Duodenal mucosal resurfacing (DMR)	Roux-en-Y gastric bypass (RYGB)
Incisionless magnetic anastomotic system (IMAS)	Modified duodenal switch/ileal transposition

2.3.2.1 Gastric Suturing

Several systems of endoluminal suturing have been investigated with both disappointing and promising results. The EndoCinch suturing system and its modified version, the RESTORe Suturing System device, do not provide durable sutures and plications because they do not acquire the required full-thickness and transmural suturing and have been abandoned. The Primary Obesity Surgery Endolumenal (POSE) and the endoscopic sleeve gastroplasty (ESG) on the other side are so promising that US pivotal trials to support regulatory approval are in progress or just finished. Both companies (USGI-POSE and Apollo-Overstitch) have their systems already approved by the FDA for tissue apposition in the management of post-bariatric complications [31] (see Chaps. 5 and 6).

Endoluminal Vertical Gastroplasty (EVG) (Bard EndoCinch Suturing System – Bard Inc., Murray Hill, NJ, USA; Product Currently Discontinued)

Fogel et al. used the EndoCinch Suturing system which is mounted on an endoscope and fires a straight-threaded needle through a tissue fold formed by suction. One continuous suture, following a specific woven pattern, runs through anterior and posterior parts of the gastric wall from the proximal fundus to the distal body. When tightened the suture approximates anterior and posterior walls of the stomach creating an endoluminal vertical gastroplasty (EVG) from fundus to distal corpus. The EVG reduces the capacity of the stomach and gives a functional restrictive component. The EVG differs from its surgical analogue, the vertical banded gastroplasty (VBG), in some aspects: the plication does not start at the angle of His, it is not parallel to the lesser curvature and there is no formation of a narrow outlet to delay gastric emptying [180] (Table 2.5). Fogel et al. treated 64 patients (BMI of 39.9 kg/m^2) without any significant adverse event apart from one case with vomiting [181]. After 12 months 59 of these 64 patients had an EWL of 58% and a significant 9.3 units reduction in BMI. Follow-up endoscopy was done when they reported loss of satiety. Fourteen endoscopies were done and revealed an intact EVG in five, a loosened but still intact EVG in six and a disrupted EVG in three. Two of the three had a repeat stitching procedure [181]. The device was then modified and named the RESTORe (Davol, Murray Hill, NJ, USA), and was capable of both full-thickness suturing and suture reloading in vivo.

Transoral Gastric Volume Reduction (TGVR) (RESTORe – Davol, Murray Hill, NJ, USA; Product Currently Discontinued)

Brethauer et al. used the RESTORe Suturing System device in their TRIM study – "Transoral gastric volume Reduction as Intervention for weight Management" [182, 183]. It is a single-intubation, multi-stitch, endoscopic suturing system. The suction capsule is placed at the end of the endoscope and the suturing system and suture fastening system are placed through the working channel of the endoscope. The system used interrupted sutures, apposing directly opposite tissues by suction of the mucosa into the device and deploying a suture through the gastric tissue. When the desired numbers of stitches have been made, the suture delivery device is removed. A suture fastening system is positioned over the free suture ends, pulling them

together and fastening them. An average of six gastric plications is desired to approximate the anterior and posterior wall of the stomach to achieve restriction of the upper stomach and to decrease gastric compliance. Diabetic gastroparesis and diabetes for >10 years are additional exclusion criteria (Table 2.2). The TGVR was more similar to the laparoscopic gastric plication [180] (Table 2.5). In the 18 included patients the desired number of plications were placed in 16; in two poor visibility, too much tension and insufficient place to flex the endoscope resulted in less than six plications. Four patients withdrew. A mean % EWL of 27.7% and a weight loss of 11.0 kg and 4.0 units in BMI were observed. Half of the patients had a ≥30% EWL. Average waist circumference declined by 12.6 cm and systolic and diastolic blood pressure decreased significantly. The endoscopy at 1 month revealed completely intact plications in only two subjects, a partial release was seen in 15 and plications could not be well visualised in 1. Endoscopy at 12 months showed complete release of plications in five and partial release in eight patients [183]. There were no serious adverse events and one adverse event of moderate diarrhoea. Disappointingly, although the RESTORe Suturing System proved to be safe and well tolerated, the plications were not full-thickness stitches and not durable. Both this system and its predecessor have been discontinued.

Primary Obesity Surgery Endolumenal (POSE) (IOP, USGI Medical, San Clemente, CA, USA)

The Primary Obesity Surgery Endoluminal (POSE) procedure uses the incisionless operating platform (IOP) which gained FDA approval in 2006 for grasping, mobilisation and approximation of soft tissue in minimally invasive gastroenterological procedures [31]. The Primary Obesity Surgery Endolumenal (POSE) procedure is done perorally with the incisionless operating platform (IOP), a stable platform with four working ports, which is steerable in four directions with a 360-degree rotation and has a 73 cm insertion length (Fig. 2.7a). One channel allows a 4.9 mm endoscope for endoscopic visualisation. Three channels are for the three specialised instruments: the g-ProxEZ Endoscopic Grasper with 33 mm stainless steel jaws, for grasping, mobilising and approximating full-thickness (serosa-to-serosa) tissue folds and to cut the suture; the g-Lix Tissue Grasper, a helix, to grasp tissue and pull it into the jaws of the g-Prox; and the g-CathEZ Suture Anchor Delivery system, a catheter system that penetrates the target tissue with a needle at its distal tip, installs a pair of preloaded tissue anchors and cinches the anchored tissue fold (Fig. 2.7b, c). The sutures are snow-shoe shaped. The device can be reloaded in vivo.

To perform the POSE procedure, the IOP is retroflexed and used to create two parallel rows with 4–5 plications each. This reduces the fundic apex of the stomach to the level of the gastro-oesophageal junction. After the forward view is restored and the distal gastric body is visualised, a ridge of 3–4 plications is then created at the intersection of the gastric body and gastric antrum, opposite the incisura [184] (Fig. 2.1). Care should be taken to avoid deep g-Lix insertion in this area, in order to avoid injury of adjacent viscera. The plicated area restricts contact with ingested food. The anchored plications may more rapidly activate gastric stretch receptors in response to food and the plications in the fundus are thought to defunctionalise the

fundus by limiting the ability to accommodate a meal. Additional distal plications are expected to slow antral mill contractions and to delay gastric emptying. Plicating both the fundus and distal antrum is supposed to induce early fullness and prolonged satiety. Its surgical analogue is the laparoscopic gastric plication, POSE being a partial plication with separated transmural stitches and anchors placed along the upper part and the antrum (Table 2.5). To date, there have been two open-label, prospective, single-arm trials and two randomised controlled trials assessing the

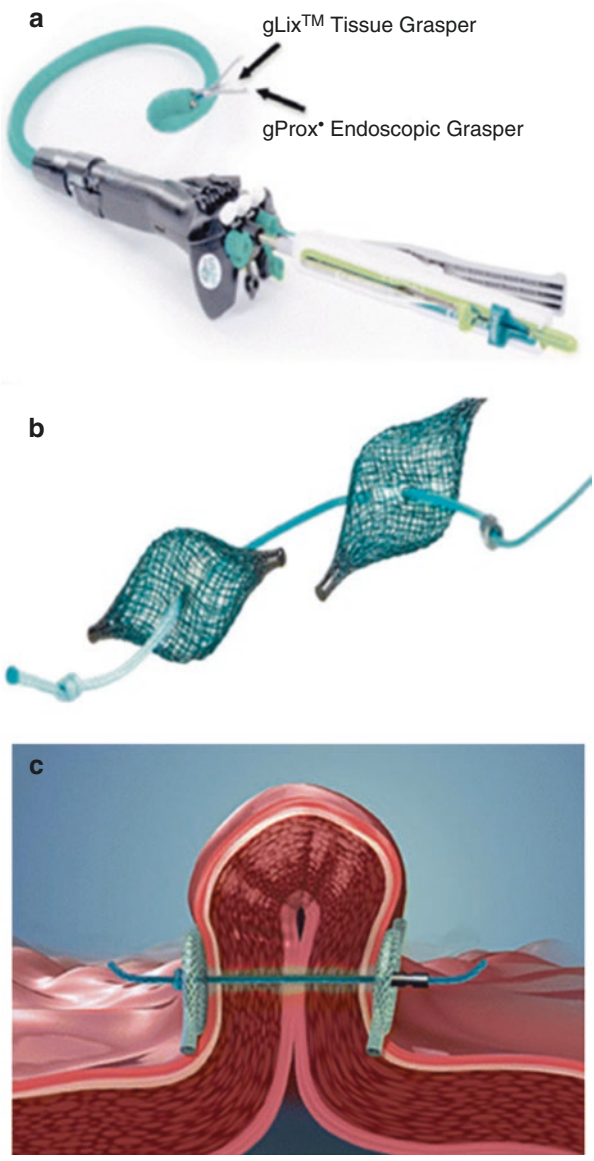
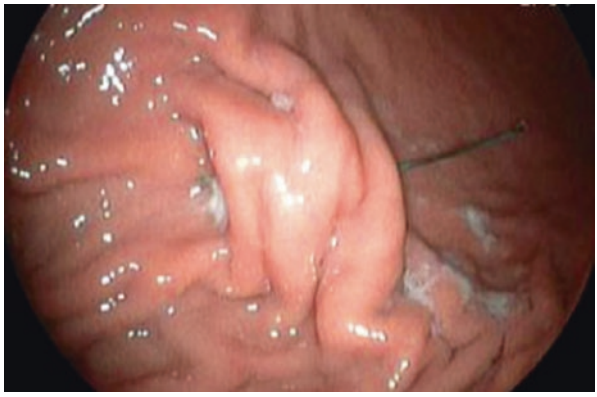


Fig. 2.7 The Primary Obesity Surgery Endolumenal (POSE) procedure: (**a**) The incisionless operating platform (IOP), a stable platform with four working ports: one channel for the endoscope and three channels for the three specialised instruments: the g-ProxEZ Endoscopic Grasper, the g-Lix Tissue Grasper and the g-CathEZ Suture Anchor Delivery system. (**b**) The sutures are snow-shoe shaped. (**c**) An anchored tissue plication [184]. Reprinted from Obes Surg 2013; 23: 1375–1383.186, Espinos JC, Turro R, Mata A, Cruz M, da Costa M, Villa V, et al. Early experience with the Incisionless Operating Platform (IOP) for the treatment of obesity: the Primary Obesity Surgery Endolumenal (POSE) procedure with permission from Springer

Fig. 2.7 (continued)



safety and efficacy of the POSE procedure [184–187]. POSE is under FDA review for approval.

Transmural plications were successfully performed in 45 subjects (BMI 36.7 kg/m^2), 8.2 in the fundus and 3 along the distal body wall by Espinos et al. [184]. After 6 months, 27 patients were available for follow-up and reported a 6-month excess weight loss of 49.4%, a weight loss of 16.3 kg or 15.5% and a BMI decrease by 5.8 kg/m^2. Over 80% of patients achieved ≥25% EWL at 6-month follow-up. There were no major adverse events and adverse events associated with the procedure included one case of low-grade fever and one case of chest pain. Lopez-Nava et al. reported the 1-year results from a study of 147 patients with class 1 and 2 obesity (BMI 38.0 kg/m^2) and showed in 116 patients a 44.9% EWL and a TBWL of 15.1% or 16.6 kg [185]. Fifty-nine patients (50.9%) had at least 15% of TBWL at 1 year post-intervention. Only minor complications were reported, including minor bleeding. One patient had a prolonged hospital stay because of a low haematocrit value. No long-term complications have been reported. Patients reported satisfaction with weight loss results, and they were found to have a 50% decrease in hunger and 60% decrease in gastric capacity. Predictive for success were age (younger patients) and BMI (higher initial BMI) [185]. Lopez-Nava also reported the top four serious adverse events reported after 1500 POSE procedures which are immediate post-operative bleeding requiring transfusion, perforation of the stomach, pneumothorax, and perihepatic/perisplenic abscess. The frequency of adverse events is 1.0% overall (15 of 1500), with 0.33% (5 of 1500) of patients requiring hospitalisation with surgery and 0.67% (10 of 1500) requiring rehospitalisation after the procedure or requiring a prolonged stay after the procedure without a surgical intervention [185].

