Bariatric embolization for the treatment of obesity

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ABSTRACT

Embolization of the left gastric artery with the intent of decreasing hunger, termed bariatric embolization, has experienced a recent surge of attention in the literature and at medical conferences. This endovascular treatment for obesity has demonstrated promising data as a potentially new and effective minimally invasive treatment for obesity. The goal of this review article is to discuss the background, rationale, and existing data on this new topic.

Keywords: Bariatric, Embolization, Obesity

Introduction

Bariatric embolization, also known as left gastric artery embolization, is a recently introduced endovascular image-guided procedure aimed at treating obesity.1 This procedure entails percutaneous transarterial particle embolization of the gastric fundus arterial supply, which is the site of the highest concentration of ghrelin-secreting cells in the body. By doing so, it is hypothesized that the intentionally induced ischemia in the gastric fundus will result in depressed serum ghrelin levels, which may decrease hunger, decrease food intake, and thereby induce weight loss. The goal of this review article is to discuss the background, rationale, and existing data on this new and burgeoning topic.

Obesity

In 1997, the World Health Organization designated obesity as a global epidemic, marking the first time in history that a noninfectious malady has been labeled as an epidemic.2 In 2008, >1.4 billion adults were overweight, with a body mass index (BMI) of ≥25. Five hundred million were obese, with a BMI of ≥30.3 Thus, 11% of the world’s population was classified as obese. The rate of obesity is growing, with an incidence that has nearly doubled since 1980.

Obesity is ranked as the fifth leading risk for mortality globally.4 Obesity has been strongly linked to numerous comorbidities, including type II diabetes, hyperlipidemia, hypertension, obstructive sleep apnea, heart disease, stroke, asthma, cancer, and depression.5 The link is actually strong – for example, the risk of diabetes increases 18-fold in obese patients. The increase in relative risk of coronary artery disease in middle-aged men is 72% higher, even with only mild obesity. In aggregate, these obesity-related comorbidities have been reported to be responsible for >2.5 million deaths per year worldwide. Not surprisingly, life expectancy is profoundly affected by obesity. For example, a 25-year-old morbidly obese man can expect a 22% reduction in lifespan.6 In fact, an expert panel convened by the National Institutes for Health stated that for the first time in history, the steadily improving worldwide life expectancy could level off or even decline within the first half of this century, specifically as the result of the increasing prevalence of obesity.5

The fundamental cause of obesity is an energy imbalance, with more calories being consumed than expended. The global rise in obesity can be attributed at least in part to the increased intake of high-calorie and high-fat foods and a decrease in physical activity related to the increasingly sedentary lifestyles resulting from modernization and automation. However, numerous additional etiologies and pathologies are also known to be responsible for obesity.

Regulation of hunger

The hormonal regulation of hunger is complex, and is primarily governed by hunger-inhibiting hormones.7 Mechanical and chemical factors associated with meals stimulate entericendocrine cells, resulting in signals transmitted neurally through vagal nerves and/or circulating hormones. The end result is modulation of hunger in the central nervous system. Short-term hunger modulation in response to meals is largely due to cholecystokinin. Longer-term regulation of energy balance and weight is controlled largely by the effects of insulin and leptin. Although >40 hormones

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Received 13 September 2014; Revised 7 October 2014; Accepted 8 October 2014
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http://dx.doi.org/10.1016/j.gi.2014.10.004
have been shown to inhibit appetite, only ghrelin has been shown to stimulate appetite.7

**Ghrelin**

Ghrelin is a peptide hormone that is secreted primarily from the gastrointestinal tract, with the highest concentration in the fundus of the stomach, with progressively decreasing concentrations in the small and large intestines. Ghrelin was first identified and reported in the literature in 1999 as an endogenous ligand for the growth hormone secretagogue receptor.8 Additionally, ghrelin directly stimulates appetite and induces positive energy balance, resulting in body weight gain. Ghrelin is also expressed in the pancreatic islets, hypothalamus, and pituitary gland. In addition to stimulating appetite, ghrelin has also been shown to increase circulating growth hormone, adrenocorticotropic hormone, cortisol, prolactin, and glucose.9 Given the relatively recent discovery of ghrelin and incomplete understanding of its functional role, it likely has additional effects on other hormones and functions. Due to the unique nature of this hormone and its effect on appetite, multiple approaches to modulate ghrelin production have been attempted. Although various reports of ghrelin suppression have been described, none to date have been clinically practical, including intraventricular and large intraperitoneal delivery of ghrelin antagonists in rats, as well as a ghrelin vaccine.10–13

