Introduction

Obesity is a well-recognized disease that has reached pandemic proportions. Approximately 30% of the world population is overweight or obese, and every year, almost 3 million patients die from complications of obesity. In the United States, a significant percentage of adults are obese, but also 17% of children suffer from obesity. Obesity and its complications represent a substantial burden on healthcare, estimated at 14.3% of the US healthcare spending, corresponding to $427.8 billion and an incremental cost of $1,429/obese person per year.1,2

Only recently, in June 2013, was obesity considered a chronic disease by the American Medical Association.3 Multiple high-quality studies have shown associations between increased body-mass index (BMI) and multi-system conditions including coronary artery disease, type II diabetes, dyslipidemia, hypertension, stroke, atrial fibrillation, and osteoporosis.4,8 Non-alcoholic fatty liver diseases (NALFD) is often considered the hepatic manifestation of obesity and metabolic syndrome.9 Obese individuals who smoke have a markedly reduced life expectancy compared to non-obese smokers.10 Nearly 3.6% of all cancer cases in 2012 were attributable to obesity. These cancers include colorectal, esophageal, gallbladder, pancreas, liver, endometrial, postmenopausal breast, and thyroid cancer.11-13

Management of obesity has traditionally revolved around two approaches: noninvasive weight-loss strategies such as dietary and lifestyle changes, and invasive options represented in bariatric surgery. Despite the superiority of bariatric surgery in achieving weight loss, only 2% of eligible patients undergo surgery due to patients’ preference, increased cost, and limited access.14

As a result, a considerable gap exists in the treatment of obesity and its complications, and effective, less-invasive approaches are critically needed.

Diet and Lifestyle Changes

Although considered the first line of therapy, both diet and lifestyle modification have low efficacy in achieving significant weight loss. Approximately 3% of patients reach their target weight with dietary changes. The well-known limitation to any dietary therapy is modest weight loss and challenges of long term adherence to the diet. Furthermore, the optimal diet to achieve weight loss remains unknown. Very low-calorie ketogenic diet (VLCKD) for weight loss has been studied for many years. In a meta-analysis of twelve studies, 10.0 Kg of total body weight loss (TBWL) was achieved with VLCKD after up to 4 weeks and was sustainable on follow up after two years. This diet was also associated with improvement in waist circumference (−12.6 cm), hemoglobin (Hb)A1C (−0.7%), total cholesterol (−28 mg/dl), triglycerides (−30 mg/dl), AST (−7 U/l), ALT (−8 U/l), GGT (−8 U/l), systolic and diastolic blood pressure (−8 and −7 mmHg, respectively).15

High-intensity interval training (HIIT), a type of exercise that involves short bursts of high-intensity exercise interrupted by light exercise or recovery periods, has been shown to lower triglycerides and fasting glucose, systolic and diastolic blood pressure, decrease oxidative stress and inflammatory markers and improve cardiac function.16 However, no difference was found in BMI or weight loss with HIIT when compared to moderate-intensity continuous training.17,18

Intermittent fasting (IF) can be defined as alternating periods of eating and fasting, although no single quantitative description exists. Several different forms of IF have been described: alternate-day fasting, alternate-day modified fasting (ADMF), 5:2 diet, fasting-mimicking diet, and time-restricted feeding. IF has shown benefits in rodent models, independent of calorie intake.19 Multiple studies have focused on ADMF, described as alternating “fast” days (25% of daily calorie needs) with "feast" days (125% of daily calorie needs). Initial reports found that ADMF induces weight loss and improves glucose and insulin levels, blood pressure, lipids, and high-sensitivity C-reactive protein (hs-CRP) in humans.20,21 ADMF also reduces binge eating and depression in humans.22 However, the largest ADMF trial in humans showed ADMF is not superior to conventional diet for improving blood glucose, insulin, blood pressure, heart rate, lipids, visceral fat, hs-CRP, and homocysteine. Notably, the dropout rate for ADMF was higher than conditional diet (38% vs. 29%, respectively).23

