Gastric Embolization to Treat Obesity

The rationale behind this therapeutic option for obese patients.

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In 2008, more than 1.6 billion adults were overweight (body mass index [BMI] ≥ 25), with more than 400 million considered obese (BMI ≥ 30). Currently, more than one-third of adults in the United States are obese, and by 2030, it is expected that more than 42% of Americans will be obese. This trend is not exclusive to adults. In 2010, more than one-third of children and adolescents were overweight or obese, and since 1980, obesity rates have almost tripled. The prevalence of obesity has increased in both males and females across all ages, education levels, and racial and ethnic groups. Obesity is on course to overtake tobacco as the main cause of preventable death in the United States.[1]

Many factors contribute to the obesity epidemic. The American diet has drastically changed over the past several decades. Americans eat, on average, almost 500 more calories per day than they did in 1970. This is not surprising considering the constant advertising for inexpensive, high-calorie, high-fat foods; the fact that Americans eat out much more than in the past; and a dramatic increase in portion size.[2] Americans are less active than they used to be due to a changing work environment that is often dominated by long work days sitting in front of a computer screen and time spent commuting. Americans also sleep less than they used to. Sleep deprivation is associated with preferring high-calorie, high-carbohydrate foods and with obesity.[3] These factors are all contributing to the growing number of obese individuals in this country and throughout the world.

CONSEQUENCES OF OBESITY

Being overweight and obese is associated with an increased risk of several diseases, including diabetes, cardiovascular disease (ie, heart disease and stroke), endometrial cancer, breast cancer, colon cancer, sleep apnea, and osteoarthritis. Of these obesity-related conditions, diabetes may be the most closely linked to obesity.[4]

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Type 2 diabetes mellitus (T2DM) affects 25.8 million Americans (8.3% of the population). In 2010, there were approximately 1.5 million new cases of T2DM in patients over 45 years of age. T2DM is associated with a two- to fourfold increase in the risk of heart disease or stroke and is a leading cause of new blindness. T2DM is also a leading cause of kidney failure in the United States, as almost 50% of new cases of renal failure occur in patients with diabetes. The annual cost of this disease was estimated at $174 billion in 2007. This cost is expected to grow dramatically by the year 2030.[5]

OBESITY PREVENTION

Following a healthy lifestyle can prevent individuals from becoming overweight and obese. The United States Department of Health and Human Services has awarded more than $119 million to states to support public health initiatives designed to reduce obesity, increase physical activity, and improve nutrition.[1] Many of these programs, such as the "Let's Move!" program championed by Michelle Obama, are aimed at children and adolescents in an effort to prevent overweight and obese youth from becoming obese adults. Other programs include improving retail access to fruits and vegetables, limiting access to sugar-sweetened beverages, promoting menu labeling policies to ensure that consumers know the nutritional