**Gastric distribution**

The detailed distribution of ghrelin-expressing cells has been reported in two separate studies.14,15 Although Kim et al14 analyzed gastric specimens from patients with gastric cancer undergoing total gastrectomy, Goitein et al15 analyzed resected gastric specimens from patients with gastric cancer undergoing vertical resection of most of the stomach volume, including the entire fundus, most of the gastric body, and part of the antrum. In both studies, polymerase chain reaction analysis of ghrelin mRNA and immunostaining for ghrelin-expressing cells were performed throughout the resected specimen. In both studies, ghrelin mRNA and ghrelin-expressing cells were identified throughout the entire stomach; however, the concentrations of ghrelin mRNA and ghrelin-expressing cells were statistically highest in the gastric fundus, and lowest in the gastric antrum. Kim et al14 reported a ghrelin/actin mRNA ratio of 0.78 in the fundus, 0.20 in the body, and 0.07 in the antrum, reflecting a 10-times higher ghrelin concentration level in the fundus compared to the antrum. Goitein et al15 similarly reported a ghrelin/ribosomal mRNA ratio of 0.043, 0.026 and 0.015, respectively, which is an approximately three-times higher level in the fundus than antrum.

**Treatment options for obesity**

Diet and exercise regimens, while effective, have been shown to be difficult to maintain in the long term.16 Plasma ghrelin levels have been shown to rise sharply shortly prior to meals, which correlates with hunger that occurs just prior to consuming meals.17 Conversely, ghrelin levels fall shortly after each meal, which correlates to the satiation of hunger after consuming food. Diet regimens to induce weight loss have been shown to be difficult to sustain, due to the increase in hunger.18 Thus, it may not be surprising that dieting induces a 24% increase in the 24-hour ghrelin profile (P = 0.006).17 This elevated ghrelin secretion may therefore be a reason why dieting is so difficult to sustain in the long term.

Pharmacological modulation of hunger would be perhaps the ultimate means of controlling appetite and weight. Despite great efforts in this area, current pharmacotherapeutics can achieve only modest levels of weight loss with a range of 2.0–6.5 kg of sustained weight loss.17

Although bariatric surgery has proven to result in substantial degrees of sustained weight loss, the surgical risk in this patient population is significant. Alterations in ghrelin levels also occur with bariatric surgery. After gastric banding, there has been shown to be a 27% increase in serum ghrelin levels, which may be undesirable if patients experience increased hunger.19 The results with roux-en-Y gastric bypass are somewhat controversial. Although some studies have demonstrated a decrease in serum ghrelin, others have shown ghrelin levels to be unchanged.19–22 However, with sleeve gastrectomy, the levels of serum ghrelin have been shown in multiple studies to be markedly decreased by ~60%.20,21 In fact, ghrelin depression has been shown to be significantly depressed even as far as 5 years post-surgery.22 Considering that the majority of the gastric fundus is removed during sleeve gastrectomy, there would certainly be a loss of a large proportion of ghrelin-secreting cells. Many have postulated this as one of the primary reasons why sleeve gastrectomy is the most effective of the bariatric surgeries, and conversely, a reason why surgeries that have no gastric tissue resection, such as gastric banding, have poor efficacy.

**Gastric artery chemical embolization**

The initial discovery that introduced the concept of destruction of ghrelin-producing cells by minimally invasive catheter-directed techniques was reported by Arepally et al23 in 2007. In this pilot study, the authors demonstrated that infusion of sodium morrhuate, a varicose vein sclerosant, into the left gastric artery of swine resulted in elevated serum ghrelin levels with low doses, but depressed serum ghrelin levels at moderate doses. Notably, at high doses, death resulted secondary to gastric necrosis and perforation. Arepally went on to perform gastric artery chemical embolization (GACE) in a larger number of swine using the higher doses, with a control arm to assess for differences in ghrelin level and weight over a 4-week period.24 Again, the serum ghrelin levels in treated animals were shown to be significantly depressed compared to controls. In these growing swine, the mean weight was statistically lower at 3 weeks and 4 weeks compared to untreated controls. However, the mean serum ghrelin levels demonstrated a 51% increase at 4 weeks, suggesting that the effect may be transient.

