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Bariatric Arterial Embolization for Obesity: A Review of Early Clinical Evidence

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Abstract

Obesity is a worldwide public health epidemic that leads to increased morbidity, mortality, and cost burden to health care. Although bariatric surgery has been recognized as a standard invasive treatment for obesity, it is accompanied by relatively high morbidity and cost burden, as well as limited treatment outcome. Therefore, alternative treatments with lower morbidity and cost for surgery that target patients who are obese, but not morbidly obese, are needed. A minimally invasive trans-catheter procedure, named Bariatric Arterial Embolization or Bariatric Embolization (BAE), has been identified as a potential solution, based on its safety and preliminary efficacy profiles. The purpose of this review is to introduce up-to-date clinical data, and discuss future directions for BAE for the treatment of obesity.

Keywords

Obesity; bariatric; embolization; left gastric artery; weight loss

Introduction

Obesity, defined as having a Body Mass Index (BMI) ≥ 30 kg/m^2, is one of the most prevalent public health issues of the 21st century [1]. It is now a major cause of morbidity and mortality worldwide, and has been recognized as a risk factor for several diseases, including type 2 diabetes, liver disease, heart disease, degenerative joint disease, obstructive sleep apnea, and even malignancy [2, 3]. In addition, mean BMI is increasing worldwide, bringing a heavy social and economic burden [4, 5]. Traditional therapies for obesity include lifestyle modifications (e.g., diet and exercise) and medical management [6–10].

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Conflict of interest

Dr. Weiss is a consultant for Medtronic and BTG.

Previous studies have demonstrated that lifestyle modifications can achieve an average weight loss of 5 to 10% in overweight (BMI between 25 and 29.9 kg/m^2) and obese (BMI between 30 and 34.9 kg/m^2) patients [6, 11]. Nevertheless Several studies have shown that patients may return to their original weight in as little as three years after initiating lifestyle changes [12, 13].

For severely obese patients or those with obesity-related comorbidity, more aggressive medical management such as bariatric surgery is often considered as a treatment option (Table 1) [14]. However, bariatric surgery is associated with a relatively high morbidity rate [15]. In addition, the cost of these surgical procedures is high, costing on average $38,000, and up to $64,000 in the U.S. and about $27,000 in Europe if complications occur [16–19].

Patients who fail to lose weight through lifestyle modifications, but are not candidates for bariatric surgery, have few other treatment options. There are currently six major U.S. Food and Drug Administration (FDA)-approved anti-obesity medications[20], most of which work through pathways in the central nervous system (CNS) that either reduce appetite, enhance satiety, or decrease the absorption of fat [20, 21]. However, pharmacotherapy can only achieve modest weight loss, with a range of 2.0 to 6.5 kg, according to previous data [22–24] (Table 2). Therefore, it is often regarded as an adjuvant therapy to lifestyle modifications [25]. Endoscopic bariatric therapies include intragastric balloons (space-occupying devices), endoscopic gastric plication, endoluminal duodenal-jejunal sleeve, and gastric pacer (Table 3) [26]. However, these endoscopic techniques have the potential to cause major complications [26–29].

Bariatric Arterial Embolization (BAE) is a minimally invasive technique performed by interventional radiologists under imaging guidance. The procedure trans-arterially embolizes the gastric fundus through the left gastric artery (LGA) and, to a lesser extent, the gastroepiploic artery (GEA). The idea of using BAE to treat obesity originates from the fact that about 90% of ghrelin is produced by the fundus of the stomach [30]. The vascular supply to the gastric fundus is predominantly from the LGA (Fig. 1) [31]. Ghrelin is a 28-amino acid peptide that plays an important role in stimulating appetite, and promoting positive energy balance to gain weight [30, 32, 33]. Plasma ghrelin levels increase significantly before meals, and decrease after meals [33, 34]. Nevertheless, obese patients fail to suppress ghrelin levels after eating food, leading to overeating [35]. Another appetite regulating hormone, leptin, is produced by adipocytes to inhibit hunger signals. Plasma leptin levels decrease in response to reductions in body fat and are associated with the amount of peripheral fat stores [36]. Leptin is suppressed when fasting and is stimulated after food intake. BAE destroys ghrelin-producing cells by causing ischemia in the gastric fundus and decreasing ghrelin production, resulting in loss of body weight (Fig. 2). The safety and preliminary efficacy of BAE for obesity have been verified by several studies. Notably, some updated data from both animal and human studies have been recently reported. Here, our goal is to provide a comprehensive review of the newest clinical and pre-clinical data for BAE for the treatment of obesity.

