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Review Article

Obesity and Current Treatment Approaches: A Comprehensive Review

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Abstract

Obesity is a global health burden and is closely associated with severe chronic co-morbidities, which remain the leading causes of death. Significant progress has been made in the treatment of hypertension, diabetes, and hyperlipidemia over the last half-century. However, advancements in the management of obesity have been slow, with some medications exhibiting inadequate efficacy and dangerous side effects. Improved understanding of the gut-brain axis has inspired the pursuit of novel medications aiming to provide sustainable and safe weight loss. Current evidence-based practices for obesity management involve multi-modal approaches, including lifestyle modification, mechanical gastric restriction, modulation in the secretion of multiple gut hormones, alteration in the composition and secretion of bile acids, and alterations of the gut microbiome. Each physician is responsible for recognizing obesity as a disease and assisting patients in appropriate management based on strong evidence and a good safety profile, aligned with the patient's goals. Through this review, we aim to inform the readers of recent approaches for managing obesity and comparing their beneficial effects and efficacy on obesity and its long-term co-morbidities.

Introduction

The relationship between diet and chronic diseases such as hypertension, diabetes, colon cancer, and obesity has undergone extensive investigation, supported by a large number of data, indicating a causal relationship between them. Globally, mortality has shown strong associations with diets low in whole grains, high in sodium, and low in fruits.[1] Recent increases in obesity rates have been attributed to unhealthy eating habits and food choices leading to excessive energy intake.[2] Many studies have recognized the positive correlations between energy density, weight, and other markers of metabolic syndrome.[3] The problem of obesity or overweight accounts for two-thirds of the U.S. population. Obesity, a global health burden, is associated with comorbidities, such as diabetes mellitus, coronary artery disease, hypertension, and other systemic health issues, which are the leading causes of death.[4] In the modern era, obesity is typically defined as a body mass index (BMI) ≥30 kg/m^2, while a BMI value of 25–29.9 kg/m^2 is classified as overweight. Dietary factors, lifestyle, genetics, and environmental factors significantly contribute to obesity. A recent analysis revealed a near doubling of worldwide obesity prevalence since 1985, affecting half a billion people worldwide, and accounting for 4 million deaths annually worldwide.[5] However, the awareness of available therapeutic options remains low, prompting us to provide insights into these options through this article.

Obesity has significant effects on the gastrointestinal system. It contributes to esophageal diseases through both mechanical and humoral factors, with proinflammatory cytokines playing a crucial role in other digestive diseases.[6] Munch *et al*. demonstrated in an experiment on L2-IL1B mice (a transgenic mouse model of Barrett's esophagus) that a high-fat diet accelerated esophageal dysplasia by enhancing local pro-inflammatory immune responses and altering intestinal microbiota, irrespective of body weight.[7] Lower esophageal sphincter abnormalities, increased risk of hiatal hernia, and increased intragastric pressure are other mechanical causes of obesity directly influencing Barrett's esophagus and adenocarcinoma.[6] Obesity is also an important risk factor for colorectal adenoma and cancer. Several factors contribute to the increased risk of colon cancer in individuals with obesity, including alterations in systemic growth factors, visceral adipose tissue, the microbiome, bile acids, inflammation, and a diet rich in fat, sugar,

Keywords: Obesity; Weight loss; Bariatric surgery; Glucagon like peptide 1; Orlistat; Probiotics; Intragastric balloon; Endoscopy.

Abbreviations: BMI, body mass index; ESG, endoscopic sleeve gastroplasty; EWL, excess weight loss; FDA, food and drug administration; GLP-1, glucagon like peptide 1; IGB, intragastric balloon; LRYGB, laparoscopic roux-en-y gastric bypass; LSG, laparoscopic sleeve gastrectomy; POSE, primary obesity surgery endoluminal; TBE, transcatheter bariatric embolization; TRL, triglyceride rich lipoproteins.

