

# Bariatric Embolization: Are Patients Actually Losing Weight?

An overview of what we currently know about weight loss expectations associated with bariatric embolization.

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Obesity is one of the most prevalent public health issues of the 21st century.<sup>1</sup> It is a major cause of morbidity and mortality worldwide and can lead to several comorbid diseases, such as type 2 diabetes, liver disease, heart disease, degenerative joint disease, stroke, obstructive sleep apnea, and cancer.<sup>2,3</sup> The problem of obesity is particularly severe in the United States, with at least 34.9% of the adult population considered obese, which is defined as body mass index (BMI)  $> 30 \text{ kg/m}^2$ .<sup>4</sup> Of this population, 6.6% are considered morbidly obese (BMI  $\geq 40 \text{ kg/m}^2$ ).<sup>5</sup> With the average BMI on the rise, not only is obesity a problem of health, but also one of significant economic burden, costing the United States health care system \$168 billion annually.<sup>6,7</sup>

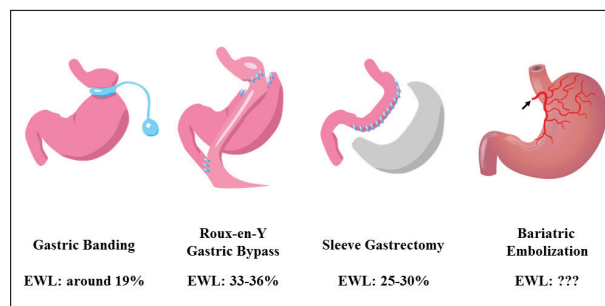
There are several options for the treatment of obesity, including lifestyle modifications (eg, diet and exercise), medical management, and surgery.<sup>8-12</sup> Lifestyle modification can achieve an average weight loss of 5% to 10% in overweight and obese patients.<sup>8,13</sup> However, the long-term efficacy of weight loss for the majority of obese patients is poor for lifestyle modification alone, with patients often experiencing weight gain and a return to prior weight within a few years of initiating lifestyle changes.<sup>7,14,15</sup> Pharmacotherapy options are also available, such as orlistat, but only as adjuncts to other therapies, as the weight reduction they can maximally provide is modest (2–6.5 kg).<sup>16-18</sup>

For morbidly obese patients, bariatric surgery, a more aggressive but highly effective therapy, is another option.<sup>19</sup> Several types of bariatric surgery are possible, but in essence, weight loss is achieved via a reduction in the amount a patient can consume (restriction) or absorb (malabsorption). When combined with lifestyle modification, bariatric surgery can result in significant and sustained weight loss (19% for gastric banding, up to 30% in sleeve gastrectomy, and up to 36% in Roux-en-Y surgeries; Figure 1).<sup>20,21</sup>

However, bariatric surgeries are associated with a relatively high morbidity rate that ranges from  $< 2\%$  to 17%.<sup>22</sup>

An interesting effect seen in bariatric surgery, which may play a significant role in weight reduction, is the change in hormone profile that occurs. One of the hormones that is affected by bariatric surgery is ghrelin, a 28-amino acid peptide that is largely responsible for initiating appetite (orexigenic). In a normal patient, ghrelin significantly increases before meals and rapidly decreases after a meal has been consumed (Figure 2). In obese patients, ghrelin often fails to decrease after a meal.<sup>23</sup> About 90% of ghrelin is produced from cells in the fundus of the stomach.<sup>24</sup> Bariatric surgery has been shown to reduce ghrelin for sustained periods of time.

Focusing on the metabolic effect of bariatric surgery, bariatric embolization for obesity is currently being explored, with the goal of inducing weight loss through a reduction of ghrelin via transarterial embolization of the gastric fundus



**Figure 1. Estimated weight loss (EWL) for various bariatric procedures.** Currently, there are many surgical options for weight loss. Each option provides a different range of expected weight loss but also comes with increasing risks for complications. Images <https://magenverkleinerung.tips> and © 2016 DBCLS TogoTV.

via the left gastric artery (LGA) and, to some extent, the gastroepiploic artery (GEA). The procedure causes ischemia in the gastric fundus, which appears to decrease ghrelin production from the hormonally active X/A-like cells, resulting in appetite suppression/early satiety and weight loss (Figures 3 and 4). Due to the rich collateral supply to the stomach, bariatric embolization appears to be well tolerated.