The MILEPOST study, a "Multicentre Study of an Incisionless Operating Platform for Primary Obesity vs. Diet and Exercise", is a prospective, unblinded RCT of 30 months' duration and the 1-year result was reported very recently [186]. Subjects with class I–II obesity were randomised in a 3:1 ratio to POSE or diet/exercise guidance only. Forty-four subjects (BMI 36.5 kg/m^2) were randomised to POSE (n = 34) or control (n = 10) groups in three centres. All procedures were carried out successfully with serious adverse events; only two minor bleedings required

prolonged hospitalisation. Weight losses were 13.0% TBWL and 45.0% EWL in the POSE versus 5.3% TBWL and 18.1% EWL in the controls ($P < 0.01$) at 12 months. At 6 months, 93.8% of POSE group subjects had achieved ≥5.0% TBWL compared with 40% of controls ($P < 0.001$). At 12 months, these percentages were 90.0% in POSE versus 55.6% in controls [186].

The ESSENTIAL trial ("A Randomised, Subject and Evaluator-blinded, Parallel-group, Multicentre Clinical Trial Using an Endoscopic Suturing Device (G-Cath EZ™ Suture Anchor Delivery catheter) for Primary Weight Loss") is a multicentre, randomised, sham-controlled double-blind trial to compare the POSE procedure with a sham procedure with an initial follow-up of 12 months, which has recently been completed [187]. Patients with a BMI between 30 and 34.9 kg/m^2 with one obesity-related comorbidity or 35 and 40 kg/m^2 with no requirement for an obesity-related comorbidity were eligible. Thirty-four patients (BMI 36.5 kg/m^2) were included in a lead-in group for the purpose of investigator training and they also followed the study protocol. In total, 332 subjects were randomised (active $n = 221$, BMI 36.0 kg/m^2; sham $n = 111$, BMI 36.2 kg/m^2) [187]. Aftercare was limited to six visits in active and sham groups, consistent with a low-intensity lifestyle therapy. Co-primary efficacy endpoints were the difference in mean percent of total body weight loss (% TBWL) and the difference in responder rate, response being defined by reaching ≥5% TBWL between the groups. A super superiority design was followed, meaning that the lower limit of the two-sided 95% confidence interval (CI) for the observed difference in % TBWL between groups had to be greater than 3% and that at least 50% of active treatment subjects should obtain a ≥5% TBWL. The 34 patients who participated in the lead-in open-label portion of the study achieved 7% TBWL at 12 months. TBWL was 4.95% in the active and 1.38% in the sham groups ($P < 0.0001$), with a mean weighted difference of 3.57% (95% CI 2.08 to 5.05; $P = 0.2256$). Mean weight loss in the active group was 3.6-fold that of the sham group but the 95% CI lower limit needed to be greater than 3% to have met the predefined super superiority efficacy endpoint which was not the case. The responder rate was 41.6% in active and 22.1% in sham groups, respectively ($P < 0.0001$); however, the super superiority margin of ≥50% of active subjects as set forth in the study design was not met [187]. The procedure success rate was 99.5%; in one patient an abnormal oesophageal anatomy precluded safe insertion of the IOP system. The rate of serious adverse events was 5.0%: 4% ($n = 8$) due to vomiting, nausea and pain, all requiring longer hospitalisation, and one extragastric bleeding requiring open surgical exploration, and one liver abscess requiring percutaneous drainage [187]. Improvement in comorbidities was only significant for diabetes with trends for serum lipids and hypertension. The authors concluded that the POSE procedure is safe and results in statistically significant and clinically meaningful weight loss over sham through 1 year, but they do not discuss the deficiency to demonstrate super superiority.

Mechanism of Action of the POSE Procedure

Espinos et al. tried to explain the working mechanism of the POSE procedure [188]. Caloric intake capacity with standardised nutrient drink test was significantly

decreased from baseline (901 kcal) by 48% ($P < 0.001$) at 2 months (473 kcal) and by 36% ($P < 0.001$) at 6 months (574 kcal) in 18 patients with the POSE procedure [188]. Gastric emptying was delayed at 2 months, but returned to normal by 6 months. Changes in hormones including ghrelin and PYY occurred, with an increase in fasting ghrelin and a greater depression of 7% at 2 months and 15% at 6 months ($P = 0.003$) following a meal. Basal PYY also decreased but after a meal the release increased by 15% and 34% at 2 and 6 months, respectively, but it is unclear if these changes are due to the procedure or due to weight loss from the procedure, as 83% obtained a ≥25% EWL at 6 months. Sixty-six percent of the variance in the 15-month weight loss could be explained by pre-procedure BMI, gastric emptying and PYY postprandial change 2 months post-procedure. Thus, weight loss at 15 months was greater in lower weight patients, those who experienced a greater delayed gastric emptying at 2 months and those who experienced a higher PYY postprandial change at 2 months. Also, the MILEPOST study showed a decreased gastric capacity during the standardised nutrient drink test [186]. The standardised nutrient drink test showed that to reach maximum satiation, POSE subjects drank on average 1176 kcal prior to the procedure and 568 kcal 12 months after it, constituting a mean change of 608 kcal ($P < 0.001$) [186].

Comparison of US Studies with Non-US Studies

As has been previously discussed in the intragastric balloon section also here, in the US pivotal study weight losses were lower. The two open and the European multicentre randomised controlled trial showed all three excess weight losses between 45% and 49%, a body weight loss around 16.5 kg and a TBWL between 13.0% and 15.5%, so rather uniform findings [184–186]. Defining a certain weight loss as successful resulted in 80% achieving a ≥25% EWL, 15% achieving a ≥15% TBWL and 93.8% achieving a ≥5% TBWL [184–186]. TBWL was only 4.95% in the blinded part and 7.0% in the unblinded part of the POSE trial with only 41.6% achieving a ≥5% TBWL [187]. Physicians should be aware of these differences and they have to put these figures into the perspective of their field of clinical activity.

Endoscopic Sleeve Gastroplasty (ESG) (OverStitch Suturing System (Apollo Endosurgery Inc., Austin, Texas, USA)

The Apollo OverStitch can place full-thickness stitches in a variety of interrupted or running patterns. Sutures can be reloaded without removal of the endoscope (Fig. 2.8). The OverStitch includes a curved needle driver attached to the tip of the endoscope, a catheter-based suture anchor and an actuating handle attached to the handle of the endoscope. A double-channel endoscope is necessary. The OverStitch can be used to perform endoscopic sleeve gastroplasty, creating a sleeve along the lesser curvature. Two parallel rows of interrupted sutures from the antrum to the fundus are applied. To create a suture, a catheter is passed through one channel of the endoscope to function as a suture anchor and through the other channel a tissue helix screw is placed that is screwed full thickness through the wall and is then retracted, pulling the gastric tissue into the device for full-thickness tissue acquisition. The same is done on the opposite site, using the free suture end of the same

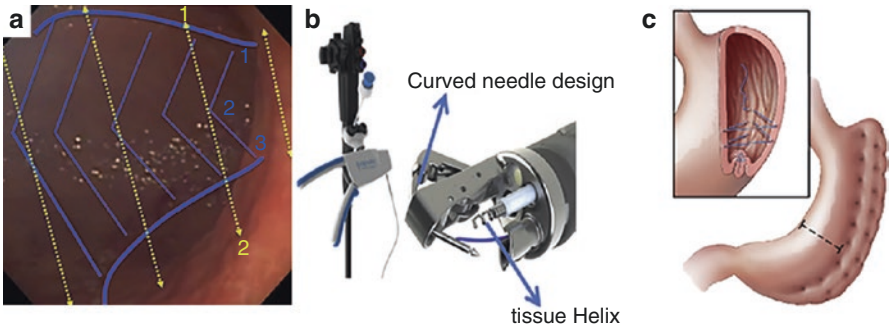


Fig. 2.8 The OverStitch suturing system with the endoscope and the suturing device in the middle, the triangular suturing mode to the left and the two rows of gastric plication to the right, mimicking a laparoscopic gastric plication surgery [189]. Reprinted from Gastrointest Endosc 2013; 78: 530–535, Abu Dayyeh BK, Rajan E, Gostout CJ. Endoscopic sleeve gastroplasty: a potential endoscopic alternative to surgical sleeve gastrectomy for treatment of obesity with permission from Elsevier

suture. The suture is tightened by using a cinching device, thereby creating a full-thickness plication. By this method, approximately 25 sutures are needed to accomplish a full reduction of the gastric capacity (Fig. 2.1). In 2013, Abu Dayyeh et al. described in a single-centre pilot trial a method in four patients (BMI 35.9 kg/m^2) to mimic the surgical sleeve [189]. They used closely spaced interrupted sutures through the gastric wall from the prepyloric antrum to the gastro-oesophageal junction in two parallel rows of anterior and posterior suture placement. Approximately ten interrupted full-thickness, opposing sutures are delivered to reduce the gastric body and create the central length of the sleeve. Finally, closure of the fundus is established with a two-layer set of as many as five sets of opposing sutures and the last suture plication in the sequence is placed at the level of the squamocolumnar junction. It was a lengthy procedure of 170–245 min [189]. About 1 year later, Kumar et al. demonstrated the feasibility and safety of a modified method in five patients [190]. Running sutures with 6–12 stitches each were placed in a triangular fashion at the anterior wall, greater curvature and posterior wall, beginning in the antrum upwards to avoid the need for retroflexion and, once the fundus was reached and closed, it was sutured to the lower oesophageal sphincter. These five patients changed their BMI from 37.4 kg/m^2 at the time of the procedure to 34.8 kg/m^2 after 5 months. The procedure was continued in a further 23 patients (BMI 34.2 kg/m^2) [190]. A median of 8 running sutures, each with 6–12 tissue stitches, was used per procedure. The procedure time was 120 min. There were no significant adverse events. Weight loss at 1 month was 8.0 kg, at 6 months 14.5 kg and at 12 months 13.1 kg. The BMI had decreased to 28.9 kg/m^2 after 6 and to 29.4 kg/m^2 after 12 months [190]. Some prefer to reinforce the suture line with interrupted stitches. The goal of the procedure is to reduce the gastric cavity to resemble a tubular lumen along the lesser curvature, with the greater curvature replaced by a line of cinched plications. It may thus be compared to a bariatric surgical plication [180] (Table 2.5).

Lopez-Nava et al. referred to this novel technique as endoscopic endoluminal greater curvature plication [191]. They also emphasised that the suturing technique is intended not only to reduce the stomach diameter, but also to shorten it substantially through an accordion effect.