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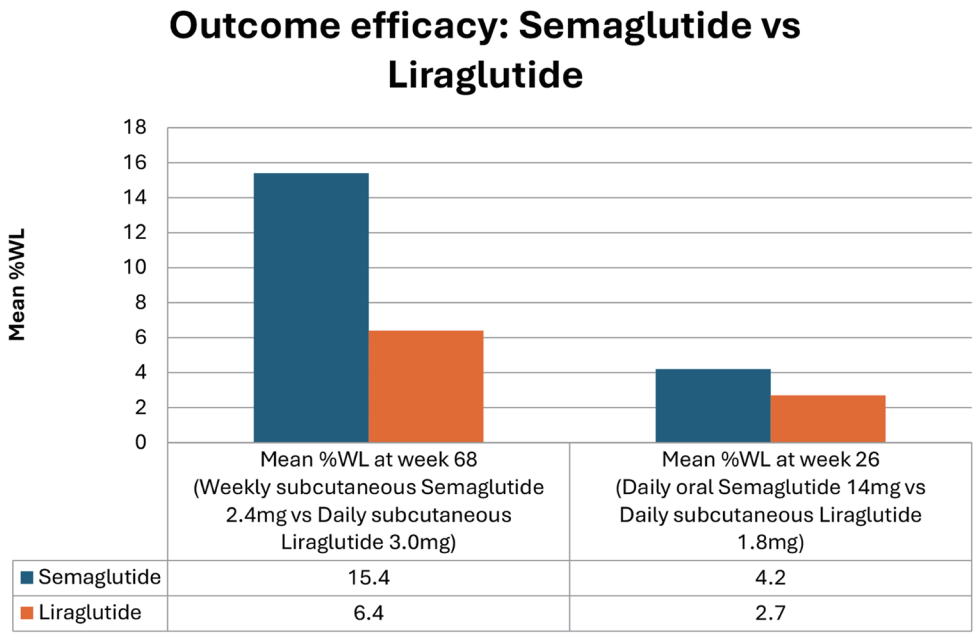

Fig. 1. Outcome efficacy of semaglutide and liraglutide. The left graph shows the mean percent weight loss (%WL) at week 68 by comparing weekly subcutaneous semaglutide to daily subcutaneous liraglutide. The right graph shows the mean percent weight loss (%WL) at week 26 by comparing daily oral semaglutide to daily subcutaneous liraglutide. %WL, percent weight loss.

high fructose corn syrup, or low vitamin D.[8] Studies have indicated that visceral adipose tissue may lead to higher circulating levels of insulin growth factor through worsening insulin resistance, thereby increasing the risk of carcinogenesis.[6] Furthermore, a high-fat diet induces colon and intestinal tumorigenesis by promoting the proliferation of intestinal stem cells.[9]

Multiple modalities, including lifestyle modification, mechanical gastric restriction, modulation in the secretion of multiple gut hormones, alteration in the composition and secretion of bile acids, and alterations of the gut microbiome, have been explored in obesity management.[10] Previous studies have primarily focused on pharmaceutical therapies, including combination therapies using different medical or interventional therapies with multiple targets for treating obesity.[11] Recently, bariatric surgical procedures have been extensively adopted and demonstrated efficacy in treating obesity.[12] As the prevalence of obesity increases, novel therapeutic approaches such as probiotics,[13,14] laparoscopic surgery,[15] topical lotions and subcutaneous medication,[16,17] transcatheter bariatric embolization,[18] low insulin method,[19] or gene therapy[20] have gained attention.

This comprehensive review aims to consolidate the recently applied medical, endoscopic, and surgical approaches for managing obesity and compare their beneficial effects and efficacy on obesity and its long-term comorbidities. We particularly aim to highlight newer experimental techniques for the management of obesity, including transcatheter bariatric embolization, intragastric balloon therapies, primary obesity surgery endoluminal procedures, and the Endobarrier procedure, which have shown promise in recent studies.