Pre-clinical studies

The first animal study of BAE was explored by Arepally et al. in 2007 [37]. The study showed ghrelin levels could be purposefully and significantly altered with chemical embolization of the gastric artery using morrhuate sodium. After this study, a series of early animal studies performed in growing swine and obese dogs showed a decrease in serum ghrelin levels, and either decreased weight gain or increased absolute weight loss when compared to the control group after embolization [38–45].

Clinical studies

Having been practiced for only a short period of time, available clinical data for BAE are limited. Excitingly, several clinical trials from different areas have been recently reported. The first clinical study focusing on this topic was performed by Gunn et al. in a retrospective fashion [46]. The patients included in this single-center study received LGA embolization, with the initial intention of stopping upper gastrointestinal bleeding (UGIB).The authors found that patients who underwent LGA embolization lost an average of 7.3% of their weight, which was significantly more than those who underwent embolization of other branches of the celiac axis (2%, $p = 0.006$). A similar retrospective study was performed by Anton et al. [47]. A group of 10 patients who underwent LGA embolization for UGIB unrelated to malignancy were compared to 22 patients who underwent embolizations of other mesenteric vessels for UGIB unrelated to malignancy. The BMI in the two groups was not significantly different (31 ± 6.8 kg/m^2 for the LGA embolization group, and 28.4 ± 6.4 kg/m^2 in the control group). The LGA embolization group had reduced their BMI by 9.8%, compared to the control group's 4% loss ($p = 0.042$) at one month, and 11.7% compared to the control group's gain of 0.1% ($p = 0.033$) at four months. The LGA embolization group continued to show greater weight loss up to one year, however not to a statistically significant extent. As with Gunn et al., the study was limited by its retrospective nature and small sample size.

The first prospective BAE study was carried out by Kipshidze et al. [48]. This single-arm study included five patients with a mean BMI of 42.2 kg/m^2. BAE was performed using 300 to 500 μm microspheres (Biocompatibles UK Limited, Surrey, United Kingdom) mixed with contrast (1:1 ratio). In regards to safety, no periprocedural complications occurred, and a follow-up endoscopy found no significant alterations to the stomach mucosa. Three patients described mild transient epigastric discomfort after the procedure, though follow-up endoscopies found no gastric ulcers. Regarding efficacy, all five patients reported a reduction in their appetite. There was significant and continuous mean weight loss within the 24-month follow-up period, which decreased from a baseline of 128 kg to 106 kg ($p < 0.05$). There was a significant decrease in serum ghrelin levels at the one and three-month follow-up (by 29% and 36% from the baseline, respectively, $p < 0.05$). Although the serum ghrelin level increased at the six-month follow-up, as compared to the three-month follow-up, it remained 19% lower than at baseline ($p < 0.05$). This first prospective study for BAE showed a promising outcome. Some limitations for this study should be noted, such as the absence of detailed inclusion criteria, absence of details on the degree of embolization, and the early timing of endoscopy, which could exclude the later discovery of gastritis or ulcers.