Indeed, Sharaiha et al. who described their experience in the first ten patients measured the length of the stomach and found a decreased length of the stomach from 36.6 to 26.1 cm [192]. These ten patients (BMI 45.2 kg/m^2) lost 33 kg, 4.9 BMI units and an excess weight of 30% after 6 months. Eight patients had postoperative abdominal pain and two had chest pain [192]. Lopez-Nava et al. treated 20 patients (BMI 38.5 kg/m^2) [191]. There were no adverse events, except for an intraprocedural bleeding in two patients that was controlled with injection therapy. These 20 patients had a 19.3 kg weight loss, a 17.8% TBWL and a 53.9% EWL and their BMI decreased with 6.6 BMI units after 6 months. On oral contrast studies and on endoscopy performed on a voluntary basis in 10 of the 20 patients an intact gastroplasty with intact sutures was seen [191]. In a further extension of the study in 25 patients they tried to find predictors of weight loss and found the frequency of nutritional and psychological contacts to be associated with TBWL [193]. They also reported the feasibility of an endoscopic revision and repeat procedure in one patient who demonstrated loosened plications on an oral contrast study.

Abu Dayyeh et al. investigated the outcome of 25 patients undergoing ESG for up to 20 months [159]. The % EWL was 53% ($n = 25$) at 6 months, 56% ($n = 17$) at 9, 54% ($n = 13$) at 12 and 45% ($n = 10$) at 20 months after ESG. Five of eight available participants (62.5%) with 20 months of follow-up had an excellent durable response to ESG with % EWL of 72% but three of eight (37.5%) regained all the weight lost at 20 months. Repeat upper endoscopy was performed at 3 months in nine sequential patients to evaluate integrity of the ESG. Six of nine (67%) had a durable, intact ESG with formation of fibrotic bridges. Three of nine (33%) had a partially intact ESG; two of the three non-responders at 20 months were among them. Complaints of pain and/or nausea required hospitalisation for eight patients. Three serious immediate adverse events occurred; one participant developed a perigastric inflammatory serous fluid collection that resolved with percutaneous drainage and antibiotics, another developed a pulmonary embolism 72 h after the procedure and a third developed pneumoperitoneum and pneumothorax requiring chest tube placement.

ESG results were also reported in a registry study, which collected data on 126 patients from 9 sites across 4 countries [194]. Of these, 82 reached 6-month follow-up and 40 reached 1-year follow-up. There were no significant adverse events. BMI decreased from 36.2 kg/m^2 at the time of the procedure to 30.9 kg/m^2 at 6 months and 29.8 kg/m^2 at 1 year. Weight loss and % TBWL at 6 months were 18.1 kg and 17.8%, respectively. These figures were 19.3 kg and 19.0% at 1 year [194].

The largest study of ESG is a clinical case series including 242 consecutive patients at two US centres and one centre in Spain but some of these data might have been included in the mentioned registry study [195]. The procedure success was 100% and ESG was associated with 16.8% ($n = 137$), 18.2% ($n = 53$) and 19.8% ($n = 30$) TBWL at 6, 12 and 18 months, respectively. Five (2%) severe adverse

events occurred, all within 30 days of the procedure: two perigastric inflammatory fluid collections (adjacent to the fundus) that resolved with percutaneous drainage and antibiotics, one self-limited haemorrhage from a splenic laceration, one pulmonary embolism 72 h after the procedure and one pneumoperitoneum and pneumothorax requiring chest tube placement. All five patients recovered fully with no need for surgery. Post-procedure symptoms such as nausea, vomiting or abdominal pain were frequent but mostly transient [195].

The OverStitch device has not been specifically approved by the FDA to perform ESG; however, it does have broad approval by the FDA for tissue apposition in the gastrointestinal tract [31]. No randomised controlled trials have been completed with ESG. The PROMISE trial, the "Primary Obesity Multicenter Incisionless Suturing Evaluation" trial to study efficacy of endoscopic sleeve gastroplasty using OverStitch, is currently ongoing.

Mechanism of Action of the Endoscopic Sleeve Gastroplasty

Abu Dayyeh et al. subjected 4 of their 25 patients undergoing ESG to a very detailed assessment of gastric motility and fasting and meal-released hormone levels prior to and 3 months after ESG [159]. A significant delay in gastric emptying of solids with an increase in time with 90 min for 50% emptying of solids was observed compared with pretreatment values without a significant change in the gastric emptying of liquids. During a standardised nutrient drink test ESG was found to decrease caloric intake needed to reach maximum satiety by 59%, signifying earlier satiation and reduced calorie intake and leading to a decrease of meal duration from 35.2 to 11.5 minutes. Despite significant weight loss, fasting and postprandial ghrelin levels decreased by 29.4% 3 months after ESG. ESG significantly improved insulin sensitivity and postprandial glucose values, measured by using the area under the curve, demonstrated a significant decrease (36%). There were no statistically significant changes in leptin, GLP-1 and PYY levels [159].

Techniques with Unknown Status

Two new techniques have been reported. The transoral mucosal excision sutured gastroplasty has been described in a first-in-man study in four patients and the second, the transoral anterior-to-posterior greater curvature plication (Endolumina), reports their preliminary data in 11 patients.

Transoral Mucosal Excision Sutured Gastroplasty (SafeStitch Medical Inc., Miami, USA)

Aiming for full-thickness durable plications the method is used both for obesity and for GORD. The procedure consists of mucosal excision, suturing of the excision beds for apposition and suture knotting at the level of the gastro-oesophageal junction. An excision device retracts gastric tissue of the greater curvature by applying a vacuum. A hypertonic saline and adrenaline solution is injected in the retracted tissue for vasoconstriction and the (sub)mucosa is excised. This is repeated twice to create a confluent adjacent excision bed. Two sets of full-thickness sutures are placed on the sides of the excision bed. The sutures are tightened and knotted using

a stitch knotter. The plication of the treated area also partially closes the gastro-oesophageal junction. By injecting hypertonic saline in the proximal lesser curvature a restrictive fibrotic ring ensues. Three patients with GORD and four obese patients have been treated but the first two GORD patients had incomplete procedures due to instrument malfunction [196]. After the procedure the endoscopist rated the suture and excision not optimal in three and satisfactory in one. One of these patients suffered from a pneumoperitoneum without evidence of a perforation at laparoscopy and was treated conservatively. She developed repeated vomiting and at 6 and 12 months the gastroplasty integrity was disturbed with small gaps of 2 mm; she also had the least beneficial weight loss outcomes. No gaps were observed in the other three patients. Weight losses at 3 months varied between 2 and 19% EWL, at 6 months between 4 and 25%, at 12 months between −0.08 and 37% and at 24 months between 0 and 68% EWL. One patient suffered from intermittent dysphagia [196]. The current status of the technique is unknown.

The Transoral Anterior-to-Posterior Greater Curvature Plication (Endomina, EndoTool SA [STT], Gosselies, Belgium)

This system creates transoral anterior-to-posterior greater curvature plications to reduce gastric volume, using an over-the-scope triangulation platform capable of delivering a single interrupted suture anchored by two T-tags. Two guidewires are introduced down to the duodenum. Then, the Endomina platform system is gently introduced over the guidewires into the stomach. The endoscope follows the system and when arrived in the stomach the guidewires are retrieved, the system is opened like the jaws of a crocodile and between them the endoscope is inserted and fixed to the system. Next, a 5 French needle preloaded with a T-tag fixed at a suture (Transmural Anterio-Posterior Endoscopic Suture [TAPES, ETT, Gosselies, Belgium]) is introduced into the flexible arm of the platform. This arm is bent perpendicular to the axis of vision. The stomach wall is grasped with a forceps via the endoscope and pulled back into the platform. The needle is pushed through the wall, under visual control, and a first T-tag, attached to the suture and a pre-tied knot are released. The needle is retracted, the first plication is released and a second plication is made with a second T-tag at the opposite wall of the stomach. APC is applied around the two wire entry points to destroy the mucosa and ensure adhesion of tissue apposition. Then, the pre-tied knot is grasped with a hook and tightened until both plications are firmly apposed. The double plication involves now two serosa-to-serosa appositions and one mucosa-to-mucosa apposition at the level of the coagulation. Huberty et al. reported 6-month weight loss outcomes of 11% TBWL in ten patients with no major adverse events [197]. Although the results are encouraging and in par with those of other gastric remodelling techniques, final data on the safety of this device as well as long-term efficacy are still unavailable.

2.3.2.2 Gastric Stapling

Three systems of endoscopic stapling exist but, in contrast to the USGI-POSE and the Apollo OverStitch which were first applied in patients with post-bariatric complications and had their systems already approved by the FDA for tissue apposition

for this indication, and thus easily rolled into the application of their method as primary treatment, these systems had to make a fresh start with a lot of development costs. To demonstrate this more in detail, BaroSense first explored a range of device prototypes and design implants, surgical technique and gastric attachment schemes in over 200 dogs. Then safety and durability of the plication method over time were demonstrated in a series of 18 animals, and finally the ability to transorally create and cannulate plications, place anchors, and deliver and attach the restrictive implant needed an additional series of 50 animals [198]. The high development costs and the costs of different human trials, with many adaptations and subsequent new animal work, and in the end, despite all the work, negative outcomes, are the reasons why these companies went into bankruptcy. Only one, the ACE stapler, was promising enough to be taken over by another company.

TransOral Gastroplasty (TOGa) (Satiety Inc., Palo Alto, CA, USA)

The TransOral Gastroplasty uses an endoscopic stapling device, the TOGa Sleeve Stapler, to create full-thickness, serosa-to-serosa, plications of the anterior and posterior walls in the proximal stomach. The TOGa system is composed of a flexible 18 mm shaft device that is introduced into the proximal stomach over a guidewire. The endoscope is passed through a special channel within the shaft. Once its position is confirmed endoscopically, a "sail septum" is deployed to stabilise the anterior and posterior walls of the body and greater curvature and to prevent their incorporation into the sleeve. Suction pods located within the stapling device are activated, bringing lesser curvature tissue within the jaws of the device. The stapler is then fired and three rows of 11 titanium staples each are delivered to create a transmural suture, with serosa-to-serosa apposition. This process is repeated to create a sleeve of the desired length extending over a length of 8–9 cm distally from the oesophagus beginning at the angle of His and parallel to the lesser curve. The sleeve outlet is then constricted from 20 mm to approximately 12 mm using the TOGa restrictor which clamps and staples gastric folds together after acquiring tissue via suction. The surgical analogue of this operation is the vertical banded gastroplasty [180] (Table 2.5). Devière et al. reported the first results in 21 patients (BMI 43.3 kg/m^2) with a weight loss of 12 kg, an EWL of 24.4% and BMI loss of 4.8 BMI units at 6 months [199]. There were no serious adverse events, although pain, nausea, vomiting and temporary dysphagia were reported. However, at the 6-month endoscopy, gaps between the two staple lines were evident and a fully intact sleeve was present in only 5 of 21 patients. A re-restriction was allowed but only one patient underwent a re-restriction. With improved techniques and perioperative administration of methylprednisolone and diclofenac, a second trial in 11 patients demonstrated a 24.0 kg weight loss, a 46.0% EWL and a decrease in BMI with 8.5 units at 6 months [200]. An intact sleeve persisted in 7 of the 11 patients at 6 months. Two patients underwent additional restrictions at 3 months because of insufficient weight loss and five restrictions could be placed. The TOGa multicentre study involved 67 patients who underwent the procedure successfully with two complications of a respiratory insufficiency and an asymptomatic pneumoperitoneum [201]. Fourteen patients did not complete the follow-up: 53 patients showed a weight loss of 19.5 kg,

a 7.6 kg/m^2 decrease in BMI, a 44.8% excess BMI loss and 38.7% EWL at 12 months. Patients with a BMI ≥40 kg/m^2 had 52.2% EWL and patients with BMI <40 kg/m^2 had 41.3% EWL. There were significant improvements in haemoglobin A1c (decline from 7.0% to 5.7%), HDL cholesterol and triglycerides. Partial dehiscence of the staple line was seen in 25 at the 12-month endoscopy, 7 proximally and 16 distally, and 2 patients had the combination, without a deleterious effect on weight loss. The conversion of TOGa into a laparoscopic RYGB or sleeve was easy without excess time and difficulty [200, 201]. Nanni et al. reported the results of 29 patients enrolled in the FDA-approved pilot study "Endoscopic Bariatric Stapling Pilot Study (TOGa®)" which would include 86 patients [202]. The average weight loss was 16.8 kg, 14.9% TBWL and a loss of 6.2 BMI units. The pilot study was never completed and the application is at present interrupted because of bankruptcy of the company.