Pharmacotherapy

Patients are considered candidates for drug therapy after failure to achieve at least 5% of TBWL with diet and lifestyle interventions alone. Suitable candidates generally have BMI > 30 kg/m2 or BMI > 27 kg/m2 with related comorbidity. Lorcaserin was recommended first-line pharmacotherapy in non-diabetic...
patients by some experts. It reduces appetite as a selective sero-
tolin 2C receptor agonist. The drug was initially approved by
the US Food and Drugs Administration (FDA) in 2012, but was
recently voluntarily withdrawn from the market due to concerns
about long term adverse effects. Adverse effects (AEs) include
headache, nausea, upper respiratory tract infection, pharyngitis,
and dizziness. Caution should be taken with type 2 diabetes due
to risks of hypoglycemia.

Phentermine is a noradrenergic, sympathomimetic amine that
decreases appetite through its central nervous system (CNS)
effects and the stimulation of the hypothalamus. It is one of the
most commonly prescribed and least expensive drug therapies
for weight loss. Common AEs include tachycardia, hypertension, tremor, overstimulation of CNS, dry mouth, and constipation. A combination of extended-release topiramate and phentermine was approved by the FDA in 2012 for weight loss. Phentermine-topiramate can lead to 8-10% TBWL. However, this drug combination should be avoided in patients with hypertension or coronary artery disease and is contraindicated in pregnancy.

Liraglutide is preferred in patients with type 2 diabetes. It is a
chemically modified glucagon-like peptide-1 (GLP-1) agonist, stimulates insulin release from pancreatic islets, and inhibits gastric emptying and reduces appetite through action on central satiety centers. When used at a higher dose (3mg daily injections) than usual doses in diabetes (1.8mg injection maximum daily dose), liraglutide was associated with a weight reduction of 2-4 kg compared to placebo. Saxenda is the trade name for the higher dose of liraglutide prescribed for weight loss. Liraglutide causes thyroid C-cell tumors in both rats and mice of both genders. No evidence of these tumors was found in human studies, and liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome types 2, 3, and 4.

Bupropion-Naltrexone combination can be considered in obese
smokers. Although the exact mechanism of action for weight
loss is unclear, the combination is thought to work in the
hypothalamus to promote satiety and inhibit the “reward
system” that various food induce. Bupropion-Naltrexone leads to approximately 5% TBWL at 56 weeks. After initial rejection by the FDA in 2011 for concerns of cardiovascular AEs, the combination drug was approved in 2014 following additional clinical trials addressing its safety.

Orlistat is one of the earliest pharmacotherapies approved for
weight loss (FDA approval in 1999 for obesity manage-
ment). It works by inhibiting gastrointestinal lipase and
reducing dietary fat absorption by approximately 30%. Compared to placebo, orlistat results in 3 kg average additional
weight loss when combined with behavioral interventions,
according to a meta-analysis of 12 trials. Use is limited by side
effects. Approximately 15-30% of patients taking orlistat experience abdominal cramps, flatus, and fecal inconti-
nence. Low levels of fat-soluble vitamins, especially vitamin
D, are common with Orlistat use. Acute kidney injury secondary
to oxalate has been reported, although the incidence is rare.

In general, the efficacy of the current pharmacotherapy is
limited to 5-10% TBWL in the majority of responding patients.
It is important to recognize that individual responses to drugs
vary widely. Weight regain is expected after medication dis-
continuation. Therefore, medications are usually used as an
adjunct to lifestyle changes and sometimes adjunct to surgery
or endoscopic interventions.

Endoscopic Interventions for Weight Loss

There are three main types of bariatric surgeries currently per-
formed for weight loss. Roux-en Y gastric bypass (RYGB) is
the most effective surgery, usually leading to 45%-55% TBWL.
Laparoscopic sleeve gastrectomy (LSG) has been gaining more
popularity over the last decade and has recently emerged as the
most commonly performed bariatric surgery. It leads to ap-
proximately 25% TBWL. The adjustable gastric band is now
less commonly used.