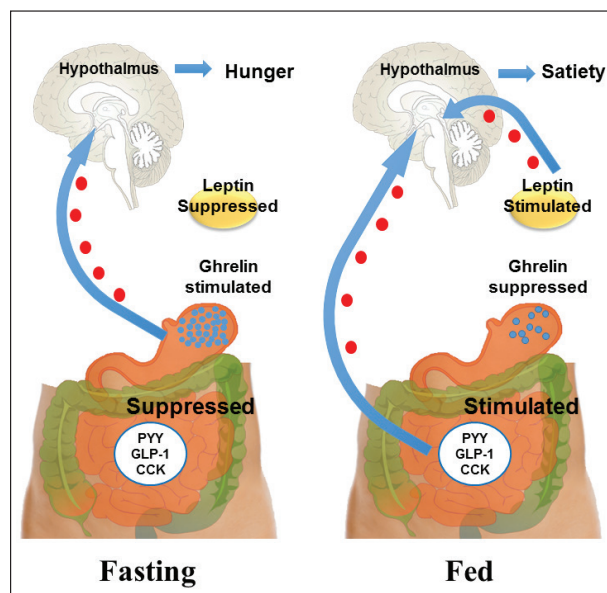
## EARLY STUDIES

Several animal studies with swine and dogs have demonstrated the safety of bariatric embolization and the desired effect of decreased ghrelin production, as well as either decreased weight gain or weight loss (depending on the animal model). The safety and preliminary efficacy of bariatric embolization for obesity in humans has been examined in several studies.<sup>25-31</sup> A retrospective study conducted by Gunn et al demonstrated that patients who underwent LGA embolization lost an average of 7.3% more weight than patients who underwent embolization of other branches of the celiac axis to stop upper gastrointestinal bleeding.<sup>32</sup> A similar retrospective study by Anton et al demonstrated that patients who underwent LGA embolization had a 7.3% average weight loss after 3 months and continued to weigh less than the baseline level as compared with a 2% loss in the control group who eventually returned to baseline.<sup>33</sup> These retrospective studies are promising but are limited by their retrospective nature, the use of multiple embolic methods, and the presence of extensive comorbidities, including malignancy.<sup>32</sup>

In 2015, Kipshidze et al conducted the first prospective study and performed bariatric embolization on five Eastern European patients (mean BMI,  $42.2 \pm 6.8$  kg/m<sup>2</sup>) using a 300–500- $\mu$ m Bead Block particles (BTG International). The authors demonstrated that bariatric embolization was a safe procedure with no periprocedural complications or alterations to the stomach mucosa.<sup>34</sup> In addition, all five patients reported reduced appetite and a mean weight change of 45.2 lb (17.2%) after 24 months. Plasma ghrelin levels decreased by 24% at 3-month follow-up and remained lower than baseline at 12-month follow-up. Although this early study showed very promising results, it was not a US Food and Drug Administration (FDA)–approved study, and details about the published protocol are scant.

## ONGOING TRIALS WITH PUBLISHED PRELIMINARY RESULTS

To date, in addition to the study by Kipshidze et al, there are three ongoing clinical trials focused on bariatric embolization, all of which have reported and published their preliminary results (Table 1).<sup>34-37</sup> The first trial, GET LEAN, is an FDA-approved, single-arm pilot study of four morbidly obese patients (mean BMI,  $42.4 \pm 2.6$  kg/m<sup>2</sup>).<sup>35</sup> The LGA



**Figure 2. Hormone cycle during fasting and fed states.** Ghrelin is secreted by X/A-like cells in the fundus of the stomach during a fasting state, initiating the hunger drive. After feeding, leptin is secreted from adipose tissue, suppressing hunger. CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide tyrosine tyrosine. Adapted from Häggström M (2014). Medical gallery of Mikael Häggström 2014. WikiJournal of Medicine. 2014;1(2):8. doi:10.15347/wjm/2014.008. ISSN 2002-4436.

was embolized using 300–500- $\mu$ m Bead Block particles. Complete cessation of flow (ie, stasis) of the LGA and its branches was the endpoint of the bariatric embolization procedure, with stasis defined as visualization of contrast medium within the main LGA for at least five cardiac cycles. There were no major adverse events or major complications. 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 by 30 days. Mean body weight loss among the four patients at 6 months postprocedure was  $20.3 \pm 24.34$  lb (8.5% reduction in total weight or 17.2% of excess body weight). Among the four included patients, the first patient had a weight loss of 48 lb at 1 year, representing 49% of excess body weight. One patient had type 2 diabetes and had a weight loss of 20.3 lb at 6 months in addition to a reduction of the glycated hemoglobin (HbA1c) level from 7.4% preprocedure to 6.3% at 3 months postprocedure, remaining at this level at 6 months. Plasma ghrelin levels decreased in two patients and increased in another two patients at 6 months, with an average increase from 612 pg/mL at baseline to 645 pg/mL at 6 months. Plasma leptin levels exhibited a decrease overall, except in one



**Figure 3.** Pre-embolization selection on a left gastric arteriogram. Left gastric arterial branches cover a large part of the fundus of the stomach. Vasospasm was present in the proximal portion.

patient who lost the least amount of weight, which is logical, given that leptin is produced by adipose cells.