Ongoing trials with published preliminary results

To date, there are three ongoing clinical trials focused on BAE, all of which have published their preliminary results [49–51]. Among them, the first reported study was the Gastric artery Embolization Trial for Lessening of Appetite Nonsurgically (GET LEAN) trial at Dayton Interventional Radiology and Ohio State University in the U.S., with FDA approval [49]. According to the study protocol of GET LEAN on clinicaltrials.gov (Identifier: NCT02248688), the purpose of this pilot study was to collect safety and efficacy data in patients undergoing left gastric artery embolization (LGAE) for morbid obesity in the U.S., with five patients included and undergoing a one-year follow up. The primary outcome measure was the safety assessment of BAE at one year post-procedure. The secondary outcome measures included changes in BMI, quality of life, appetite hormone levels, and change in overall weight of the subjects at one year post-procedure. The estimated primary completion date was October 2017.

In the results of the GET LEAN study, four morbidly obese patients were included, one of which was diabetic. All of the patients underwent BAE through the right common femoral artery or left radial artery. The LGA and its branches were embolized using 300 to 500 μm Bead Block particles (BTG Interventional Medicine, West Conshohocken, PA) mixed with 5 mL of contrast medium. Complete cessation of flow (i.e., stasis) of the LGA and its branches was the endpoint of the procedure. Stasis was defined as visualization of contrast medium within the main LGA for at least five cardiac cycles. No major complications occurred. Three minor adverse events, including superficial gastric ulcerations, nausea, and vomiting were observed in three patients. These three patients required only nominal therapy without hospitalization, and all adverse events resolved within 30 days. Mean body weight loss among the four patients at six months post-procedure was 9.2 kg ($p = 0.0775$). Body weight loss as a percentage was 8.5%, and average excess body weight loss at six months was 17.2%. Among the four included patients, the first one had a weight loss of 17.2 kg representing 38.5% of excess body weight after one year, which seemed equivalent to the effect obtained with bariatric surgery. The diabetic patient showed a weight loss of 12.7 kg and 18.4% of excess body weight at six months post-procedure. The HBA1C level of this patient nearly normalized (7.4% pre-procedure to 6.3% at three months post-procedure), and remained at this level after six months. Serum ghrelin levels decreased in two patients and increased in another two patients after six months, with the mean increasing from 612 pg/mL at baseline to 645 pg/mL at six months. Leptin levels decreased overall, except in one patient who lost the least amount of weight.

The second reported study was the Bariatric Embolization of Arteries for the Treatment of Obesity (BEAT Obesity) trial carried out at the Johns Hopkins Hospital in the U.S. [50]. This study was a physician-sponsored Investigational Device Exemption (IDE) from the FDA, and Weiss et al. published the preliminary results in 2017. According to clinicallrials.gov (Identifier: NCT02165124), the BEAT Obesity trial aimed to observe weight loss at 12 months post-procedure as the primary outcome measure, and adverse event assessment as the secondary outcome measure within 30 days after BAE. The study aimed to include 20 patients at two centers, the Johns Hopkins Hospital in Baltimore, MD and the Mount Sinai Hospital in New York, NY.

The primary safety endpoint preliminarily reported was 30-day complications according to the American Society for Metabolic and Bariatric Surgery, and the secondary efficacy endpoint was weight loss at the three-month follow-up [52]. Five obese patients with a mean BMI of 43.8 ± 2.9 kg/m^2 were included in the preliminary report. Notably, obese patients with diabetes were excluded from the study. Patients underwent BAE via a femoral artery approach. Embolization of one or more fundal arteries was performed with 300 to 500 μm Embosphere microspheres (Merit Medical, Dundalk, MD). The fundus was also embolized via the GEA, if needed. The results of this preliminary study showed that no major complications occurred during the follow-up. There were two minor adverse events. One patient had a transient, chemical pancreatitis that recovered and remained asymptomatic at the one-week follow-up visit. Another patient had a small asymptomatic superficial ulcer in the fundus/lesser curvature observed at the two-week follow-up endoscopy, which resolved by the time of the three-month follow-up endoscopy. In terms of efficacy, there was 5.9% excess weight loss at one month (n = 5) and 9.0% at three months (n = 4), respectively. Mean fasting serum ghrelin was relatively unchanged within the first two weeks post-procedure. It increased by 8.7% and decreased by 17.5% from baseline at one and three months, respectively. The preliminary results of the BEAT Obesity trial also demonstrated the safety and potential efficacy of BAE.