However, all current bariatric surgeries present multiple
challenges. The post-surgical morbidity rate can be high at 3-
20%. Mortality rates are approximately 0.1-0.5%. The need for
re-operation is around 8%, and 15% of patients become
malnourished. Additionally, 25% of patients regain weight
following initial weight loss.

In a survey of 284 patients with a BMI >40 or a BMI >35 with
obesity-related comorbidity, only 2% of eligible patients under-
go surgery. Further questioning showed that half of the patients
expressed a fear of operation, and 32% had a fear of dying.

Therefore, endoscopic bariatric (endobariatric) treatment is an
attractive option. This approach is minimally invasive, scar-
less, can be performed in an outpatient procedure room, and is
likely to be less costly than surgery. It is almost always reverse-
ble and repeatable. Most importantly, this approach may fill a
large unmet need in the management of obesity. (Figure 1)

Endoscopic intervention for weight loss can be divided into
stomach-focused interventions, and small bowel-focused
interventions.

A. Stomach Focused Approaches

1. Endoscopic Sleeve Gastroplasty

Endoscopic sleeve gastropasty (ESG) is a novel, incision-less,
minimally-invasive procedure developed as a non-surgical
alternative to sleeve gastrectomy for the management of
obesity. The procedure incorporates applying intraluminal full-
thickness sutures to plicate the stomach, resulting in significant
shortening and reduction in gastric volume.
Efficacy of ESG

There are consistent outcomes across multiple studies showing that ESG leads to TBWL in the range of 15-20.9% at six months, 12 months and 24 months. In a case-matched study, ESG resulted in significantly more TBWL at 12 months compared to high-intensity diet and lifestyle therapy (20.6% versus 14.3%, respectively, P < 0.001). More recently, five-year outcome data report TBWL of 18.1%, 17.3%, 20.8%, and 18.7% at 1-year, 2-years, 3-years, and 5-years, respectively. Importantly, ESG resulted in a significant reduction in metabolic comorbidities. In prediabetic and diabetic patients, HbA1C levels were reduced from an average of 6.6% to 5.6% one year following ESG. Some patients were able to stop insulin therapy. Systolic blood pressures decreased significantly by an average of 7mmHg and triglyceride levels by an average of 40mmol/dL after one year. Non-alcoholic fatty liver disease surrogates also improved following ESG. These alterations in metabolic profiles with ESG are similar to previously published surgical series and suggest potential alternative benefits beyond weight loss.

Learning Curve for ESG

To achieve competency in performing ESG, endoscopists need experience in endoscopic suturing and plication. To date, there is one study involving one operator examining the learning curve to competently perform the procedure. Efficiency was reached at 38 cases and mastery at 55 cases. Given the obesity epidemic, mastery of ESG with sufficient experience is possible and has the potential for wide adaptation in the care of bariatric patients.

PIVI Criteria

The Preservation and Incorporation of Valuable endoscopic Innovation (PIVI) thresholds, set jointly by the American Society of Gastrointestinal Endoscopy (ASGE) and the American Society for Metabolic & Bariatric Surgery (ASMSB), recommend efficacy targets of > 25% EWL at 12 months, and a safety threshold of < 5% risk of major complication for endoscopic bariatric treatments. ESG appears to meet these criteria.

2. Intragastric Balloon

Intragastric balloons (IGB) have been the major space-occupying stomach focused therapy for weight loss. Multiple balloons are currently available for commercial use and we discuss the commonly used IGBs:

ReShape Balloon: The ReShape Dual Integrated Balloon System (ReShape Medical) consists of two connected saline-filled spheres that are endoscopically placed and removed six months later. The device was FDA approved in 2015 following the REDUCE trial, a randomized sham-controlled trial comparing ReShape with diet and exercise against lifestyle modification alone. ReShape subjects had 6.8% TBWL compared to 3.3% in the sham controls. However, AEs were seen in 7.5-75% of patients, largely due to accommodative symptoms. Gastric ulcers were seen in 10.3% of patients with some improvement when decreasing balloon size. In 2018, ReShape Medical was purchased with plans for phasing out the balloon in favor of an alternative, the Orbera.