Transoral Endoscopic Restrictive Implant System (TERIS) (BaroSense, Redwood City, CA, USA)

The transoral endoscopic restrictive implant system (TERIS) is aimed at endoscopically implanting a prosthesis at the level of the cardia, to decrease the size of the food reservoir of the upper part of the stomach creating a restrictive pouch, with a 10 mm orifice for food entering the distal stomach, being an endoscopic equivalent to gastric banding [180, 203] (Table 2.5). Five plications were made at the level of the cardia, 3–5 cm under the gastro-oesophageal junction. These plications were used to attach the gastric restrictor using silicone anchors inserted in the plications. Each plication was made using an articulated endoscopic circular stapler. This stapler can acquire a full-thickness gastric plication through suction, compressing the tissue and then creating two concentric rings of 3.5 mm staples, and excise the tissue within the ring to create a plication hole. Then a silicone anchor was brought down and the proximal end was pulled under direct visualisation through the plication hole and then released. Four other anchors were placed in a similar fashion. Five locking anchor graspers were advanced through a multilumen guide and attached to the anchors. The multilumen tube was then removed and the restrictor was advanced into the cardia. The anchors were then pulled through the restrictor's attachment holes one by one. After each anchor had been attached the graspers were removed, and finally the position of the restrictor was inspected. If needed, the silicone implant is removable. For a device-removal procedure, a 22 mm endogastric tube was advanced and a specially designed removal instrument system was advanced through the endogastric tube. With the assistance of an endoscope, graspers were used to pull the head of an anchor into the shaft of the removal instrument. An internal cutting snare was activated to cut the anchor. The grasper removed the anchor and this process was repeated for all anchors. After all anchors were cut and removed, the restrictor was grasped with a grasper and withdrawn through the endogastric tube.

In total, 12 of 13 implantation procedures were successful with three complications in the first seven patients, once a gastric perforation due to stapler malfunction – this patient was operated and the perforation oversewn – and twice an

asymptomatic pneumoperitoneum, once treated conservatively and once by deflation by a hollow 16-gauge needle placed in the left flank [204]. In one patient due to limited manoeuvrability only four anchors could be placed. The study was put on hold and after technical improvements restarted and no procedural adverse events were seen in the next five patients. At 3 months an EWL of 22.2%, a decrease in body weight of 16.9 kg and a decrease in BMI from 42.1 to 37.9 kg/m^2 were observed [204]. As the system was designed as a 6-month bridge to surgery, the safety and efficacy results were investigated in the total number of 18 patients [198]. At 6 months, weight loss was 15.1% and EWL and excess BMI loss were 30.1% and 37.7%, respectively, demonstrating that TERIS was feasible and effective as a bridge to surgery. Mean waist circumference decreased by 18.7 cm. HDL cholesterol increased and HbA1C decreased significantly at 6 months. Two insulin-dependent diabetic patients did not need any insulin injections during the course of the study, and two other diabetics lowered the doses of oral medication. Four patients underwent an uncomplicated surgical procedure (three a gastric bypass and one a gastric band procedure) [198]. However, at the 6-month endoscopy 6 of the 16 successfully implanted patients had 1–3 detached anchors (37.5%). Their implants were removed. Of those who wanted to continue the treatment till up to 12 months, only two had a fully attached and intact device on the 12-month endoscopy. The colours of the anchors helped in the orientation and showed that mainly the lesser curvature anchors appeared to detach. The lesser curve seems to be a difficult area to attach to due to the thin muscle layer in this area of the stomach [198]. This terminated the TERIS technique. However, the stapling system functioned well, firing circular staples at a pressure of 6 bar and guaranteeing a full-thickness stapling with serosa-to-serosa application. A redesigned version of the stapler could make even larger plications, and studies with the articulating circular endoscopic (ACE) stapler as a means of endoscopic gastric volume reduction continued.

Articulating Circular Endoscopy (ACE) stapler (BaroSense, Redwood City, CA, USA, acquisition by Boston Scientific Corporation, Marlborough, MA, USA)

The articulating circular endoscopic (ACE) stapler is an endoscopic stapler with a head capable of 360-degree rotation and complete retroflexion. Vacuum suction is used to acquire tissue. Full-thickness plications are created by firing 10 mm plastic rings with eight titanium staples. After the placement of an overtube the ACE system and an ultrathin endoscope used for visualisation are introduced. The stomach tissue is imbibed inside the cover of the stapler by applying a vacuum at 6 bar, the tissue is then compressed by hydraulics inside the stapler and a 10 mm plastic ring with eight staples is fired creating full-thickness plications. The procedure starts high in the fundus in retroflexion with eight plications in the fundus to reduce the gastric volume. Two plications are created in the antrum to delay gastric emptying. The technique resembles the laparoscopic gastric plication surgery (Table 2.5).

Verlaan et al. included 17 patients (median BMI 40.2 kg/m^2) of whom 15 were available after 12-month follow-up [205]. They reported the safe placement of 160 plications in 17 patients which were still evident and appeared durable at endoscopy 12 months later. At that time endoscopy in 11 of the 17 patients revealed 6–9

plications and an important gastric volume reduction. The % EWL after 3, 6 and 12 months were 16.0%, 25.6% and 34.9%, respectively. Median BMI fell from 40.2 kg/m^2 to 34.5 kg/m^2 and median TBWL was 15.3% at 12 months. There were no serious adverse events and the most common adverse event was abdominal pain (seven patients). A sore throat, diarrhoea, nausea, constipation and vomiting were also reported but all were self-limited. Comorbidities including dyslipidaemia, hypertension, diabetes and obstructive sleep apnoea improved [205]. Van der Wielen et al. studied 10 of these 17 morbidly obese patients (BMI 39.8 kg/m^2) to gain insight into the long-term effects and underlying mechanisms of gastroplication [206]. Plasma adiponectin, HbA1c, and number of interleukins such as IL-1β, IL-6, IL-7, IL-8, tumour necrosis factor α (TNF-α), interferon-γ (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-1 (TGF-1) and C-reactive protein (CRP) levels were determined at the start and after 12 months. At these times, also mucosal biopsies were collected from the fundus, antrum and duodenum and studied for gene expression using microarray analysis. After 12 months the BMI decreased to 33.4 kg/m^2 and the % EWL was 37.9%. Glycated haemoglobin (HbA1c) was significantly decreased ($P = 0.004$) by the treatment from 6.17% to 5.32%. Adiponectin showed a 1.64-fold increase and plasma IL-6 showed a tendency to decrease following ACE stapler treatment by a factor of 1.47. MCP-1 levels also showed a decrease (1.3-fold), but this effect did not reach statistical significance [206]. Fasted plasma ghrelin increased but on biopsies of the fundus there was a downregulation of MBOAT4, the gene encoding the ghrelin-activating enzyme GOAT4 and a trend for downregulation of ghrelin expression itself. Downregulation of inflammatory genes and gene sets was also observed on biopsies which coincided with improved HbA1c and adiponectin levels [206]. They could, however, not establish – by lack of a control group with a similar weight loss without the device – whether the reduction of inflammatory tone in the upper gastrointestinal tract might be a consequence of an improved metabolic health status and weight loss or alternatively caused by the procedure itself. Unfortunately, studies are at present on hold because the company went into bankruptcy and is taken over by Boston Scientific Corporation.

2.4 Intestinal Endoscopic Bariatric and Metabolic Therapies

2.4.1 Non-invasive Endoscopic Bariatric and Metabolic Therapies

2.4.1.1 The Duodenojejunal Bypass Sleeve (DJBS) or Duodenojejunal Bypass Liner (DJBL) or Endobarrier (GI Dynamics, Boston, MA, USA)

Until recently, the second-in-line in frequency and ease of application after balloon treatment was certainly the bypass of duodenum and proximal jejunum by the duodenojejunal bypass sleeve, also known as EndoBarrier gastrointestinal liner or simply the Endobarrier (Fig. 2.1). This is a totally different concept when compared to

the gastric EMBTs, which, in addition to early satiety and delayed gastric emptying, aims at creating a duodenojejunal bypass. As the nutrients flow inside the sleeve and the pancreatobiliary secretions remain at the outside, it creates a barrier to nutrient absorption in the duodenum and proximal jejunum and delays the mixing of food with pancreaticobiliary secretions until more distally in the jejunum. Its surgical analogue is the Roux-en-Y gastric bypass (Table 2.5). The device is a 60 cm long, ultrathin, impermeable Teflon sleeve that is anchored in the duodenal bulb and extends into the proximal jejunum. By endoscopy a guidewire is introduced into the duodenum. After removal of the endoscope, the device which consists of a capsule at the distal end, holding the sleeve and the anchor, is advanced into the small bowel under fluoroscopy. First, the impermeable 60 cm Teflon sleeve is deployed by pushing the inner sheath of the catheter with an atraumatic ball at the end into the proximal jejunum. The ball and the sleeve are then released from the inner catheter and the ball passes under peristalsis. Once the sleeve is fully extended, a self-expanding 5.5 cm nitinol (nickel-titanium alloy) stent or crown with barbs is released into the duodenal bulb, 5 mm distally from the pylorus, to hold the device in place, under direct endoscopic visualisation. Ten barbs allow for stent or crown stabilisation and secure the crown to the muscularis propria. To remove the DJBS polypropylene drawstrings attached to the stent allow for collapse of the stent and retraction of the barbs from the duodenal bulb. The collapsed stent is then withdrawn into a protective plastic foreign-body retrieval hood mounted on the endoscope to avoid trauma to the stomach or oesophagus, and the entire device is withdrawn from the gastrointestinal tract along with removal of the endoscope. Escalona et al. modified the DJBS with a proximal flow-restricting orifice of 4 mm diameter in a small study of ten patients with an average BMI of 40.8 kg/m^2 which resulted in a percentage of EWL of 40% at 24 weeks [207]. Episodes of nausea, vomiting and abdominal pain required endoscopic dilation of the restrictor orifice in eight patients, with no clinically significant adverse events.