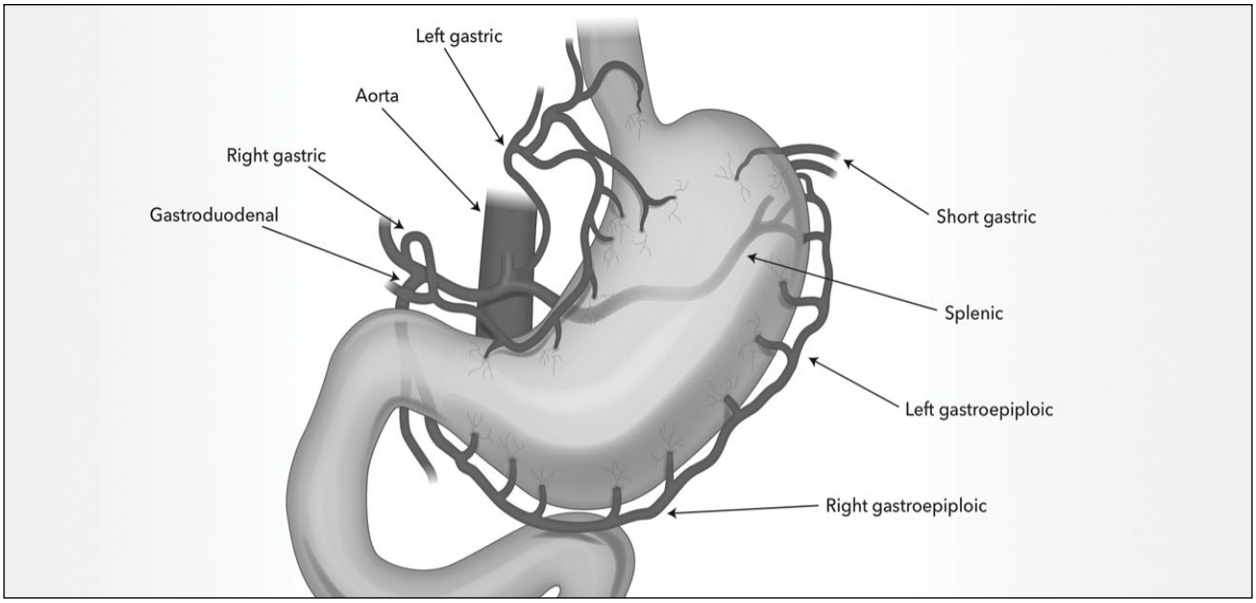

Figure 1. Vascular supply to the stomach. Adapted from the Johns Hopkins University, Department of Medicine, Division of Gastroenterology and Hepatology website.

content of food items, and urban design and transportation policies to facilitate walking and bicycling to work.

OBESITY TREATMENT

Diet, exercise, and behavioral modification have long been the mainstay of weight loss plans. The National Institutes of Health (NIH) advises a 1,000 to 1,200 kcal/day diet for most women and a 1,200 to 1,600 kcal/day diet for most men, with a gradual weight loss goal of 1 to 2 lbs per week until weight is within a healthy BMI category (18.5–24.9).[6] Safe weight loss can occur with diet, exercise, and behavioral modification, but it is typically only maintained for 1 to 5 years.[7]

Pharmacological interventions are rapidly being investigated. The current criteria used by the US Food and Drug Administration to demonstrate efficacy is a statistically significant weight reduction of 5% greater than the placebo group.[7] Patients who are unable to lose weight with diet, exercise, and behavioral modification and have a BMI ≥ 30 (or ≥ 27 with a comorbid medical condition) are eligible for drug treatment. Examples of drugs used to treat obesity include sibutramine and orlistat. Sibutramine exerts its effects by inhibiting the reuptake of norepinephrine, serotonin, and dopamine; this product was removed from the market in 2010 due to adverse events. Orlistat works by inhibiting the action of gastric and pancreatic lipases. The short-term weight loss associated with these drugs is typically 5% to 10% of total body weight. Orlistat has common side effects, including flatulence and loose stools.

Bariatric surgery is indicated in patients with morbid obesity (BMI ≥ 40 or a BMI ≥ 35 with comorbid conditions). There are two general types of operations performed: those that restrict gastric volume (banded gastroplasty and sleeve gastrectomy) and those that alter digestion (Roux-en-Y gastric bypass).[6] Bariatric surgery is considered the best long-term treatment for weight loss in these patients and also causes significant improvement in comorbid conditions, including T2DM, hypertension, and sleep apnea. In morbidly obese patients, bariatric surgery significantly reduced global, cardiovascular, and all-cause mortality.[7]

Although bariatric surgery in general has low perioperative risks, complications vary significantly with weight and the overall health of the individual. In young patients without comorbidities and with BMI ≤ 50, mortality rates are quoted at < 1%. In patients with BMI ≥ 60 with diabetes, hypertension, and cardiopulmonary failure, mortality rates range from 2% to 4%. In addition, there are significant potential long-term complications, including development of incisional hernias, gallstones, dumping syndrome, and vitamin and mineral deficiencies. In certain populations, the role of bariatric surgery is not clearly defined, including those with class I obesity (BMI = 30–35), very obese patients (BMI > 60), morbidly obese adolescents, and obese patients requiring weight reduction for another procedure.