Medical management

Glucagon-like peptide 1 agonist

Long-acting glucagon-like peptide 1 (GLP-1) agonists such as semaglutide, liraglutide, and tirzepatide are currently available in the U.S. for the management of obesity, especially in patients with impaired glucose tolerance.[21,22] The primary outcome of a recent study indicated that the mean weight loss with weekly subcutaneous injections of semaglutide 2.4 mg was 15.4% at week 68, compared to a mean weight loss of 6.4% in those receiving daily subcutaneous liraglutide 3.0 mg.[23] Another analysis compared daily oral semaglutide 14 mg with daily subcutaneous liraglutide 1.8 mg for obesity management in diabetic patients whose glycemic indicators were stable on metformin. The outcomes indicated a placebo-subtracted average weight loss of 4.2% with oral semaglutide compared to a placebo-subtracted mean weight loss of 2.7% with subcutaneous liraglutide at the end of the 26th week.[24] Thus, whether administered orally or subcutaneously, semaglutide appears to be superior to subcutaneous liraglutide for the management of obesity. Figure 1 shows a comparison of the results from these two studies. Tirzepatide is a newer dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist.[25] Although trials comparing the efficacy of tirzepatide and other GLP-1 are still underway, recent studies have demonstrated encouraging outcomes. An open-label, 40-week, phase III randomized trial comparing weekly tirzepatide and semaglutide in type 2 diabetes mellitus patients indicated that reductions in body weight were greater and statistically significant with tirzepatide than with semaglutide in the secondary endpoints.[25] A more recent phase III placebo-controlled, double-blind, randomized trial comparing percentage weight loss for three different doses of weekly tirzepatide showed a significant and sustained reduction in weight, with a higher percentage of weight loss observed with higher doses.[26]

Orlistat

Orlistat is a reversible inhibitor of gastrointestinal lipases, traditionally employed for obesity management.[21,22] Orlistat, combined with lifestyle changes, contributed to a reduction in weight by 5.8

kg compared to 3.3 kg with placebo over 4 years.[27] A 37.3% reduction in the risk of diabetes mellitus was observed in patients treated with orlistat vs. placebo. Orlistat has an excellent long-term safety profile, and serious adverse events are rare.[28] Despite this, a high rate of gastrointestinal side effects such as oily stools, diarrhea, abdominal pain, and fecal spotting, as well as interactions with several drugs affecting their bioavailability and effectiveness, limits its adherence and makes it a less popular option.[29]

Lorcaserin

Lorcaserin is a serotonin 2C receptor agonist. Research indicates that it contributes to a reduction in body weight of 5.8 kg in 47.5% of the subjects over a year, compared to a weight reduction of 2.2 kg in 20.3% of the subjects in the placebo group. Weight loss was sustained in a significantly greater number of patients in the Lorcaserin group during the second year.[30] The CAMELLIA–TIMI 61 trial (Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients–Thrombolysis in Myocardial Infarction 61) investigated the long-term cardiovascular safety and efficacy of lorcaserin in obese or overweight patients with cardiovascular disease or risk factors. The rates of several cardiovascular and metabolic risk factors, such as blood pressure, heart rate, low density lipoprotein, and triglycerides were slightly lower in the intervention group than in the placebo group. At one year, the rate of cardiovascular events was similar in both groups.[31] A safety review of this study also identified a potential signal for increased cancer incidence, however, the study was not powered for cancer end-points.[32] A review conducted by the Food and Drug Administration (FDA) in 2020, based on a large post-marketing clinical trial revealed a higher frequency of cancer diagnosis for 13 types of cancer, including colorectal cancer, pancreatic cancer, and lung cancer, in the lorcaserin group compared to the placebo group.[32] Consequently, the FDA requested manufacturers to voluntarily withdraw their products from the market due to these safety concerns.

Combination therapies

Combination pharmacotherapy is increasingly being adopted worldwide for obesity treatment due to its heightened efficacy and beneficial outcomes.[21] The combined implication of pramlintide and phentermine was found to be eight times more efficacious than pramlintide monotherapy in reducing human weight. This combined pharmacotherapy resulted in a weight reduction of approximately 10.5%, compared to 2.5% for pramlintide alone after 24 weeks.[11] Exenatide once weekly, combined with daily dapagliflozin, induced greater weight reduction than either of the individual therapies, with results sustained over a year, suggesting long-term sustainable benefits in weight reduction.[11] The combination of phentermine and topiramate resulted in an overall placebo-subtracted weight loss of 3.5% at low doses and 9.3% at higher doses. Major studies leading to the approval of naltrexone/bupropion reported an average placebo-subtracted weight loss of 3.7% at a dose of 16/360 mg, and 4.8% at a dose of 32/360 mg.[33] Similarly, co-infusion of sub-anorectic doses of GLP-1 and glucagon demonstrated a 13% reduction in food intake[34] while simultaneously increasing energy expenditure, thus improving obesity and glycemia.[35] Therefore, combination therapies are not only more efficacious in treating obesity but also have more long-lasting effects than monotherapies. Some of the commonly prescribed medications for the management of obesity are summarized in Table 1.