The latest published preliminary study of an ongoing trial was carried out by Bai et al. in China [51]. The protocol of this study on clinicaltrials.gov (Identifier: NCT02786108) showed that an estimated 50 patients would be included, with the weight loss at 12 months after BAE as the primary endpoint, and blood pressure, lipid profile, number of patients with adverse events, ghrelin levels, abdominal fat content, leptin levels, results of endoscopic examination, and quality of life as secondary endpoints. The trial included Chinese patients with BMI no less than 30 kg/m^2. Patients underwent BAE via the superior-most branch of the LGA closest to the junction between the cardia and fundus, using 500 to 710 μm polyvinyl alcohol (PVA) particles (COOK Incorporated, Bloomington, IN). The PVA dosage used during embolization was based on real-time observation of the stasis of blood flow in the LGA. The follow-up period was nine months. The results showed no major complications occurred during the follow-up. A superficial linear ulceration below the cardia was observed in one patient at the three-day follow-up endoscopy, which resolved by the time of the 30-day follow-up endoscopy. The mean body weight showed significant and continuing loss during the follow-up (mean weight loss at three, six, and nine months was 8.28, 10.42, and 12.9 kg, respectively). Serum ghrelin levels decreased by 40.83%, 31.94%, and 24.82% at three, six, and nine months post-procedure, respectively. Magnetic resonance imaging showed that the subcutaneous adipose tissue decreased significantly during the follow-up period. Similar to previous studies, the preliminary results of this study verified the safety and potential efficacy of BAE.

Discussion

A systematic review published in 2016 gave the conclusion that data regarding the potential role of BAE in decreasing the ghrelin and potential weight loss is scarce [53]. As several pre- and early clinical studies of BAE have been carried out, more and more data support the safety and early effectiveness of this minimally invasive procedure (Table 4). Currently,

there are future trials in the works that will explore BAE's effects on different populations. A randomized control trial testing the efficacy of BAE has also recently begun in New Zealand, targeting morbidly obese patients not fit for bariatric surgery. The study will include 24 patients with BMI greater than 30 kg/m^2. Primary outcome measures include weight loss at 60 months.

Despite promising results and the addition of new studies, there are still several key questions that remain unanswered. First, the ideal candidate for BAE is unclear. The patients' BMI in the GET LEAN and BEAT Obesity trials was no less than 40 kg/m^2. However, patients with BMI no less than 30 kg/m^2 were included in the latest trial in China [51]. Despite having different inclusion criteria for BMI, all three trials demonstrated positive preliminary results for weight loss. It is likely that BAE may be more effective in treating obese, but not severely or morbidly obese patients. In addition, the effect of BAE on diabetic or pre-diabetic patients is unknown. The GET LEAN and Chinese trials included diabetic, obese patients, while the BEAT Obesity trial excluded them. In the GET LEAN trial, the sole diabetic patient's HbA1c dropped from 7.4 to 6.3 at three months, and remained at this level at six months. Due to the limited sample sizes of the trials, no statistically significant results were reported. Further long-term results with larger sample sizes are warranted to show the correlation between treatment efficacy and HbA1C.

Second, since prior animal studies have shown that weight and ghrelin levels trend toward baseline after BAE, it is important to identify the long-term treatment outcome of the procedure [37–40, 43]. However, the relative ages of the subjects have greatly differed in the pre-clinical and clinical trials. Most animals in the pre-clinical trials have been still-growing swine, possibly countering the effects of the procedure, while patients in the current clinical trials are generally past the period of maximum growth in humans.