Despite the efficacy of bariatric surgery, it is currently utilized in < 1% of patients who meet the NIH criteria of BMI ≥ 35.[7] Weight gain after bariatric surgery can

TABLE 1. SUMMARY OF PRECLINICAL DATA ON GASTRIC EMBOLIZATION FOR OBESITY IN ANIMAL STUDIES

Author	Year	N	Embolic Agent	Outcome
Arepally et al[13]	2007	6	Morrhuate sodium	Weight gain
Arepally et al[14]	2008	10	Morrhuate sodium	Weight gain
Bawudun et al[15]	2012	10	Bleomycin, PVA 500–700 µm*	Weight loss
Paxton et al[17]	2013	12	Particles, 40 µm**	Weight loss

**Less nontarget embolization and greater weight loss and decreases in serum ghrelin levels with PVA particles.*
***Significant incidence of ulcers, gastritis, and esophageal strictures. Significant reduction in ghrelin-expressing cell in the fundus of the stomach.*

occur when patients fail to exercise and return to old eating habits.

GASTRIC ARTERY EMBOLIZATION

Recently, the peptide ghrelin was identified as a regulator of long-term appetite regulation and energy homeostasis.[8] Ghrelin is a powerful appetite stimulant that is produced in the mucosa of the gastric fundus in response to hunger and starvation, signaling the brain to stimulate feeding.[9] Ghrelin release results in increased growth hormone secretion, increased gastric acid secretion, gastric motility, and decreased gastric emptying. Ghrelin administration results in increased appetite and adiposity. Ghrelin levels have been shown to be associated with obesity.[10]

The stomach typically receives its arterial supply via the celiac axis (Figure 1). The left gastric artery most commonly arises directly from the celiac axis and supplies the superior portion of the lesser curvature of the stomach, as well as the distal esophagus; it is the primary supply to the fundus of the stomach. The right gastric artery most commonly arises from the proper hepatic artery (or, less commonly, from the common hepatic artery) and supplies the inferior portion of the lesser curvature of the stomach to the pylorus. It can also arise from the gastroduodenal or left hepatic artery. The right gastroepiploic artery is a terminal branch of the gastroduodenal artery and supplies the inferior portion of the greater curvature of the stomach. The left gastroepiploic artery is the largest branch of the splenic artery and supplies the superior portion of the greater curvature of the stomach. The short gastric arteries are small branches arising from the splenic artery to supply the greater curvature of the stomach, anastomosing with the left gastric and left gastroepiploic arteries. Embolization has been employed in the upper gastrointestinal (GI) tract since the 1970s for the management of GI bleeding.[11] Ischemic complications rarely occur, as a result of the foregut's rich collateral blood supply.[12] With this background in mind, it has recently been suggested that catheter-directed gastric embolization could serve as a treatment option for bariatric patients. The rationale behind this idea is that left gastric artery embolization can cause localized ischemia in the region of ghrelin production, which can therefore reduce ghrelin levels and reduce appetite. This idea has been supported by several preclinical studies (Table 1).

Arepally et al were the first to report their data on this procedure in 2007.[13] They evaluated this hypothesis in eight healthy swine. Selective catheterization of the arteries supplying the fundus of the stomach was performed, and these vessels were embolized with morrhuate sodium reconstituted with nonionic contrast in six of the animals; two animals served as control subjects. The swine that received the highest dose of morrhuate sodium (2,000 mg) developed a perforated ulcer in the gastric fundus and was killed on day 1 after the procedure. In the swine that received a low dose of morrhuate sodium, there was a significant increase in serum ghrelin levels. When higher doses were used, the ghrelin levels decreased (466 pg/mL to 187 pg/mL).

All swine experienced increases in weight, but the increase seen in embolized swine was less than that seen in the control animals (1.4% vs 8.6%). Histologically, the tissue architecture was well preserved. However, there was decreased ghrelin content in the gastric fundus of embolized swine. These investigators concluded that this technique could allow for selective embolization of the ghrelin-producing portion of the stomach, with suppression of systemic ghrelin levels.

One year later, Arepally et al reported the results of a second animal study.[14] Ten swine were studied in this research. They were divided equally, with five undergo-

ing a sham procedure and five undergoing an embolization with 125 µg of sodium morrhuate (50 mg/mL, 5%). The dose was selected based on their initial study. Each treated subject underwent injection of at least two gastric arteries (arising from the celiac axis and hepatic artery). In this study, the embolized subjects demonstrated a significant decrease in ghrelin levels compared with the controls (1,006.3 pg/mL to 578.4 pg/mL at week 3; although still decreased, levels did rise at week 4 to 876.6 pg/mL). In addition, the embolized swine gained less weight than the control swine (7.8% vs 15.1%). They concluded that embolization can suppress ghrelin levels and affect weight gain.