**Bariatric embolization in a porcine model**

The use of sodium morrhuate, while promising in the initial studies, would be difficult to translate to use in humans. This long-used sclerotherapy agent is used to induce direct damage to the endothelium of varicose veins. As a liquid agent, control of the distribution of flow can be difficult to control. The appropriate amount to administer would also be difficult to ascertain given variability in stomach size and vascularity. A well-described complication of sodium morrhuate use in venous sclerotherapy is inadvertent flow to the lungs, which causes pulmonary arterial injury and even respiratory failure.25 Even more worrisome is its ability to induce transmural necrosis and perforation when infused into the gastric arteries.26

**Rationale**

In an effort to destroy ghrelin-secreting cells in the gastric fundus using an agent that is benign, more controllable, and potentially easily translatable to human trials, our research group investigated the effect of ischemia by means of particle embolization of the gastric fundus as a method to potentially impair the
functionality and viability of these ghrelin-producing cells. The initial results by Arepally et al.\textsuperscript{23} were achieved using a highly toxic substance, therefore, we sought to maximize the amount of ischemic damage, and thus used the smallest commercially available particles (40 μm diameter calibrated microspheres) and embolized all identifiable arteries supplying the gastric fundus.

**Results**

Over the 8-week study, the ghrelin levels in animals undergoing bariatric embolization were significantly lower compared to control animals that underwent a sham procedure ($P = 0.004$). The resulting weights at the end of the study were also significantly lower in treated animals ($P = 0.025$). While the results of particle embolization of the gastric fundus were similar to the results with chemicals of Arepally et al.,\textsuperscript{23} there were no animals with transmural necrosis or perforation. Endoscopic evaluation at 1 week and histopathological evaluation of postmortem specimens did reveal that half of all animals had evidence of healing ulcers. Notably, none of the animals undergoing bariatric embolization did show evidence of healing ulcers. Although all animals undergoing bariatric embolization did show evidence of gastritis, 83% of control animals undergoing a sham procedure also had evidence of gastritis. It is known that the stress of captivity in a new environment, as well as general anesthesia, is sufficient to induce gastritis and ulcers in swine. Of note, 75% of swine raised in farms have an ulcer or pre-ulcer changes.\textsuperscript{26}

Histopathological evaluation of the explanted gastric mucosa was an important goal of our studies, to determine the actual sequelae of bariatric embolization.\textsuperscript{27} Although there was a trend towards increased fibrosis in the gastric fundus of treated animals, it did not reach statistical significance. However, analysis of the ghrelin-secreting cell density showed a significantly lower cell density in treated animals compared to controls ($P = 0.03$). This finding importantly established that the ischemia induced by particle embolization of the stomach is sufficient to destroy ghrelin-secreting cells, without causing profound architectural destruction of the gastric wall.

Given the natural inclination of the body towards homeostasis, it is a concern that upregulation of ghrelin-secreting cells eventually occurs elsewhere in the body, thus returning serum ghrelin levels to baseline over time. In order to explore this phenomenon, all animals in our study also underwent evaluation of the duodenum, since this is the second-richest source of ghrelin-secreting cells. The ghrelin-secreting cell density was demonstrated to be equivalent, comparing the treated gastric fundus to the untreated duodenum ($P = 0.89$), although the time interval was relatively short at 8 weeks.

In additional studies, we sought to determine whether gastroprotective agents could mitigate the risk of ulceration, by administering sucralfate and a proton-pump inhibitor to animals prior to and after bariatric embolization.\textsuperscript{28} We also hypothesized that embolization of a greater number of embolized arteries would affect the extent and severity of ulceration. In these additional experiments, neither gastroprotective agents nor number of arteries embolized prevented ulceration. Thus, gastric ulceration may be an innate risk of bariatric embolization, although it must be kept in mind that the particle size may be related, and that swine may be at higher risk than humans for this side effect.

**Animal model limitations**

The animals used in this study were young, growing pigs, approximately 10–14 weeks old, weighing 30–47 kg. This represents a different physiological circumstance when compared to obese adults that have stopped growing but have excessive caloric intake. Thus, weight gain in these growing pigs was due to not only adipose tissue, but more significantly to muscle, bone, and organ growth. Thus, the results attained in swine may not be generalizable to humans. That being said, perhaps it is more difficult to impair growth in growing pigs than to induce weight loss in obese adults. Swine were the choice of animals for this study due to the high prevalence of swine in the literature for analyzing ghrelin levels, and their anatomy that is similar in size and configuration to humans.