Probiotics

Probiotics can modify gut microbiota and have been shown to contribute to body weight reduction in experimental animal studies. In an 8-week-old Apoe knock-out mouse model, the group of mice receiving *Lactobacillus reuteri* strain ATCC PTA 4659 indicated a significant reduction in body weight, adipose, and liver weight, and decreased serum insulin levels, attributing to increased β-oxidation.[13] Another study demonstrated that the oral administration of *Saccharomyces boulardii* over 4 weeks resulted in a 15% reduction in body weight gain, accompanied by a significant decrease in whole-body fat mass, without altering food intake in a mouse model.[14] Additionally, supplementation with S. boulardii and superoxide dismutase for 60 days in obese population led to significant weight loss and fat loss, while preserving fat-free mass in a randomized clinical trial (RCT).[36]

Herbal supplements

The use of herbal weight loss supplements has recently attracted increased amounts of attention due to the increasing prevalence of obesity. Garcinia cambogia supplements containing hydroxycitric acid are marketed for weight loss;[37] however, the FDA has recently issued a warning following post-marketing surveillance indicating an increased risk of hepatotoxicity associated with garcinia cambogia. Conjugated linoleic acid supplementation has shown limited evidence for weight loss, but studies have demonstrated an increase in oxidative stress and insulin resistance with regular consumption of conjugated linoleic acid, which limits its utilization.[38] L-carnitine, an amino acid naturally produced in the liver and kidneys, is thought to aid in managing obesity through its effects on glycemic control and lipid-lowering activities. However, analyses have shown that it produces only a moderate effect on weight loss.[39]

Other novel medical approaches

There are several other promising medical approaches for the management of obesity. The administration of transforming growth factor beta superfamily ligands, including GDF15 and MIC-1, has been shown to reduce body weight and food intake in mouse and human models, respectively, making them advantageous in the treatment of obesity.[40,41] Similarly, twice-daily topical application of a lotion containing aminophylline, caffeine, yohimbe, L-carnitine, and gotu kola, combined with exercise and restricted calorie intake for 28 days effectively reduced body mass, fat mass, and circumference in the treated area.[16]

Surgical management

The surgical approach for managing obesity has long been used to achieve sustainable results, especially in obese patients resistant to pharmacotherapy. Bariatric procedures are widely employed surgical interventions for treating obesity and its associated morbidities, consistently yielding desirable outcomes. Bariatric surgeries are considered the treatment of choice for patients with a BMI >40 kg/m2 or BMI >35 kg/m2 with severe associated comorbidities.[10]

Two major surgical approaches are laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB). Figure 2 illustrates a compilation of studies comparing the post-surgical benefits and metabolic effects of LSG and LRYGB. Peterli *et al*. compared the post-surgical effects of LSG and LRYGB over 3 years in an RCT.[15] The study concluded that both LSG and LRYGB groups demonstrated statistically equal efficacy in reducing excessive body mass index and improving quality of life up to 3 years after surgery. After 3 years, the improvement in comorbidities was similar for both groups, except for dyslipidemia