Third, BAE may prove modestly effective on its own, but may have its efficacy enhanced if performed in combination with other therapies, lifestyle modifications, and/or pharmacotherapy. The rebound of weight and ghrelin levels may be due to re-vascularization of the gastric fundus [38, 43]. Another possibility may be a return of appetite not due solely to ghrelin, but recovery of the patient from ischemic injury. Therefore, technical points regarding BAE and studies including a diagnostic digital subtraction angiography (DSA) during follow-up, may need to be designed first to show whether a gastric fundus revascularization exists or not.

Fourth, the ideal embolic agents are uncertain. Several different kinds of embolic agents with various sizes have been used in both animal and clinical studies (Table 5). The GET LEAN and BEAT Obesity trials used 300 to 500 μm embolic agents, while the Chinese trial used 500 to 710 μm embolic agents. In addition, all three trials used different kinds of agents.

Lastly, the ideal degree of embolization needs to be demonstrated. A previous animal study demonstrated that only animals in which all gastric arteries were embolized showed significant decreases in serum ghrelin levels. Additionally, a lower degree of embolization did not prevent gastric ulceration [42]. The three current trials have demonstrated different

targets and endpoints for embolization. GET LEAN targeted all distal branches of the LGA, while BEAT Obesity targeted all arteries supplying the fundus, including the GEA if applicable, and the trial in China embolized only select branches of the LGA. What effect different degrees of embolization have, if any, has not been explored in clinical trials to date.

In conclusion, BAE may be a promising method to treat obese patients via changes in hormonal balance. More and more pre-clinical and clinical studies have been carried out to explore the safety and preliminary efficacy of BAE to treat obesity. Nevertheless, no clinical trial with long-term follow-up and relatively large sample sizes has been reported. Some ongoing prospective trials may fill this gap in the near future. There are still many questions that remain to be answered. Once these key points are addressed, further randomized controlled trials should be performed to explore the efficacy of BAE compared to diet and exercise or sham embolization.