A systematic review by Patel et al. and a meta-analysis by Zechmeister-Koss et al. reviewed the ten available studies [208, 209]. There were six open studies [207, 210–214] and four randomised studies [215–218]. Of the four randomised studies, two are truly double blind and sham controlled [215, 217]. The 4 RCTs involved 95 DJBS patients, of whom two-thirds (61 patients) completed the study duration of 12–24 weeks, and 60 controls, 25 on a diet and 35 having sham placement, of whom 75% (43 patients) completed the trial [215–218]. Three of the four studies were designed to achieve preoperative weight loss and one to treat diabetic patients. The meta-analysis of these four RCTs concluded that in patients with obesity ≥grade I (BMI 30–34.9 kg/m^2) and type 2 diabetes there was a marginal greater reduction in weight loss (8 kg vs. 7 kg, NS) and in patients with obesity ≥grade II (BMI of 35–39.9 kg/m^2) (+ comorbidities) a significant and clinically relevant reduction in excess weight (12–22%) up to 12 weeks was seen, but effects on metabolic function expressed in terms of HbA1c and fasting blood glucose were unclear [209]. The 4 RCTs and the 6 non-RCTs were included in the safety analysis with in total 282 patients [209, 219]. Positioning of the device failed in 18 and succeeded only after several attempts in five. Mainly a too short duodenal bulb or a sharp

angulation hindered successful positioning. There was a high number of early removals (n = 60; 24%) because of migration or rotation in 27, dislocation in 5, obstruction in 5, bleeding in 9 and intolerance in 10. Incompliance was the reason of early removal in four. The meta-analysis concluded that "While promising, the DJBS is not recommended for routine use but should be restricted to research settings only" [209]. Despite this scientific statement, the device was launched – outside the USA – as a metabolic intervention for those with a BMI >30 kg/m^2 and type 2 diabetes for the duration of 12 months. A recent meta-analysis in 2016 included 5 randomised controlled trials (235 subjects) and 10 observational studies (211 subjects) [220]. The risk of bias was evaluated as high in all studies. DJBS treatment compared with diet and/or lifestyle modifications alone resulted in a higher weight loss in obese subjects with significant mean differences in body weight loss of 5.1 kg and a 12.6% greater excess weight loss. The reductions in HbA1c and fasting plasma glucose were not significantly different and no changes in antidiabetic medication among the groups of obese patients were seen. In 20 patients the devices were not implanted. Adverse events were dominated by abdominal pain, nausea and vomiting. A total of 33 serious adverse events occurred. Additionally, 66 devices (19%) were explanted earlier than planned because of device migration, gastrointestinal bleeding, obstruction and abdominal pain or on investigator request. Furthermore, mucosal laceration during device removal was reported in three cases [220]. With respect to the many biases and distorting factors in the study design and data reporting, the authors requested future high-quality long-term RCTs to further assess efficacy and safety.

An important point to know is that the device did not interfere with subsequent gastric bypass or gastric banding in 12 patients and that intra-abdominal changes due to the device, as has been observed in animals, were not seen [217]. An interesting observation in the largest randomised study to date by Koehestani et al. requires further study: they found that significant differences in % EWL (19.8% in DJBS vs. 11.7% in controls) and HbA1c levels between the groups persisted for 6 months after the study completion [221]. A recent study by Vilarassa et al. confirmed these findings: 26 patients achieved a weight loss of 14.9% at the end of the 12-month DJBS period and retained 6.5% weight loss 12 months later [222]. At that time their HbA1c returned to pretreatment baselines, but of the 26.3% of patients who attained a HbA1c level of ≤7% during the DJBS period, 40% sustained this level over the next 12 months and the remainder experienced a lower increase of 0.7% [222].

The PIVI thresholds (Preservation and Incorporation of Valuable endoscopic Innovations (PIVI)) were also examined for the EndoBarrier/DJBS as this was the only device that had enough studies to evaluate (11 studies), besides the Orbera balloon with 82 studies [41]. For the DJBS meta-analyses, 11 studies met inclusion criteria. Of these, 9 reported adverse events and early removal rates, 3 reported % EWL at 12 months, 4 RCTs reported % EWL compared with a sham or control group at device removal, 9 reported changes in glycosylated haemoglobin (HbA1c) and three reported changes in HbA1c compared with a sham or control group in RCTs. Three studies enrolling 105 patients indicated that the DJBS may exceed the PIVI threshold of 25% EWL at 12 months by achieving a % EWL of 35.3% at

12 months. Four RCTs compared 12 to 24 weeks of treatment with the DJBS (90 subjects) with a sham or control arm (84 subjects). The mean % EWL difference compared with a control group was significant at 9.4%. However, the pooled % EWL of the DJBS over control did not meet the 15% PIVI threshold. So, the criteria for primary obesity treatment were not met [41]. Both of the above findings were associated with a high degree of heterogeneity. The DJBS demonstrated an impact on diabetic control after implantation, with decreases in HbA1c from 0.7% (NS) at 12 weeks to 1.7% ($P < 0.001$) at 24 weeks, and 1.5% ($P < 0.001$) after 52-week implantation. This improvement in HbA1c is statistically significant compared with a sham or control diabetic group, whereas it resulted in an additional 1% ($P = 0.001$) improvement in HbA1c compared with that seen in normal controls [41]. The published safety profile of the DJBS appears favourable based on experience with 271 implantations detailed in the literature (Fig. 2.9). Pain occurred in 58.7%, and nausea/vomiting in 39.4%. Early removal was needed in 18.4%. Serious adverse events included migration (4.9%), pain requiring early removal (4.2%), gastrointestinal bleeding (3.9%), sleeve obstruction (3.5%), liver abscess (0.13%), cholangitis (0.13%), acute cholecystitis (0.13%) and oesophageal perforation (0.13%) secondary to trauma from an uncovered barb at withdrawal [41].

Enrolment in the multicentre US pivotal trial, the ENDO trial, which compares the EndoBarrier DJBS with a sham endoscopic procedure in which no sleeve is

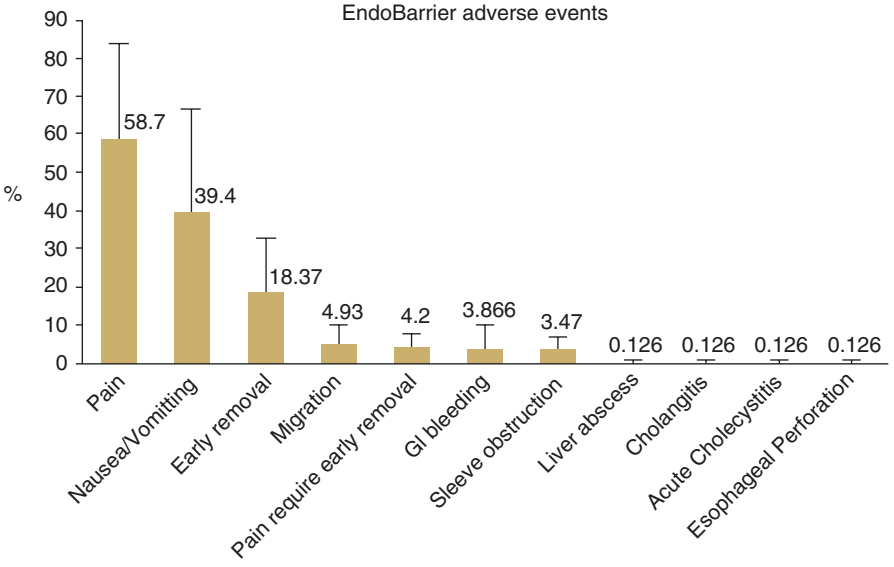


Fig. 2.9 Adverse events with the duodenojejunal bypass liner balloon as retrieved from 271 implantations detailed in the literature [41]. Reprinted from Gastrointest Endosc 2015; 82: 425–438, ASGE Bariatric Endoscopy Task Force and ASGE Technology Committee. Abu Dayyeh BK, Kumar N, Edmundowicz SA, Jonnalagadda S, Larsen M, Sullivan S, et al. ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies with permission from Elsevier

inserted, was placed on hold in March 2015 by the US FDA, because of a higher-than-expected incidence of liver abscesses (i.e. 3.5%, so higher than the established safety threshold of 2%). These adverse events, adequately managed with intravenous antibiotics and percutaneous drainage, were most likely related to translocation of bacteria from the anchoring system but posed a prohibitive risk for continuing the trial. Brethauer et al. reported a worldwide incidence of liver abscesses of 0.9% (29/3000) [111]. At the time of suspension of the study, 325 of the needed 500 subjects (active group $n = 216$, sham control $n = 109$; starting values HbA1c 8.8%; BMI 38.3 kg/m^2) had been included [223]. With two-third enrolment, subjects who received the DJBS lost significantly more weight compared with the sham group at 12 months (7.7% TBWL vs. 2.1%; $P < 0.001$) and had more significant improvement in HbA1c level (−1.1% vs. -0.3%) [223]. Efficacy endpoints were met with 60% of the DJBS patients losing 5% or more TWL and 34.8% achieving a HbA1c level of 7% or less (compared with 20% and 9.8% in the sham arm, respectively) [223]. Ninety-four percent of active subjects had successful DJBS placement. Early device retrieval owing to adverse events was present in 11% of patients [223].

Second-generation DJBSs with atraumatic anchoring and retrieval systems are currently investigated in clinical human trials.

2.4.1.2 Valen-Tx Bypass Sleeve (ValenTx, Inc., Carpinteria, CA, USA)

The ValenTx is an implantable sleeve that runs from the oesophagus down to the jejunum and is 120 cm in length (Fig. 2.1). The device acts to mimic the effects of the traditional gastric bypass by restricting the amount of food intake, excluding food from the stomach, the ghrelin-secreting gastric fundus and small intestine, and leaving undigested food exposed to the jejunum (Table 2.5). The procedure begins with placement of a long overtube, extending through the pylorus, into the duodenal bulb. Through this overtube the gastroduodenojejunal bypass sleeve (GJBS) is delivered via a delivery catheter under fluoroscopic guidance into the proximal jejunum. Once the sleeve is adequately deployed downstream into the bowel, the delivery catheter is removed, and the overtube is exchanged for a shorter overtube. The polyester proximal cuff is then positioned endoscopically at the gastro-oesophageal junction. The attachment is performed with eight endoscopically delivered, nitinol suture anchors, deployed circumferentially, with the assistance of laparoscopic visualisation to ensure transmural anchor placement and to avoid any visceral injury. Future applications will aim to secure the device by endoscopy alone. When removal is needed the device can be explanted with endoscopic cutting of the sutures.

In 24 patients (BMI 42 kg/m^2) the device was successfully delivered in 22 and endoscopically retrieved in all 22 [224]. Two patients had no placement, one because of non-compliance, and the other had severe inflammation at the gastro-oesophageal junction. Of the 22 patients with successful implantation, 17 retained the device for 12 weeks; these patients had 39.7% EWL or a 16.8 kg weight loss. Early post-operative dysphagia was the main reason for removal in five. Seven patients with diabetes had normal glucose levels and did not require medication. All four with elevated HbA1c had significantly improved levels. In 2015, Sandler et al. reported the results of 1 year in 13 morbidly obese subjects (BMI 42 kg/m^2), meeting the

NIH criteria for bariatric surgery [224]. One patient had no placement and two did not tolerate the device. In ten patients, the ValenTx remained in place for 1 year, six patients had fully attached and functional sleeves at the 1-year follow-up evaluation, and four patients had partial cuff detachment seen at follow-up endoscopy. For these ten patients, the mean percentage excess weight loss at 1 year was 35.9% whereas it was 54% EWL among the six patients with intact sleeves [225]. 70% of all comorbidities resolved or significantly improved. Upon endoscopic removal, no cuff ingrowth was noted at the gastro-oesophageal junction, no adhesions were noted between the sleeve and mucosa in the stomach or small bowel and the mucosa appeared healthy and normal. No significant bleeding, erosion or oesophageal leakage was experienced at the time of removal. Of the six patients with a fully attached device, five were followed for an average of 14 months post-explant, so 26 months from the time of device implant. These five patients maintained an average percentage EWL of 30% at the 14-month post-explant follow-up [225]. In contrast to the DJBS, liver abscesses are not to be expected but due to its position at the gastro-oesophageal junction complaints of dysphagia and odynophagia may occur. The company is currently planning a US trial.