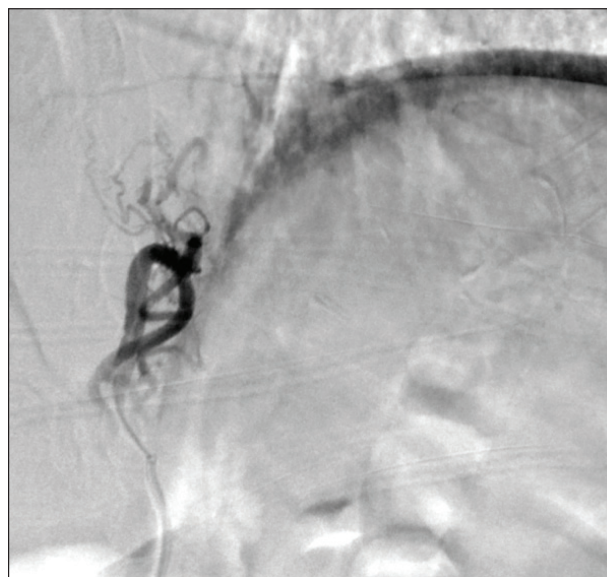
BEAT Obesity is an FDA-approved, single-arm, multicenter pilot study, which will include 20 patients with a BMI between 40 and 60 kg/m<sup>2</sup> and body weight < 400 lb.<sup>36</sup> According to the preliminary report, five nondiabetic, obese patients with a mean BMI of  $43.8 \pm 2.9$  kg/m<sup>2</sup> have been enrolled. Embolization of the LGA, as well as the distal GEA (if deemed necessary), was performed with 300–500- $\mu$ m Embosphere microspheres (Merit Medical Systems, Inc.). There were no major adverse events at 3-month follow-up. One patient acquired transient subclinical pancreatitis that had resolved by the 1-week follow-up visit. Another patient developed a small asymptomatic superficial ulcer in the fundus that was observed at the 2-week follow-up endoscopy, which had resolved by the time of the 3-month follow-up endoscopy. At 1 and 3 months, the reported average excess body weight loss was  $13.0 \pm 5.3$  lb (9.1%) and  $19.8 \pm 9.0$  lb (13.9%), respectively, among four patients. Serum ghrelin increased 8.7% at 1 month from a mean baseline value of  $894.8 \pm 251.1$  pg/mL but decreased 17.5% from baseline at 3 months. The final results of the study will include the 1-year follow-up data of 20 patients from the Johns Hopkins Hospital in Baltimore, Maryland, and the Mount Sinai Hospital in New York, New York.

The most recent ongoing trial with published preliminary data is the Chinese trial being undertaken by Bai et al.<sup>37</sup> The trial aims to include 50 patients, and the published preliminary study included five patients with a BMI  $\geq 30$  kg/m<sup>2</sup>. Patients underwent bariatric embolization of selected superior branches of the LGA using 500–710- $\mu$ m polyvinyl alcohol particles (Cook Medical), avoiding nontarget embolization of the body of the stomach as much as possible. In this

study, there were no major adverse events reported during the 9-month follow-up period. One patient developed a superficial linear ulceration below the cardia, which was noted at the 3-day follow-up endoscopy and had resolved by the 30-day follow-up endoscopy. Patients demonstrated an average weight loss at 3, 6, and 9 months of  $18.25 \pm 16.09$  lb (7.58%),  $22.97 \pm 18.10$  lb (9.79%), and  $28.44 \pm 32.32$  lb (12.64%), respectively. Ghrelin levels decreased by 40.83%, 31.94%, and 24.82% at 3, 6, and 9 months after the procedure, respectively, from a baseline of  $310.4 \pm 95.79$  pg/mL. In addition, postprocedure MRI demonstrated that subcutaneous adipose tissue significantly decreased during the follow-up period.

## DISCUSSION

Preliminary data from these pilot trials demonstrate that weight loss appears to be achievable in the short- to medium-term with bariatric embolization. The weight loss in these trials appears to correlate with a decrease in serum ghrelin, but neither the degree of weight loss nor the correlation with serum ghrelin has yet been definitively proven. When considering patients from the aforementioned studies,<sup>34–37</sup> one might expect an 8% to 10% total weight loss over a 6- to 12-month period on average. It also appears that bariatric embolization is well tolerated; pain, nausea, vomiting (all limited to ~48 hours), and superficial gastric ulcerations (healed by 1–3 months) were the most common postprocedural occurrences. Although these results are promising, there are several open questions regarding the efficacy of bariatric embolization.



**Figure 4.** Postembolization selection on a left gastric arteriogram. Distal branches show clear embolization, while the main branch continues to show some filling, ensuring future collateralization.