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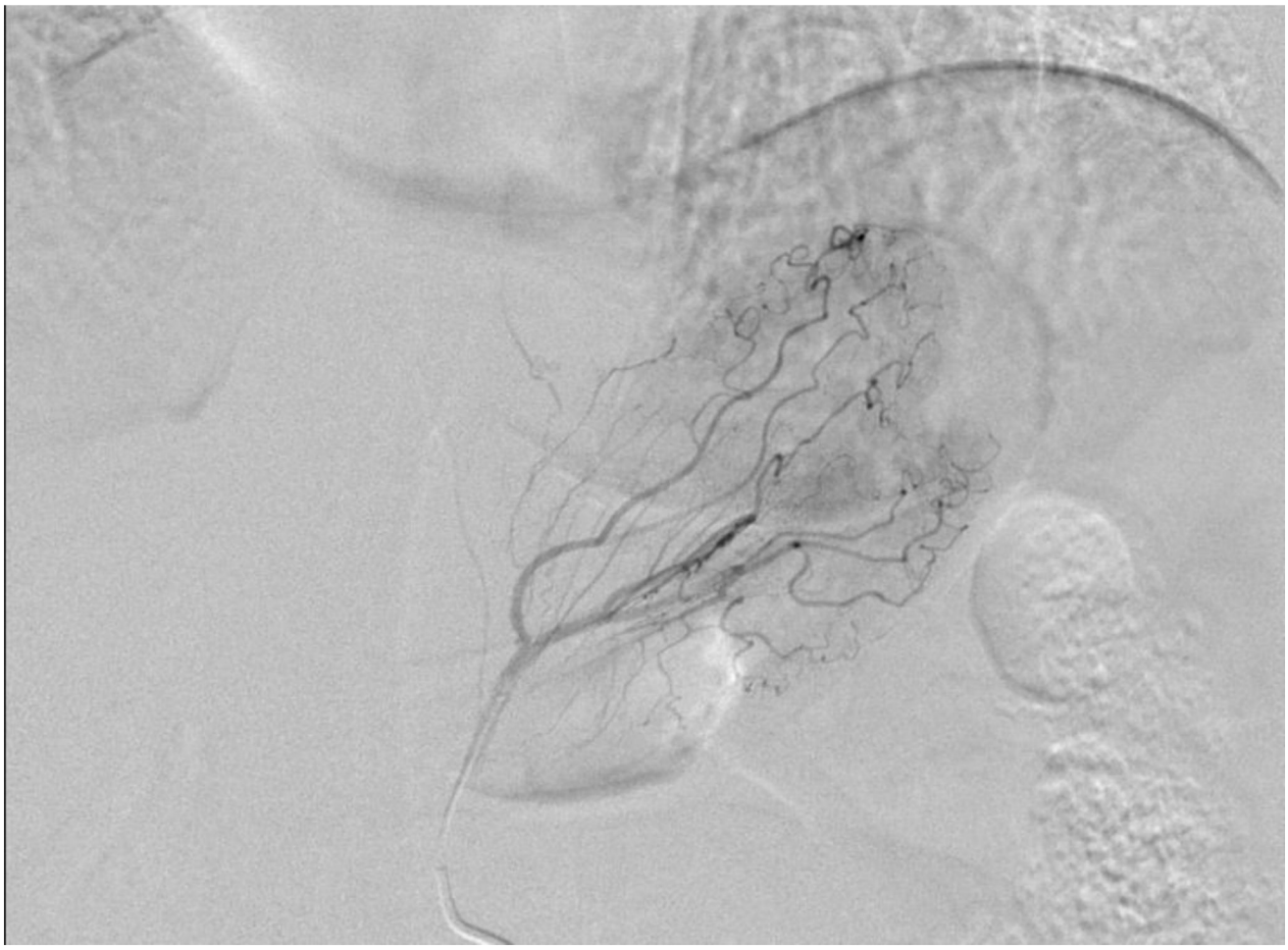

Figure 1.
Angiography of the left gastric artery. Left gastric arterial branches cover a large part of the fundus of the stomach.