2.4.1.3 Mechanisms of Action of Endoscopic Bypass Procedures

The duodenojejunal and the gastroduodenojejunal bypass sleeves mimic the effects of a gastric bypass by creating a physical barrier that allows food to bypass the duodenum and proximal jejunum without mixing with bile and pancreatic enzymes until later in the gut, thus potentially altering the incretin pathways and the enteroinsular system [148]. In gastric bypass surgery, the rapid improvement of diabetes before any weight reduction has occurred can be explained by two hypotheses: the foregut and the hindgut hypothesis [226–228]. De Jonge et al. have shown that after 24 weeks of implantation of the DJBS, patients had lost 12.7 kg ($P < 0.01$), while haemoglobin A1c had improved from 8.4% to 7.0% ($P < 0.01$) [229]. Both fasting glucose levels and the postprandial glucose response were decreased at 1 week after implantation and remained decreased at 24 weeks. The foregut hypothesis suggests that improved glycaemic control results from a reduced secretion of diabetogenic hormones or anti-incretin factors due to the absence of nutrients in the proximal small intestine. Intestinal glucagon synthesis and gastric inhibitory peptide or glucose-dependent insulinotropic polypeptide (GIP) have been suggested to decrease after exclusion of the proximal small intestine [226]. In accordance with the foregut hypothesis de Jong et al. discovered that prevention of digestion and uptake of nutrients by the DJBS were associated with a decreased secretion of glucagon, a diabetogenic factor, as well as a decreased secretion of GIP, which is secreted in the proximal small intestine and affects glucagon secretion [229]. The second hypothesis is the hindgut hypothesis which attributes the improved glycaemic control to the enhanced secretion of incretins such as glucagon-like peptide-1 (GLP-1) and enhanced secretion of peptide YY (PYY) in response to undigested nutrients in the distal small bowel [227, 228]. The observed increased GLP-1 secretion of de Jong et al. is in agreement with the hindgut hypothesis [229]. Furthermore,

they investigated whether the early improvement of diabetes could be explained by a decreased inflammatory state which was not the case [230]. One other study found an increase in fasting peptide YY (PYY), a gut hormone involved in appetite suppression [222]. However, increased fasting ghrelin levels, a gut hormone which stimulates hunger, was identified in two studies and could be related to the fasting state or to the decrease in weight, which both increase the orexigenic ghrelin levels [222, 231]. These two studies were also at variance with the study of de Jonge et al. as they could not demonstrate an effect on GLP-1 [222, 229, 231]. Moreover, whereas de Jonge et al. found a decreased secretion of glucagon in their 6-month DJBS treatment, fasting plasma glucagon concentrations in Vilarassa's study decreased at month 1 and were found to be increased at the end of their 12-months DJBS study, but unfortunately no data are available at the 6-month point of time [222, 229]. Parallel herewith HbA1c decreased 1.3% in the first month, but at the end of the 12-month study, the reduction was only 0.6% [222]. The primary endpoint of success, a HbA1c $\leq$7%, was achieved in only 26.3% of patients [222]. These conflicting findings may be the result of small sample sizes, difference in duration of DJBS treatment, differences in characteristics of patients regarding their diabetes such as duration, oral medication or insulin requirement, and differences in hormone level measurements either as fasting values or repeated samples before and during a standardised meal.

Gastric emptying was also studied in 25 patients with DJBS treatment [232]. While there was a significant decrease in gastric emptying, 16 weeks after DJBS implantation, compared to the basal situation, this recovered almost completely to normal after DJBS removal [232]. However, the delayed gastric emptying provoked by the DJBS did not correlate with glycated haemoglobin concentrations or weight loss success but might explain the abdominal side effects. The delayed emptying was explained by duodenal irritation and duodenal distension by the anchor of the sleeve, resulting in gastric relaxation [222, 232]. Unfortunately, no blood samples for gut hormones were taken, as cholecystokinin (CCK), GLP-1 and PYY are particularly important in the control of gastric emptying and are known to delay the gastric emptying. A delayed gastric emptying was also found when 15 sham patients and 14 patients with lifestyle modification therapy were compared with 25 DJBS patients: while the former had a normal gastric emptying (median % increase in gastric retention at 2 h of −1%) the DBJS had a 24% increase in gastric retention [70]. Further studies are necessary to elucidate the mechanisms responsible for weight loss and improved blood glucose control with the DJBS.

2.4.2 Invasive Endoscopic Bariatric and Metabolic Therapies

These rather new techniques are invasive as in the case of duodenal mucosa resurfacing they destroy temporarily the normal anatomy of the duodenum by burning the mucosa, and in the case of an incisionless magnetic anastomosis system they divert the digestive flow partly from the normal way through a jejunoileal shortcut.

2.4.2.1 Duodenal Mucosa Resurfacing (Revita, Fractyl Laboratories, Cambridge, MA, USA)

Duodenal mucosal resurfacing (DMR) or the Revita procedure is an endolumenal procedure, consisting of determination of the duodenal size, saline expansion of the submucosal space and hydrothermal ablation of the superficial mucosa layers. The duodenal mucosa is abnormal in patients with diabetes and exhibits abnormal hypertrophy and endocrine hyperplasia. From bariatric Roux-en-Y gastric bypass surgery, the beneficial effects of exclusion of an abnormal duodenal surface in type 2 diabetes from nutrient contact were known, perhaps through the reduction of putative anti-incretin mechanisms [148, 180, 226] (Table 2.5). By mucosa ablation at denaturation temperatures the triggering of a rejuvenative healing response was hypothesised [233]. First, a catheter with a terminal balloon is passed into the duodenum that has three needles spaced at 120° around the balloon's circumference. The needles are used to inject saline into the submucosal space in order to circumferentially separate and lift the mucosa from underlying tissues in the duodenal wall from 1 cm distal to the ampulla of Vater to proximal to the ligament of Treitz (Fig. 2.10a). After removal of the initial catheter, a second balloon catheter was introduced to perform thermal ablations of ≈10 s each at temperatures of ≈90 °C on the lifted area (Fig. 2.10b). A total of 39 patients out of 44 included with type 2 diabetes (screening HbA1c 9.5% [80 mmol/mol]; BMI 31 kg/m^2) could be treated: 28 had a long duodenal segment ablated (LS; ∼9.3 cm) and 11 had a short segment ablated (SS; ∼3.4 cm) [233]. Overall, DMR was well tolerated with minimal gastrointestinal symptoms of transient abdominal pain in 20%. Three patients experienced duodenal stenosis treated successfully by balloon dilation. HbA1c was reduced by 1.2% at 6 months in the full cohort ($P < 0.001$). At 6 months 29 of the 39 had some HbA1c reduction. More potent effects were observed among the LS cohort, who experienced a 2.5% reduction in mean HbA1c at 3 months versus 1.2% in the SS group ($P < 0.05$) and a 1.4% reduction at 6 months versus 0.7% in the SS group ($P = 0.3$) [234]. Interestingly, these beneficial effects were obtained without a dietary energy restriction and without any significant weight body loss (4.6% TBWL at 3 months and 3% TBWL at 6 months). The mixed meal data suggest that an insulin-sensitising mechanism is responsible for the effects on fasting glucose and HbA1c [233].

However, a very critical comment touched the authors on the raw: the observed reduction of HbA1c can also be achieved by medication and the effect on HbA1c is waning as it was less at 6 months compared with 3 months [234]. Five of the 44 patents were not suited for the treatment (10%) and 10 of the 39 patients (26%) were primary failures. Furthermore, the effects of the very-low-calorie diet immediately after the procedure which was built up over 2 weeks and the weight loss which are both adequate to restore insulin sensitivity might have been partly responsible for the observed changes [228, 234].

There are two ways of thermal ablation, either through the use of radiofrequency or through a recirculating hot-water-filled balloon. Currently, a multicentre study is being conducted in Europe and after modification and optimisation of the DMR procedure, by avoiding overlap of burns and adequate attention to the lifting of the mucosa at all sites, no additional duodenal stenosis or other serious adverse events have developed [235]. A US pivotal trial is planned.

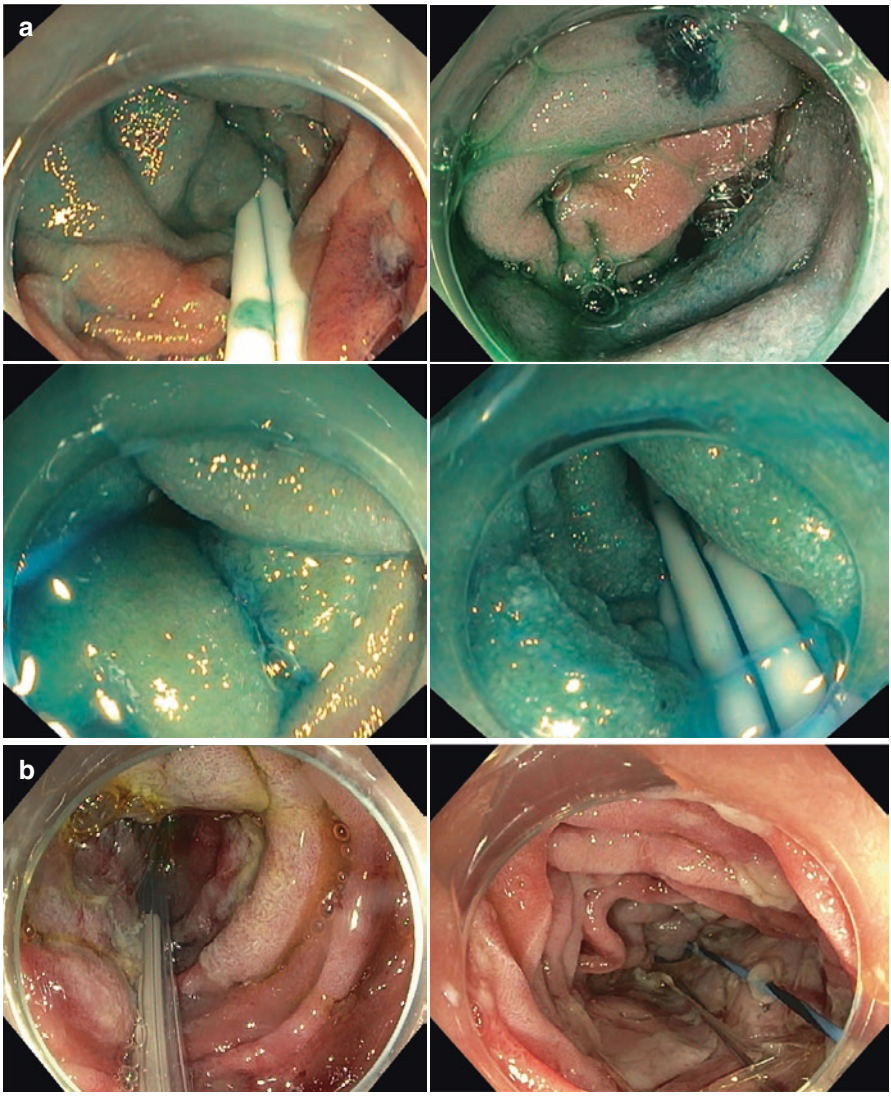


Fig. 2.10 Duodenal mucosa resurfacing: (**a**) the lifting of the mucosa with submucosal saline and methylene blue; (**b**) the white areas of mucosal ablation by heat. Pictures by courtesy of professor Dr. Jacques Bergman et al., Department of Gastroenterology and Hepatology, Academic Medical Centre, University of Amsterdam, the Netherlands

2.4.2.2 Incisionless Magnetic Anastomotic Systems (IMAS) (GI Windows, West Bridgewater, MA, USA)

An endoscopic incisionless magnetic anastomotic system (IMAS) has been developed using self-assembling magnets [236, 237]. The IMAS is preloaded into the instrumentation channel of the endoscope and by using simultaneous enteroscopy and colonoscopy two magnets are deployed in the gastrointestinal tract in the

jejunum and ileum under endoscopic and fluoroscopic visualisation and they form octagonal rings (Fig. 2.11a, b). Laparoscopic assistance confirms the adequate mating of the magnets and measures the end position of the anastomosis. The magnets mate, apply compressive force to the tissue between them, and create pressure necrosis and a large-bore compression anastomosis over several days. The magnets then disassemble and pass down the gastrointestinal tract. The magnets were expelled fully intact without pain at a mean of 23 days, without obstruction. The result is a large-bore anastomosis and a dual-path enteral bypass with the flow of food down both limbs via the native anatomy and through the jejunoileal anastomosis (Fig. 2.11c). The surgical analogue is the modified duodenal switch or ileal transposition (Table 2.5). A trial in ten subjects (six males) with BMI of 41 kg/m^2 reported successful device placement and anastomosis formation in all cases [238, 239]. Anastomoses owere widely patent at the 2 and 6 month's control endoscopy. Transient nausea and diarrhoea were reported in most cases. Diarrhoea, that persisted in a few cases, could be managed by diet adjustments. Without any lifestyle intervention or calorie-restricted diet, mean weight loss at 6 months was 12.9 kg, 10.6% TBWL or 28.3% EWL. Four patients with type 2 diabetes experienced a 1.8% haemoglobin A1c reduction and a 3.6 mmol/L lower fasting glucose. Three patients with prediabetes normalised their HbA1c and glucose levels. All diabetic patients were able to reduce or discontinue their diabetic medication within 6 months [240].