TABLE 1. CHARACTERISTICS AND RESULTS OF THE AVAILABLE PROSPECTIVE CLINICAL TRIALS

Study	Sample Size	Embolic Agent	Embolic Size (µm)	Follow-Up (mo)	Primary Endpoint	Adverse Events	Mean Baseline BMI (kg/m <sup>2</sup> )	Absolute Weight Loss	Excess Weight Loss
Kipshidze et al <sup>34</sup>	5	Bead Block particles	300–500	24	Weight loss	Mild transient epigastric discomfort	42.2	17.2%	Unknown
Syed et al <sup>35</sup>	4	Bead Block particles	300–500	6	Safety	Mild nausea, occasional vomiting, mild epigastric discomfort	42.4	7.8%	17.2%
Weiss et al <sup>36</sup>	5	Embosphere microspheres	300–500	3	30-day adverse events	Transient pancreatitis, asymptomatic superficial ulcer	43.8	4.7%	9%
Bai et al <sup>37</sup>	5	PVA particles	500–710	9	Safety	Superficial linear ulceration, hematoma at puncture site	38.1	Unknown	12.64%

Abbreviations: BMI, body mass index; PVA, polyvinyl alcohol.

#### Who Is the Ideal Candidate for Bariatric Embolization?

Patients in the GET LEAN and BEAT Obesity trials had a BMI  $\geq 40$  kg/m<sup>2</sup>; however, patients with a BMI  $\geq 30$  kg/m<sup>2</sup> were included in the latest Chinese trial. Although the difference in BMI can be attributed to cultural differences, all three trials demonstrated a similar range of weight loss. These data suggest that bariatric embolization may be more effective in treating patients with varying levels of obesity (ie, overweight vs obese vs morbidly obese), but this needs to be studied further.

#### Does Bariatric Embolization Have an Effect on Diabetes, and Is It Independent of Weight Loss?

A clinically significant effect was seen in the single diabetic patient included in the GET LEAN trial, and while no diabetic patients were included the BEAT Obesity trial, a reduction in HbA1c was observed. This question will likely be answered as future trials expand to include diabetic patients.

#### What Is the Long-Term Efficacy of Bariatric Embolization?

Because previous animal studies have shown that weight and ghrelin levels eventually trend toward the baseline after bariatric embolization, it is important to identify the long-term treatment effects of bariatric embolization.<sup>25-28,31</sup> Of note, the animals in many of these experiments were growing juveniles, unlike the adult patients studied in all human

trials to date. However, it has been suggested that the reversal or slowing of the procedural effect is due to revascularization of the stomach.<sup>26,31</sup> If these results are reflected in current ongoing clinical trials (ie, if the treatment effect tapers off at 6 to 12 months or if the patients experience rebound weight gain), it will help to define the role of bariatric embolization for the treatment of obese patients. If the treatment effect is shown to be transient only, then questions regarding repeat embolization or whether the procedure should be supplemented with other treatments, such as banding, may need to be explored. Combining bariatric embolization with ongoing dieting and pharmacology may play a larger role in the maintenance of weight loss.

#### What Is the Best Way to Perform Bariatric Embolization?

Clearly, the specific technique of bariatric embolization has not been standardized with regard to the ideal embolic agent (ie, composition and size), the exact blood vessels that should be embolized, or the embolization endpoint. Several different embolic agents of various sizes were used both in preclinical and clinical studies. To date, the LGA is the most common main target for embolization. However, the GET LEAN trial involved embolization of all the distal branches of the LGA, and Bai et al performed selective embolization of the cranial-most branches of the LGA. In BEAT Obesity, the embolization target was “fundal arteries,” which included LGA branches, as well as the distal GEA, if it was considered

a significant source of fundal perfusion. Embolization endpoints also differed among the trials, with varying definitions of observed stasis or lack of perfusion through the main LGA or its branches.

## What Is the Mechanism of Action of Bariatric Embolization?

It is believed that transient ischemia leads to decreased ghrelin production in the gastric fundus, but this may merely be a correlative, not a causative fact. It is likely that other factors play a role. One possible contribution may come from decreased gastric motility that results from partial stomach fibrosis. Other hormonal changes may exert a larger effect on appetite and satiety than were initially appreciated. In addition, the effects of bariatric embolization may be primarily due to patient education or psychological factors.

## CONCLUSION

The early preliminary pilot data on bariatric embolization show a promising and fairly consistent weight loss for at least 6 months. Longer-term results will be very important in helping to determine the long-term effects of bariatric embolization on weight loss, if any. Clearly, this is an exciting and active area of research, and more well-designed clinical trials are needed. ■

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*Disclosures: Grant support from NIH/NIBIB R01EB017615, NIH/NIBIB T32EB006351, SIR Foundation (FSDG), Siemens Healthcare, BTG International, Merit Medical, Medtronic; material support from SureFire Medical, BTG International, Merit Medical Systems, Inc., Siemens Healthcare; consultant to BTG, Medtronic.*