Table 1. Commonly prescribed medications for obesity management

Drug Class	Generic Names	Doses	Comments
Glucagon-like Peptide 1 agonist	Semaglutide	Start with 0.25 mg subcutaneous (SC) once a week. Increase the dose every 4 weeks by 0.25 mg till a maximum of 2.4 mg is reached.	Monitor for eye complications in patients with Diabetic retinopathy.
	Liraglutide	Start with 0.6 mg SC daily and increase at weekly intervals by 0.6 until maximum 3 mg.	
	Tirzepatide	Start with 2.5 mg weekly and increase by 2.5 every 4 weeks to maximum 15 mg.	Currently approved for type 2 diabetes and obesity management.
			All: Hypoglycemia if co-administered with other diabetes medications. Rarely reported: pancreatitis. Contraindicated in pregnancy and patients with a family history of medullary thyroid cancer (based on murine models) or multiple endocrine neoplasia.
Gastric/pancreatic lipase inhibitors	Orlistat	120 mg TID with fat containing meals (60 mg TID for those who cannot tolerate 120 mg).	Good safety profile for long-term use. GI side effects could be the limiting factor.
Combination Therapies	Phentermine and Topiramate	Start with 3.75 phentermine and 23 mg topiramate daily for 14 days, increase by 3.75/23 for 12 weeks. Then increase based on response to a maximum of 15/92.	Phentermine has abuse potential. Side effects include dry mouth, paresthesia, cognitive deficits, anxiety, insomnia, etc. Contraindicated in pregnancy (note topiramate is teratogenic), hyperthyroidism, glaucoma, and co-administration with MAO inhibitors.
	Naltrexone and bupropion	Start with 8 mg naltrexone and 90 mg bupropion daily (1 combination pill). Increase by 1 pill every week to a maximum of 4 tablets daily.	Nausea, vomiting, insomnia, dry mouth, increase in blood pressure. Contraindicated in poorly controlled hypertension, seizure disorder, opioid use disorder, opioid agonist therapy, pregnancy, and breastfeeding.
Noradrenergic sympathomimetics	phentermine	15 mg to 37.5 mg daily.	Several side effects and usually avoided unless it is short term only (<12 weeks).

MAO, monoamine oxidase; SC, subcutaneous; TID, ter in die.

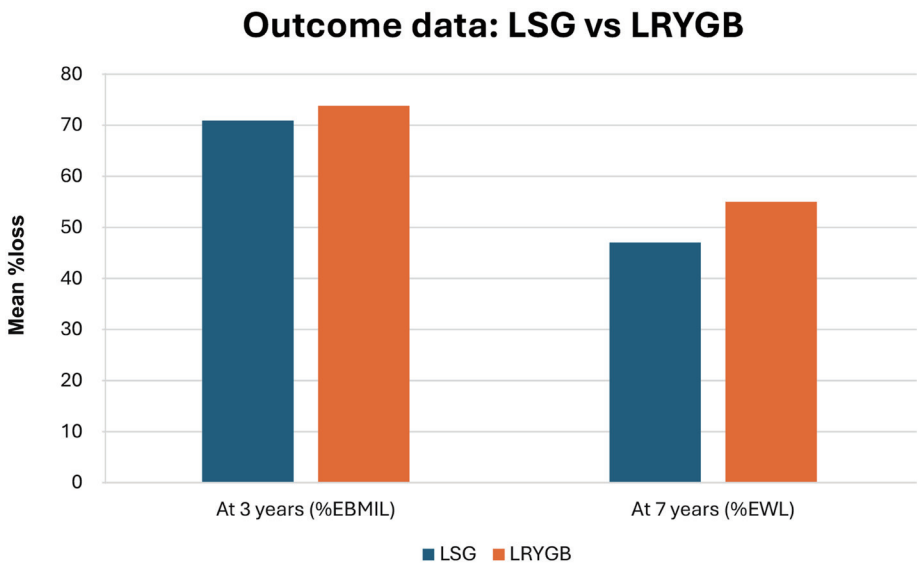

Fig. 2. Outcomes of laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB). The left graph shows the mean percent excess BMI loss (%EBMIL) between LSG and LRYGB at 3 years. The right graph displays the mean percent excess weight loss (%EWL) between LSG and LRYGB at 7 years. %EBMIL, percent excess body mass index loss; %EWL, excess weight loss; LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy.

and gastroesophageal reflux disease, which responded more effectively to LRYGB treatment. Gronroos *et al*. performed another RCT comparing the post-surgical effects of LSG and LRYGB over a 7-year period.[42] The results indicated that in a follow-up after 7 years, the mean percentage of excess weight loss was higher after LRYGB (55%) than after LSG (47%). Although LRYGB resulted in greater weight loss, it was associated with a 4.6% higher total morbidity rate. The long-term quality of life was similar after both procedures.