In 2012, Bawudun reported the results of a similar study in dogs.[15] They studied 15 dogs and divided them into two groups based on weight. They then divided each of those two groups into three subgroups: a control group, a group embolized with a sclerosant consisting of bleomycin and lipiodol, and a group embolized with 500- to 700-µm polyvinyl alcohol (PVA) particles. Each animal underwent an upper GI series and a CT scan of the abdomen before the procedure and 8 weeks after the procedure. Nontarget embolization was seen in three dogs receiving lipiodol based on the finding of contrast in the liver on CT. This study showed that embolization with both agents led to decreased plasma ghrelin levels, body weight, and subcutaneous fat size (based on CT measurement). The decreases were more pronounced when PVA particles were used (30.2% vs 15.8%). Histopathologic evaluation 8 weeks after embolization showed no ulceration and intact architecture.

In 2013, Paxton et al studied 12 swine, with six undergoing gastric artery embolization with 40-µm particles and six undergoing a sham procedure.[16,17] This study also demonstrated significant changes in ghrelin levels over time in the embolized group when compared to the control group. In addition, the pattern of weight change between the two groups was significantly different. In this study, endoscopy and pathologic evaluation demonstrated ulcers, gastritis, and a distal esophageal stricture in treated animals; the pathologic findings correlated well with the endoscopic findings. They concluded that embolization could significantly suppress ghrelin levels and affect weight gain. However, the complications were concerning, and they suggested a role for gastroprotective agents in association with this procedure. Pathologically, these investigators later showed that embolization resulted in a significant reduction in ghrelin-expressing cells in the gastric fundus.[18]

These four studies highlight the potential that gastric artery embolization may have in the treatment of this difficult patient population. Although similar in design, these four studies each have differences that become important when putting together a protocol for investigation of this technique in humans. The initial studies by Arepally et al used a sclerosant as the embolic agent. This sclerosant only appeared to be effective when used at lower doses, and even then, weight gain was seen in all animals, albeit to a lesser degree in the treated patients than in the control patients. Paxton et al[17] used very small particles as the embolic agent. With this technique, they noted decreases in weight and ghrelin levels, but the complication rate was quite high, which may be due to the distal level of occlusion with the use of such small particles. Given these complications, it is also possible that the decrease in ghrelin levels may be attributed in some part to an Helicobacter pylori infection in association with gastritis and ulceration. Bawudun et al[15] found the greatest success with the use of PVA particles measuring 500 to 700 µm in diameter. This embolic agent led to significant weight loss and decreases in ghrelin levels to a greater degree than a sclerosant, but did so without complications (based on an upper GI and pathologic evaluation).

IN-HUMAN STUDIES

In March 2013, the results of a first-in-human study performed by Kipshidze et al in Tblisi, Georgia, were presented.[19] These authors reported the results of left gastric artery embolization performed in five patients. Bead Block microspheres (BTG International, West Conshohocken, PA), PVA-hydrogel microspheres measuring 300 to 500 µm in diameter, were used for embolization. Endoscopy and ghrelin levels were obtained before and after embolization. All patients reported decreased appetite during the first week after the procedure. Weight loss was observed in all patients at 1-month follow-up. The mean initial weight decreased from 128 kg to 114 kg, and the mean initial BMI decreased from 42.3 to 37.9 between initial measurement and 1-month follow-up. No complications were observed in this population of patients. Even though this is only a small sample of patients, this study does demonstrate the potential efficacy of this procedure.

Finally, in 2013, Gunn et al presented the results of a retrospective study evaluating patients who underwent left gastric embolization for GI bleeding.[20] When comparing patients undergoing this procedure with a matched control group, they found that patients undergoing embolization lost an average of 7.9% of their body weight within 3 months. The control group lost 1.2% of their body weight during the same amount of time, which was a statistically significant difference. Although this last study was not well con-

trolled, it does provide additional signal in support of this procedure.

CONCLUSION

Gastric embolization is potentially an exciting advance in the treatment of obesity for patients who are not considered appropriate candidates for bariatric surgery. It is clear that we need a better understanding of this procedure and its safety, efficacy, and relationship to hormone reduction. Therefore, significant research through performance of well-designed clinical trials is necessary before this procedure can become part of the daily practice of interventional radiology. ■

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