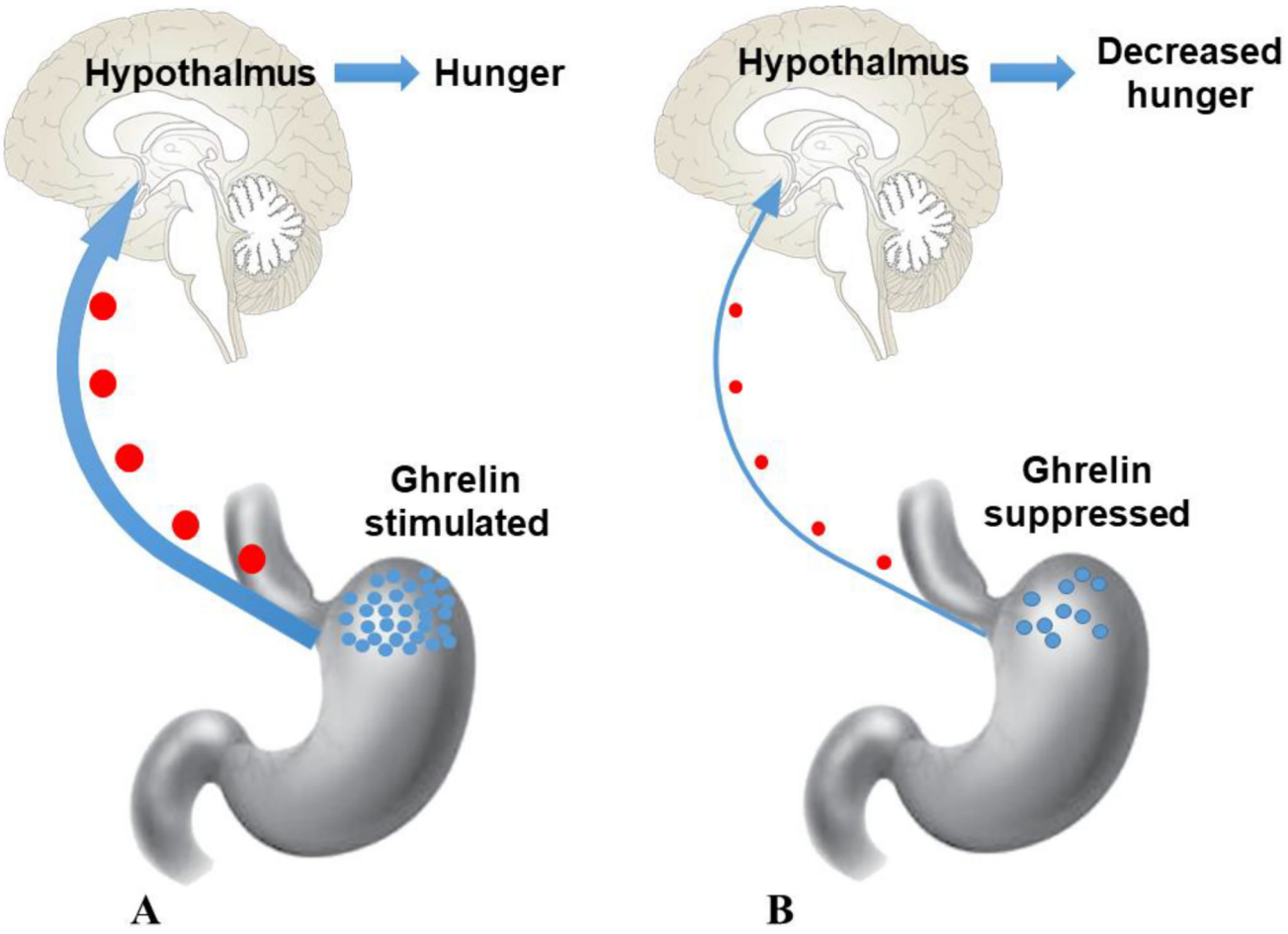

Figure 2.

Ghrelin change pre- and post-Bariatric Arterial Embolization (BAE). *A*, Before BAE, ghrelin is secreted by X/A cells in the fundus of the stomach during the fasting state, initiating the hunger drive. *B*, After BAE, ghrelin-producing cells are destroyed by causing ischemia in the gastric fundus, decreasing ghrelin production and resulting in loss of body weight.

Table 1

Bariatric Surgery Options [54]

Procedure	Advantages	Disadvantages	EWL
Adjustable gastric banding	Low complications Good weight loss	Reoperations Implanted device	About 19%
Sleeve gastrectomy	Continuous GI tract Good weight loss	Long staple line Nutritional deficit	25–30%
Roux-en-Y gastric bypass	Better weight loss	Anastomoses Nutritional deficit	33–36%
Biliopancreatic diversion duodenal switch	Best weight loss	Anastomoses Nutritional deficit	34%+

EWL, estimated weight loss

Table 2

Pharmacotherapy for Obesity [20]

Medication	Mechanism	Side effects	Weight loss
Phentermine	Sympathomimetic amine	Increase in HR and/or BP, dizziness, dry mouth, constipation, insomnia, and irritability	5.1% at 28 weeks
Orlistat	Pancreatic lipase inhibitor	Decreased absorption of fat-soluble vitamins, fecal urgency, fatty stool, fecal incontinence	Mean 5.0 kg vs. 3.8 kg with placebo
Phentermine/topiramate ER	Sympathomimetic, raises concentration of norepinephrine	Dizziness, insomnia, constipation, paresthesias	9.3–10.5% vs. 1.8% loss of baseline weight in 2 years compared to placebo
Lorcaserin	Selective serotonin 2C receptor agonist	Headache, dizziness, fatigue, dry mouth, constipation	5.0% vs. 1.5% total body weight loss in 1 year compared to placebo
Naltrexone/bupropion SR	Bupropion: dopamine/ norepinephrine reuptake inhibitor Naltrexone: opiod receptor agonist	Nausea, constipation headache, and psychiatric and sleep disturbances	Up to 9.3% loss of initial body weight
Liraglutide	GLP-1 agonist	Nausea, hypoglycemia, and diarrhea, among others	8.0% vs. 2.5% mean weight loss after 56 weeks compared to placebo