In a study comparing the metabolic effects of LSG and LRYGB, the number of significantly altered lipid metabolites was higher following LSG than LRYGB, mainly due to anatomical differences between the two surgeries and factors related to gut microbiota.[43] LSG was associated with alterations in amino acid metabolism, while LRYGB was associated with changes in bile acids. Studies conducted on triglyceride-rich lipoproteins (TRL) 6 months after surgery revealed that both TRL-apoB-100 and TRL-apoB-48 declined after LSG due to decreased production rates of both lipoproteins and an increased fractional catabolic rate of TRL-apoB-100 only. In contrast, the TRL-apoB-48 level did not significantly decrease after LRYGB.[44]

Laparoscopic vertical banded gastroplasty is another bariatric procedure effective in reducing body fat; however, it is less efficacious than LRYGB.[45]

Endoscopic management

As minimally invasive surgery is favored by patients, there has been significant development in endoscopic weight reduction procedures and devices. The major endoscopic procedures currently available are listed as follows:

Transcatheter bariatric embolization

Transcatheter bariatric embolization (TBE) uses a balloon microcatheter to occlude the left gastric artery, thereby promoting weight loss. The LOSEIT study (The Lowering Weight in Severe Obesity by Embolization of the Gastric Artery Trial) was a randomized pilot study that established the proof-of-principle demonstrating that TBE is well-tolerated and effective in weight reduction.[18] In the intention-to-treat population, total body weight loss was 7.4 kg with TBE (6.4% reduction) compared to 3.0 kg with sham (2.8% reduction) at 6 months after the procedure. Subjects treated with TBE had significant improvements in physical function, self-esteem, and overall quality of life at 6 and 12 months.

Endoscopic sleeve gastroplasty

Endoscopic sleeve gastroplasty (ESG) is a minimally invasive procedure that effectively induces a reduction in body weight by decreasing the size of the gastric reservoir. Subjects who underwent ESG experienced a significant reduction in excess body weight of 53% at 6 months.[46] In a physiological analysis, there was a 59% decrease in caloric intake to reach gastric fullness, along with decreased gastric emptying time for solids and increased insulin sensitivity.

Percutaneous gastrostomy devices

In a recent RCT by Thompson *et al*., an endoscopic device comprising an endoscopically placed percutaneous gastrostomy tube and an external device to facilitate drainage was utilized. The study demonstrated that 58.6% of participants in the intervention group lost 25% of their excess body weight, compared to 15.3% of participants in the control group. Notably, only 3.6% of the intervention group participants developed serious postoperative adverse effects.[47]

Primary obesity surgery endoluminal procedure

The primary obesity surgery endoluminal (POSE) procedure is an endoscopic incision procedure aimed to reduce the size of the stomach and decrease hunger cravings. A recent study reported that 79% of patients who underwent POSE procedures had a mean percent excess weight loss of approximately 50% after 1 year, with no development of any serious side effects.[48]

Endoluminal endoscopic gastric jejunal bypass sleeve

Gastro-duodeno-jejunal bypass sleeve is a novel technique that serves as an alternative to bariatric surgery in patients with morbid obesity. It consists of a 120 cm long sleeve device, placed endoscopically to create an endoluminal bypass tract from the lower gastroesophageal junction to the jejunum. A prospective trial designed to study the effectiveness of endoluminal, endoscopic gastric bypass sleeve implants in morbidly obese individuals concluded that almost half of the participants experienced a mean percentage excess weight loss (EWL) of 54% after 12 months and sustained a mean %EWL of 30% at the 14-month post-explant follow-up, while the remaining required explantation or experienced partial cuff detachment before completing 1 year.[49] This trial demonstrated that the gastro-duodenal-jejunal bypass sleeve could be an effective treatment option for the long-term management of morbid obesity.