Orbera: The Orbera Intragastric Balloon System (Apollo Endosurgery) consists of a single saline-filled sphere that,
similar to ReShape, is endoscopically placed and removed six months later. It received FDA approval in 2015. In a multicenter randomized trial published in 2017, the Orbera arm achieved 10.2% TBWL compared to 3.3% in the lifestyle arm in 6 months. Over 50% of patients had accommodative symptoms of nausea, vomiting, and abdominal pain. Due to device intolerance or per patient request, 18.8% of patients had the Orbera removed early. The Orbera balloon is currently being investigated as bridging therapy to bariatric surgery in superobese patients.

**Obalon**: The Obalon Balloon System (Obalon Therapeutics) consists of three gas-filled balloons that are swallowed as deflated capsules. Placement of the capsules is confirmed under fluoroscopy and then inflated with a gaseous mixture with eventual removal after six months. The Obalon was FDA approved in 2016. The SMART trial, a randomized sham-controlled trial, showed an average 6.6% TBWL in the treatment arm after two years versus 3.4% TBWL in the control arm. Patients who completed at least twenty weeks of the balloons in place achieved a mean 10.0% TBWL.

Other intragastric balloons are under clinical investigation. The Elipse balloon (Allurion Technologies) differs in design compared to the other balloons. It is a swallowed saline-filled balloon that self-deflates and eventually excretes through the GI tract in roughly 16 weeks. The Sptaz3 Adjustable Balloon System (Spatz FGIA) is a fluid-filled balloon placed endoscopically, and its size can be further adjusted endoscopically in response to intolerance or weight loss.

**3. Aspire Assist Device**

The Aspire Assist device® (Aspire Bariatrics) consists of the placement of a large percutaneous gastrostomy tube, subsequently connected with a skin port to the external part of the device. Patients use this system to siphon off a portion of the ingested meal, typically one-third of the volume around twenty minutes after ingesting the food. The mechanism is an alternative to space-occupying therapies through partial disposal of ingested food to decrease the caloric burden following a meal. Unlike the standard PEG tubes, the Aspire requires both endoscopic placement and removal (Figure 4). The pilot study of aspiration therapy showed a 49% EWL after one year without any AE on eating behavior or compensatory eating. A 52-week clinical trial showed a mean 31.5% TBWL with Aspire Assist compared to lifestyle counseling in patients with BMI of 35.0-55.0 kg/m². They also reported clinically significant improvement in co-morbid metabolic parameters such as HbA1C and cholesterol, and a moderate improvement in blood pressure and low-density lipoprotein. Complications were mostly associated with gastrostomy tube placement and managed conservatively. The biggest concern is whether the Aspire Assist promotes bulimic tendencies however, multiple studies have demonstrated improved cognitive food restraint and increased satiety. For these reasons, this approach may be a good candidate for bridge therapy in high BMI patients to bariatric surgery.

**4. Transoral Outlet Reduction (TORe)**

One in four patients undergoing bariatric surgery regain weight. Enlarged gastric pouch and gastrojejunal anastomosis (GJA) is an independent predictor of weight regain following RYGB. Studies report a linear correlation between weight regain and dilation in the GJA. Surgical revision is associated with increased morbidity and limited efficacy and can be technically challenging. Endoscopic transoral outlet reduction (TORe) is a minimally-invasive endoscopic approach that can be used to restore the ideal pouch size and reduce the GJA outlet. Full-thickness sutures are placed using an endoscopic suturing device in a purse-string or interrupted fashion. A large multicenter international trial of TORe reported a mean weight loss of 9.31 ± 6.7 kg at six months and 8 ± 8.8 kg at 18 months following the procedure. A validation meta-analysis of 330 patients confirmed the efficacy and safety of TORe. The procedure duration is usually under 60 minutes, and it can be performed in an outpatient procedure room.