HR, heart rate; BP, blood pressure; ER, extended release; SR, sustained release

Table 3

Endoscopic Bariatric Procedures [27]

Procedure	Advantages	Disadvantages	EWL
Space-occupying devices	Easily placed endoscopically; restrict food consumption; well tolerated; effective; can be reversed/removed	Balloon may deflate over long term; can migrate, leading to perforation; FDA-required removal at 6 months with poor long-term weight loss	39% at 1 year after removal
Restrictive procedures	Permanently reduces stomach capacity; effective; well tolerated	Not easily reversible; plication durability varies according to device	Up to 54% ± 40% at 12 months
Bypass liners	Pancreaticobiliary secretions can still travel along the sleeve, as opposed to surgical bypass	High risk of hepatic abscesses; not currently available in the U.S. because of complications	Up to 36% at 1 year
Gastric stimulation	Effective at treating moderate (class 1 and class 2) obesity	All use stimuli that are essentially not perceived by subjects, which may limit their long-term efficacy	Lose ≥15% of body weight at 1 year
Transpyloric shuttle	Does not take up considerable space, but results in delayed gastric emptying, and likely has additional mechanisms of action	High risk of gastric ulcer	8.9% total body weight loss at 3 months, and 14.5% at 6 months

EWL, excess weight loss; FDA, U.S. Food and Drug Administration

Table 4

Treatment outcomes of early clinical studies

Author /year	AEs	Pre-procedure		Post-procedure
		Weight (kg)	BMI (kg/m^2)	Weight (kg)
Gunn AJ/2014 [46]	Unknown	Unknown	30.3	Unknown
Anton K/2015 [47]	Unknown	97.3	31	Unknown
Kipshidze N/2015 [48]	Mild, transient epigastric discomfort	128	42.2	106
Syed MI/2016 [49]	Mild nausea, occasional vomiting, mild epigastric discomfort	117.6	42.4	108.4
Weiss CR/2017 [50]	Transient pancreatitis, asymptomatic superficial ulcer	127.8	43.8	123.1
Bai ZB/2017 [51]	Superficial linear ulceration, hematoma in puncture site	102.02	38.1	89.12

AEs, adverse events; BMI, body mass index

Table 5

Characteristics of Early Clinical Studies

Author /year	Sample size	Nature	Embolicagent	Embolic size (μm)	Diabetes	Follow -up (months)	Endoscopy	Primary endpoint
Gunn AJ/2014 [46]	19	R	Coils, gelfoam, PVA	300–500 500–710 710–1000	Unknown	13.6	Unknown	Weight loss
Anton K/2014 [47]	10	R	Coils, gelatin sponge pledget suspension	Unknown	Included	12	Unknown	Weight loss
Kipshidze N/2015 [48]	5	P	Bead Block	300–500	Unknown	24	Day after procedure	Weight loss
Syed MI/2016 [49]	4	P	Bead Block	300–500	Included	6	Baseline and 3 days post-procedure	Safety
Weiss CR/2017 [50]	5	P	Embosphere	300–500	Excluded	3	Baseline, 2 weeks, and 3 months post-procedure	30-day AEs
Bai ZB/2017 [51]	5	P	PVA	500–710	Included	9	Baseline and 3 days post-procedure	Safety

R, retrospective; P, prospective; PVA, polyvinyl alcohol; AEs, adverse events