Intragastric balloon therapy

Intragastric balloon (IGB) therapy has become an attractive tool for weight loss, owing to its sustained efficacy, low complication rate, and broad application, extending to class I and II obesity. This therapy involves a space-occupying device that alters gastric emptying and gastrointestinal neurohumoral pathways, leading to early satiety.[50] Several different types of IGBs are commercially available in the U.S. Among patients with a BMI range of 30–40 kg/m^2, IGB has shown superior outcomes in terms of weight loss compared to lifestyle modification alone. IGBs lead to greater weight loss at 6, 9, and 12 months after initial balloon placement; however, the amount of weight loss decreases during each successive time-period.[51] A pooled analysis of 7 RCTs revealed that the percent total body weight loss (%TBWL) at the end of 6–8 months was 7.4–14.9% for patients with IGB compared to 2.4–5.4% for those receiving standard care.[50]

IGB use is associated with the improvement in various metabolic parameters and medical conditions compared with noninvasive measures for weight loss.[51] IGB decreased the incidence of metabolic syndrome from 34.8% (pre-IGB) to 11.6% at 12 months post-IGB removal. The incidences of type 2 diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, and hypertension decreased from 32.6%, 37.7%, 33.4%, and 44.9% (pre-IGB) to 21.3%, 17.4%, 18.9%, and 34.8% respectively at 12 months post IGB removal.[52] Among patients undergoing bio-enteric IGB placement, the prevalence of hypertension, diabetes, hypercholesterolemia, and osteoarthropathy decreased from 29%, 15%, 32%, and 25% (pre-IGB), respectively, to 16%, 10%, 21%, and 13% at 3 years post-IGB removal.[53] Device intolerance (sense of fullness) and symptomatic intolerance (including epigastric pain, reflux, nausea, or emesis) remain the primary reasons for early IGB removal, occurring in approximately 9.4% of patients. More serious adverse events, such as gastrointestinal perforation (0.3%), esophageal mucosal injury (0.8%), gastric ulcer/bleeding (0.76%),

and gastric outlet/bowel obstruction (0.12%), are relatively rare. No mortality was reported during the 6–8 month period following balloon placement.[51]

Endoluminal duodenal-jejunal bypass liner (endobarrier)

Procedure

The application of endoluminal duodenal-jejunal bypass liner (DJBL), commonly referred to as endobarrier, has demonstrated effectiveness in managing chronic morbid obesity.[54] In patients with class I obesity and long-term type 2 diabetes mellitus, the DJBL procedure resulted in a 15% reduction in total body weight and a 0.6% reduction in Hb1Ac at 12 months. Only 9.5% of the patients with the DJBL procedure experienced major side effects, including severe abdominal pain in one patient and acute cholecystitis with duodenal fistula due to bulbar transmural penetration and gall bladder impaction by one of the anchors.[54] In an RCT for DJBL in patients with type 2 diabetes mellitus and obesity, 24% of the patients in the DJBL group achieved a ≥15% reduction in body weight compared to 4% in the control group at 12 months. DJBL demonstrated superior reductions in serum cholesterol, systolic blood pressure, and alanine transaminase levels at 12 months, while there was no significant difference in glycemic control.[55]

Duodenal mucosal resurfacing

Duodenal mucosal resurfacing (DMR) is a minimally invasive endoscopic procedure for circumferential hydrothermal ablation. DMR, particularly when combined with hypocaloric intake, has long-lasting efficacy in controlling diabetes and reducing both intramyocellular and intrahepatocellular lipids, while favoring the mobilization of abdominal fat and improving glycemia.[56]

Conclusions

Obesity has been a primary target for medical and surgical therapy. Various monotherapy options, such as GLP-1 agonists, have shown success in reducing weight. The combination pharmacotherapies have demonstrated significantly greater efficacy in weight loss compared to the individual drugs. Bariatric surgical methods provide more effective and long-lasting outcomes and carry a relatively higher risk of complications, which limits their widespread adoption. Several novel endoscopic devices and procedures are promising due to their satisfactory results, relatively lower cost, and lower risk. Further studies assessing the safety, effectiveness, and sustainability of these novel endoscopic techniques are warranted.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (KMa, MR and SJ), drafting of manuscript (KMa, MR), proofreading (SJ and KMu), critical revision of the manuscript (KMu).

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