**B. Small Bowels-Focused Approaches**

1. Trans-pyloric shuttle

The trans-pyloric shuttle (TPS) (BAROnova) is a non-balloon space-occupying device that is inserted and removed endoscopically. It consists of a ball connected to a tether and passed through the pylorus into the duodenum to cause intermittent obstruction to stomach emptying (Figure 5). A small feasibility study of twenty patients, reported 25.1% and 41.0% EWL at 3 and 6 months, respectively. The TPS system was FDA approved in 2016 for use in obese adults with a BMI of 35-40 kg/m² or those with BMI 30-35 kg/m² with co-morbidities.

2. Dual-path Enteral Bypass / Incision-less Anastomosis System

The paradigm of creating a permanent anatomic alteration using mechanical compression was first described by Kaneshin et al. in 1978, to create a sutureless side-to-side anastomosis. Multiple IAS have been developed in the last decade, with the latest version by Ryou et al. using modified nitinol exoskeleton magnets to innately endoscopically recreate a Roux-en-Y gastrojejunal anastomosis. The self-forming octagonal magnets are placed endoscopically and aligned within the gastrointestinal lumen to create an anchoring window. From a technical standpoint, two endoscopes are required to access the small bowel – one magnet is placed 50-100 cm distal to the ligament of Treitz, and the other magnet placed 50-100cm proximal to the ileocecal valve. Placement is confirmed either fluoroscopically or surgically in earlier trials, prior to deployment. Through compression and focal ischemia, a large caliber fistula is formed creating a partial jejunal diversion. The magnets eventually disengage within a few weeks of placement. The goal of the diversion is for digested food to circumvent a large portion of the small intestine to reduce nutritional absorption, resulting in increased secretions of gut hormones.
The first pilot study of 10 patients showed a mean TBWL of 14.6% and EWL of 40.2% after one year. There was also a reduction in HbA1C of 1.9% from baseline. One surgical AEs was reported, with trochar disruption of the gastric serosa, repaired with sutures. Common AEs were nausea and vomiting, as well as recurrent diarrhea in 40% of patients, which resolved with dietary intervention. Long term data are still pending.

3. Duodenal Mucosal Resurfacing

Endoscopic duodenal mucosal resurfacing (DMR) is a minimally invasive procedure that incorporates circumferential thermal ablation of the duodenal mucosa, using catheters (Fractyl Laboratories). This is hypothesised to alter nutrient interactions with the duodenal mucosa to improve metabolic homeostasis. In a study of 36 obese patients with type 2 diabetes, HbA1C and fasting blood glucose improved significantly following DMR. However, only modest weight loss (−2.5±0.6 kg) was reported and one patient developed serious AEs of fever, malaise, and elevated CRP.

Who is the ideal candidate for endoscopic interventions?

It is unknown which patients would be ideal for endoscopic interventions, and further studies are needed to address this question. However, the available procedures can be offered to patients who fail to reach their target weight with diet and lifestyle changes. The following criteria can be used when choosing endoscopic therapy:

- BMI 30-44 kg/m².
- Poor surgical candidate.
- Bridge to surgery (such as knee replacement or transplant surgery).
- Failed treatment of post-surgery complications.
- Early intervention.

Conclusions

Weight-loss approaches with the highest chance to succeed should be individualized and can include different therapeutic modalities, and should focus on the long-term outcomes. Endobariatric treatment is emerging as a safe, minimally-invasive, cost-effective approach. Endoscopic sleeve gastoplasty has been endorsed for broader use by experts, but further research is needed to optimize patient selection before greater adoption of the new techniques.

Figures

Figure 1: Endoscopic interventions for weight loss can fill in the gap in the management of obesity

Figure 2: Apollo OverStitch device
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