The theory behind this technology is that nutrient delivery to the distal small bowel will induce an ileal break phenomenon by PYY release, which will delay the gastric emptying and decrease food intake. The diversion of nutrients and bile to the terminal ileum will also activate bile-signalling pathways and enhance incretin secretion with an increase in GLP-1 levels postprandially [180, 240]. It is functionally similar to the biliopancreatic diversion with duodenal switch (without the sleeve or partial gastrectomy) and mechanistically similar to ileal transposition [180, 240].

2.5 Perspective of Endoscopic Bariatric and Metabolic Therapies

Because of the obesity epidemic and the obesity-associated diseases a large number of individuals will need treatment. Endoscopic treatment has the advantage of being cheap, minimally invasive, moderately time consuming, reversible and feasible as an ambulant procedure, without a steep learning curve as is the case with bariatric surgery. It has the disadvantage of limited durability. Endoscopic bariatric therapy appears well suited to bridge the current management gap between medical treatment, which consists of intensive lifestyle treatment and pharmacotherapy at the one side and bariatric surgery on the other. EBTs offer an effective weight loss intervention with potentially lower risks, lower costs and higher patient acceptability than bariatric surgery. Many EBTs also offer the potential added advantages of reversibility and repeatability, depending on the individual therapy.

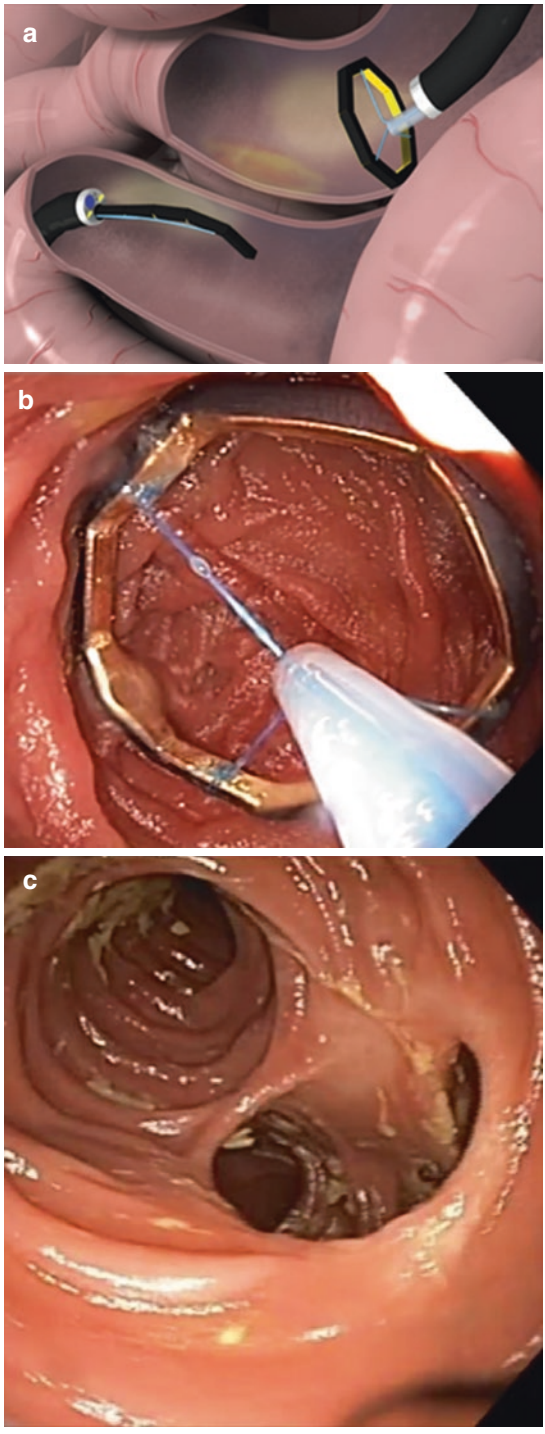


Fig. 2.11 The incisionless magnetic anastomotic system: (**a**, **b**) The deployment of two magnets by simultaneous enteroscopy and colonoscopy and the octagonal ring of the deployed magnet. (**c**) The large-bore anastomosis and a dual-path enteral bypass with the flow of food down both limbs via the native anatomy and through the jejunoileal anastomosis [240]. Reprinted from Gastrointest Endosc 2017 [published online ahead of print] doi: https://doi.org/10.1016/j.gie.2017.07.009.242, Machytka E, Bužga M, Zonca P, Lautz DB, Ryou M, Simonson DC, et al. Partial jejunal diversion using an incisionless magnetic anastomosis system: 1-year interim results in subjects with obesity and diabetes with permission from Elsevier

There are endoscopic gastric options such as balloons and aspiration therapy, which are all at the disposal of and practicable by endoscopists, but some have the disadvantage of limited durability. Yet, a 10% weight loss with improvement of obesity-associated comorbidities can be maintained after balloon removal by almost 50% for 1 year and by one-quarter of patients over 2.5 years. The FDA approved the Orbera balloon, the ReShape Duo balloon and the swallowable Obalon balloon for 6 months in subjects with a BMI between 30 and 40 kg/m^2. They also approved the AspireAssist aspiration therapy for patients with a BMI between 35 and 55 kg/m^2. Pivotal randomised multicentre trials to support regulatory approval in the USA are in progress or are planned for a number of devices.

Gastric suturing and gastric plication enable very skilled endoscopists to mimic gastric restrictive surgical operations. The gastric volume reduction devices mimic bariatric surgical interventions, but the mechanism of action of the existing endoscopic mimicry of bariatric surgery should be further investigated.

Endoscopic intestinal options are the duodenojejunal bypass sleeve, which is not available anymore because of the development of liver abscesses, but further modifications are awaited. Furthermore, data of duodenal resurfacing and jejunoileal bypass by magnet-induced wall apposition and pressure necrosis are very preliminary but look promising.

It may well be that future research will focus on the tandem and sequential use of a combination of endoscopic devices and obesity pharmacotherapies in addition to a comprehensive lifestyle intervention programme to augment and enhance the durability of weight loss with a lasting effect on obesity and its related comorbidities. However, cost-benefit analyses should always accompany these cost-enhancing combinations. Having all this information absorbed, the question "Are endoscopist definitely stepping into the arena of weight loss therapy?" which was answered with "I hope they will and I think they should" in 2015 [241] should now definitely be answered with a whole-hearted yes, when one sees what has been achieved over a period of only 2 years with four FDA approvals and two pending FDA approvals. The future is bright for "bariatric" endoscopists!

2.6 Laparoscopic Minimally Invasive Techniques

Neuromodulation represents a group of new surgical approaches to the treatment of obesity and associated metabolic disorders that involve the application of a small patterned electrical impulse to a target organ. The target organ may include true organs such as the stomach, duodenum, small intestine, adrenal glands, or brain, but also the vagal nerves. Changing the pattern and amount of energy delivered can also alter the desired effect. The impulse can augment or modify normal physiologic responses or block them. There is a growing body of research to suggest that the technology is safe. In addition, at least some of the neuromodulatory technologies have the potential to provide beneficial weight loss and positive effects on the associated metabolic conditions. To date, the published data with neuromodulation suggests that there may be potential for benefit with some of these technologies. Neuromodulation is supposed to offer safe and less complex

options to the conventional surgical approaches to morbid obesity. Although being a known part of the current bariatric armamentarium and not anymore belonging to the research field, the cost of these devices, with issues of battery replacement (which have been improved), renders them unavailable for a routine use worldwide.

Neuromodulation has the potential to evolve towards endoscopic applications. Because of extreme downsizing of current cardiac stimulators (and leads) being a reality nowadays, an endoscopic application of gastric stimulation is no challenge to conceive, albeit quite expensive. So far, this is a highly speculative topic, owing to the already important costs of current devices. Our guess is that these devices will be reconsidered as soon as downsized stimulators have been proven cost effective in the cardiology field, and pending other technical issues (such as the fixation of the device inside the gastric lumen) have been solved.

Several systems are currently competing. Two of them (Abiliti™ and Tantalus™) deal with a satiety-inducing stimulation that is monitored through gastric distension measurement, thus allowing a theoretical fine-tuning of electrical stimulation. A third one (V-Bloc™) aims at direct vagal stimulation, which has been suspected for a long time of being instrumental in decreasing hunger and enhancing satiety (as well as vagotomy). Trials are being conducted with each of these devices, some of them focusing more specifically on comorbidities such as T2DM.

2.6.1 Gastric Pacing

2.6.1.1 Surgical Implantation of Electrodes

The technical details of the positioning of the electrodes differ according to different existing devices, some of them being implanted directly on the vagal nerves, others on their branches at a variable location on the anterior part of the stomach: antrum, pes anserinus - i.e. final vagal branches on the lesser curve - or even fundus. Multiples sources are possible for implementing neurostimulation (several electrodes or just one) as well as multiple parameters of stimulation (frequency, pulse width and amplitude). Most often, the fixation of the electrode is mandatory, to avoid dislodgement or intragastric penetration, ending up with a failure to stimulate. With one current system (Abiliti), a sensor is inserted in the fundus, which is supposed to allow fine-tuning of the stimulation. These electrodes are connected to a subcutaneous pacemaker that is comparable in size and potential side effects (e.g. haematoma) to the cardiac devices, routinely implanted in the left upper quadrant of the abdomen. The device is then verified on a routine basis, a dedicated software allowing modifications of the stimulation parameters.

2.6.1.2 Involvement of an Endoscopist

While waiting for devices that can theoretically be implanted endoscopically, gastroenterologists are quite instrumental in dealing with these patients for the time being. Assessment of the gastroesophageal junction, detection of *H. pylori*, etc. are part of the routine screening. Some devices require an intraoperative check during the implantation of the electrode/sensor. Finally, endoscopy is

necessary if one suspects an electrode dislodgement or a transgastric erosion of the device.

2.6.1.3 Abiliti System (Intrapace Inc., San José, CA, USA)

This system is the direct continuation of a device initiated by Cigaina in 1999 in Italy [242], that produced variable outcomes [243]. It includes a simple stimulation electrode inserted approximately 4 cm from the gastro-oesophageal junction and 1.5 cm from the lesser curvature in the anterior wall (Fig. 2.12). This site corresponds with the point where the anterior vagal nerve (Latarjet nerve) divides into 3 branches. A transgastric food sensor is implanted in the body fundus region, about 3 cm from the greater curve with a distance between both electrodes of 3–4 cm. Peroperative endoscopy is performed to confirm the intragastric probe extension. The transgastric food sensor detects the entry of food into the stomach by distension and then triggers the gastric stimulator [244]. Horbach et al. assessed closed-loop gastric electrical stimulation (CLGES) versus laparoscopic adjustable gastric banding (LAGB) for the treatment of obesity, in a randomised 12-month multicentre

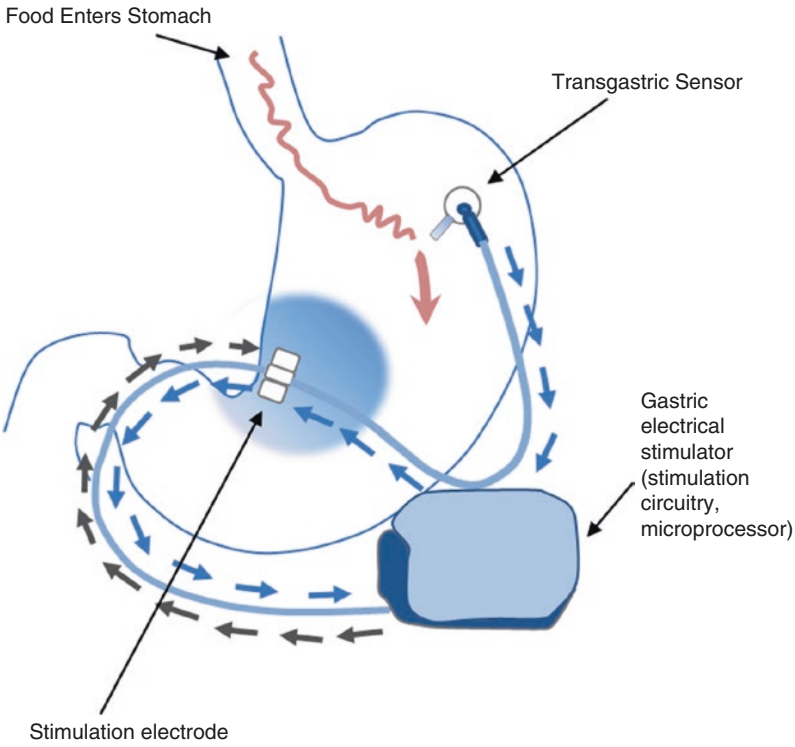


Fig. 2.12 Ability system with the transgastric sensor and gastric electrical stimulator [244]. Reprinted from Obes Surg 2015; 25: 1779–1787, Horbach T, Thalheimer A, Seyfried F, Eschenbacher F, Schuhmann P, Meyer G. Ability® closed loop gastric electrical stimulation system for treatment of obesity: clinical results with a 27-month follow-up (Open Access Article)

study [245]. This non-inferiority trial assigned the patients in a 2:1 ratio to laparoscopic CLGES versus LAGB and followed them for 1 year; 210 patients were enrolled, of whom 50 were withdrawn preoperatively. Among 160 remaining patients (age 39 years; BMI 43 kg/m^2), 106 received CLGES and 54 received LAGB. The first primary endpoint was the demonstration of non-inferiority of CLGES versus LAGB, ascertained by the proportion of patients who, at 1 year, fulfilled a ≥20% excess weight loss (EWL); no major device- or procedure-related adverse event (AE); and no major, adverse change in QOL, assuming a difference of <10% between the two procedures. The second primary endpoint was that ≥50% of patients had to reach ≥25% EWL in the CLGES group. At 1 year, the proportions of patients who reached all components of the primary study end-point were 66.7% and 73.0% for the LAGB and CLGES group, respectively, with a difference of −6.3% (upper limit of the 95% CI 7.2%, so non-inferiority proven). The second primary endpoint was also met, as 61.3% of patients in the CLGES group reached ≥25% EWL (lower 95% CI = 52.0%; $P < 0.01$). The quality of life improved significantly and similarly in both groups. Adverse events were significantly fewer and less severe in the CLGES (31%) than in the LAGB group (81%) ($P < 0.001$). More importantly, device-related adverse events were not different, 4.7% in the CLGES group and 13.0% in the LAGB group. Device replacement and lead fracture were seen in 4 subjects (4%), discomfort of the surgical pocket in eight (8%) and eight patients (8%) perceived the stimulation as painful.

2.6.1.4 Tantalus System (Metacure Inc., Australia)

The Tantalus system, now called DIAMOND, a meal-initiated gastrointestinal (GI) stimulator, aims at treating obese patients with T2DM (Fig. 2.13). Three year results were presented by Lebovitz et al. [246]. The aim was to investigate long-term benefit of non-excitatory gastric electrical stimulation (GES) by the DIAMOND device on glycaemic control and body weight in obese patients with T2DM inadequately controlled with oral agents, and to determine the magnitude of the modulating effects of fasting plasma triglyceride levels on the effects of GES. Sixty-one patients with T2DM (HbA1c between 7.0% and 10.5%) were implanted with the DIAMOND GES device and treated with meal-mediated antral electrical stimulation for up to 36 months. GES reduced mean HbA1c by 0.9% and body weight by 5.7% after 12 months. The effects were greater in patients with normal fasting plasma triglycerides (NTG, triglycerides ≤1.7 mmol/L) as compared to those with hypertriglyceridaemia (HTG, triglycerides >1.7 mmol/L). The mean decrease in HbA1c in patients with NTG averaged 1.1% and was durable over 3 years of follow-up. Improvement in HbA1c was a function of both baseline triglycerides ($P = 0.02$) and HbA1c ($P = 0.001$). However, the attrition rate was high as only 29 of the 61 device-implanted patients completed the 2 years and 8 the 3 years. There was a significantly different weight loss in NTG versus HTG patients. Whereas at 24 months a ≥10% weight loss was achieved by 7/13 patients in the NTG group; this was 0/16 in the HTG group. Also, weight losses at 12 months and 24 months were different: −4.7% and −9.4% in the 33 and 13 NGT patients, respectively, and −2.6% and −2.8% in the 24 and 16 HTG patients, respectively. One patient required device

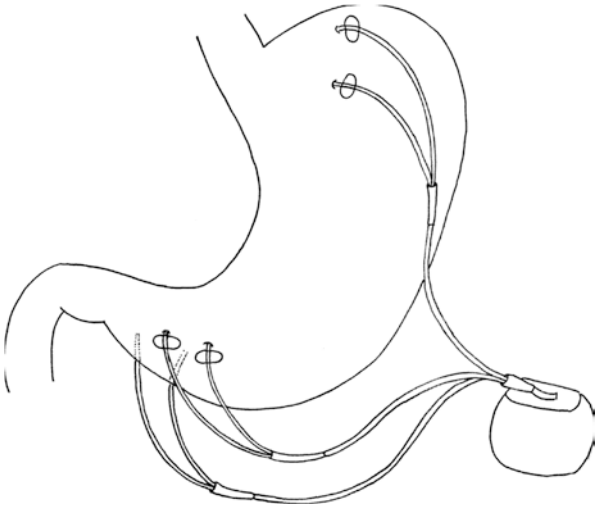


Fig. 2.13 Tantalus system with the sensing electrodes and the electrical stimulation electrodes

removal because of repeated infections around the implanted pulse generator. The authors postulated that GES creates a gut-brain interaction that modulates effects on the liver and pancreatic islets.

2.6.2 Vagal Blockade (Enteromedics Inc., St-Paul, MN, USA)

Truncal vagotomy has been suggested as an obesity treatment [247], and then advocated as an adjunct to a bariatric surgical technique such as vertical banded gastroplasty [248], but has become obsolete or had limited effects in the long term with sometimes persisting chronic side effects such as diarrhoea and vomiting. Yet, gastric pacing has taken this path, at least partially, with the vagal block stimulation from Enteromedics.

An active implantable device connected to 2 C-shaped electrodes positioned by laparoscopy on the anterior and posterior vagal trunks near the gastro-oesophageal junction is designed to induce intermittent sub-diaphragmatic vagal blocking for 12 hours or more per day in cycles of 5 minutes blockage and 5 minutes rest to allow the nerve to recover and to avoid tachyphylaxis [249]. This method has demonstrated clinically important weight loss and glycaemic control in obese T2DM subjects. Initial results were published by Shikora et al. [250]. VBloc-DM2 was a prospective, observational study of 28 subjects with T2DM and BMI 30–40 kg/m^2 to assess mid-term safety and weight loss and improvements in glycaemic parameters, and other cardiovascular risk factors with vagal blocking (VBloc) therapy. At 24 months, the mean percentage of excess weight loss was 22%, or 7.0% total body weight loss, both highly significant changes. Haemoglobin A1c decreased by 0.6 percentage points on average from 7.8% at baseline (significant). Fasting plasma glucose declined by 15 mg/dL (0.83 mmol/L) on average from 151 mg/dL (6.38 mmol/L) at baseline (non-significant). Among subjects who were hypertensive

at baseline, systolic blood pressure declined by 10 mmHg, diastolic blood pressure declined by 6 mmHg and mean arterial pressure declined by 7 mmHg (all $P < 0.05$). Waist circumference was significantly reduced by 7 cm from a baseline of 120 cm. The most common adverse events were mild or moderate heartburn, implant site pain, and constipation. Improvements in obesity and glycaemic control were largely sustained after 2 years of treatment with VBloc therapy with a well-tolerated risk profile. These results have been confirmed very recently by a large study in 162 patients of whom 123 remained in the trial at 24 months [251]. Of the withdrawals, 9 withdrew because of adverse events such as pain at the neurostimulation site in 5, the need for a MRI in 2, and heartburn and abdominal pain each in one. In the first year of the study 8 patients required nine revisions. In follow-up after this year there were only 4 revisions, 2 due to pain at the neurostimulation site, one had twisted leads and one had the inability to recharge the device. Weight loss at 24 months was 8%, and 58% of patients had a ≥5% TBWL and 34% a ≥10% TBWL. In patients with abnormal values LDL-cholesterol levels decreased, HDL-cholesterol levels increased and a significant improvement was shown in HbA1c, systolic and diastolic blood pressure. The FDA approved the device in the USA, and an ASMBS position statement acknowledged the role of vagal neurostimulation in the treatment of obesity, in a BMI range of 35–45 kg/m^2 [249].

2.7 Perspectives of Laparoscopic Minimally Invasive Techniques

It is difficult to foresee the future of gastric stimulation, but one can guess that more research will tell if current techniques have an "electrical counterpart" that could be exploited further. An important contributing information comes from sleeve gastrectomy, which results in the resection of the gastric natural pacemaker, creating aberrant ectopic pacemaker impulses or even bioelectrical quiescence, which persists long after SG, inducing chronic dysmotility [252]. It is too early to correlate these findings to potential new applications of neurostimulation, but building accurate models is an interesting start.

The main focus here is to find therapies for the treatment of T2DM by affecting the autonomic system and in particular the afferent vagal activity, whose nerves project on the brainstem on the nucleus tractus solitarius and information gathered here is translated into vagal efferent outputs that control the splanchnic organs. Biasi depicted the important role of the nucleus tractus solitarius in the treatment of T2DM and the future prospects in surgical and pharmacological modulation of the vagal transmission [253]. Among different leads, there are some examples of current clinical and experimental research. Non-invasive neurostimulation, e.g. transcranial, has been tested as a mild treatment of craving; vagal branches can also be a target, i.e. if applied to the intra-auricular cutaneous area [254]. The role of vagal nerve has even been further investigated: signalling fullness to the brain may be de-activated after long-term consumption of a high-fat diet in rats [255]. Finally, other parts of the digestive tract are being targeted, and for instance the

duodenum can be an interesting location: it has been shown that stimulation of this part of the digestive tract delayed gastric emptying and accelerated small-bowel transit while enhancing GLP-1 secretion in animal models [256].

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