**Targeting of the fundus**

Another limitation of our model for the accurate targeting of the gastric fundus is its nondiscrete arterial supply. In humans, multiple arteries supply the gastric fundus, including the left gastric artery, short gastric arteries, and left gastroepiploic artery. All of these arteries interconnect with each other, as well as the arteries that supply the body and antrum of the stomach, including the right gastric artery, right gastroepiploic artery, and gastroduodenal artery. Thus, depending on the flow dynamics, infusions of particles or any substance into any one of these arteries could have a variable amount of fundal embolization and would almost certainly have some degree of embolization of the gastric body and antrum. Due to the extensive interconnections, non-target embolization of the spleen, pancreas, liver, and duodenum are at-risk organs.

**Bariatric embolization in a canine model**

Contemporary to our study, Bawudun et al.\textsuperscript{29} conducted a similarly designed study in a canine model. However, in addition to a particle embolization treatment group, a chemical embolization group (bleomycin plus lipiodol) was also used. Bleomycin is a chemotherapeutic agent that causes strand breaks in DNA and is also used as a chemical sclerosant for pleurodesis. The particle embolization group was treated with 500–700 μm polyvinyl alcohol (PVA) particles.

Over an 8-week period, the authors reported that plasma ghrelin levels and body weight were significantly decreased in both treatment groups compared to controls. Several additional important parameters were analyzed. The abdominal body fat was quantified using computed tomography performed pre-procedurally and at 8 weeks. Both visceral and subcutaneous fat were quantified. The subcutaneous fat was significantly decreased in both treatment groups, whereas visceral fat was not. Gastric peristalsis was assessed at 8 weeks with a barium study of the stomach, with the conclusion that the gastric peristalsis appeared normal. Histopathological analysis demonstrated no difference in parietal cell structures comparing treated animals to controls. No gastric ulcers were identified.

Two important differences in the model are worth highlighting, compared to the swine model studies. First, the animals were on average 2 years old, and thus beyond the active growth stage. Thus, this model would more closely approximate the use of bariatric embolization in human adults, and the significant decrease in the amount of subcutaneous fat over 8 weeks is important and highly promising. The second and perhaps more important finding is that no gastric ulcers were detected in this study. At least two technical factors may be responsible for this finding. In this study, the authors used larger particles for embolization, measuring 500–700 μm, whereas in the swine study, 40-μm particles were used. The other factor may be that only one artery, that is, the left gastric artery, was treated in the canine study, whereas all four arteries supplying the gastric fundus were treated in the swine study. These factors may be useful for determining the optimal technique by which to perform bariatric embolization safely and efficaciously.
Human trials

In a retrospective fashion, Oklu et al.\(^\text{30}\) presented the results of a single-institution cohort study of 15 patients who underwent transcatheter embolization of the left gastric artery for the indication of gastric hemorrhage, in comparison with a cohort of 18 age-matched patients who underwent embolization of any non-left gastric artery for treatment of upper gastrointestinal hemorrhage. Analysis of resultant weights over the subsequent 3 months revealed a 7.9% mean decrease in body weight for patients undergoing left gastric artery embolization compared to a mean 1.2% decrease in body weight for those undergoing embolization of a different upper gastrointestinal artery \((P = 0.001)\). Embolic agents included particulate agents, coils, or a combination.

Kipshidze et al.\(^\text{31}\) reported the results of a first-in-human prospective study of left gastric artery embolization in five patients. In this series, patients underwent embolization of the left gastric artery with 300–500-μm microspheres. Three patients reported transient abdominal pain. Endoscopy performed in all patients at 1 week post-procedure revealed no significant abnormalities. The mean weight, body mass index, and ghrelin levels were decreased at 1 month, 3 months and 6 months post-procedure (Table 1).

Future directions

In conclusion, the concept of an endovascular treatment for obesity has demonstrated promising preliminary data in animals and humans. However, the number and power of these studies is still somewhat marginal, and thus additional preclinical studies are needed to elucidate the mechanisms of this procedure. However, given the extremely complex physiology and mechanisms affecting appetite, weight gain, and weight loss, usually human trials are crucial prior to routine clinical use. To that end, multiple human trials have been initiated in multiple countries. Although primary efforts in these clinical trials were aimed at demonstrating safety, proving efficacy in terms of ghrelin levels, hunger and weight loss were also important components of these clinical trials. Perhaps more importantly, the duration of any effects will be a crucial factor in determining the future potential of this promising therapy. Once safety and basic efficacy are shown in further preliminary clinical trials, a full randomized clinical trial comparing embolization to various other treatments of obesity is destined to take place. If proven effective and safe, this endovascular method for treatment of obesity has great promise for playing a pivotal role in the treatment of one of the biggest epidemic health issues worldwide.

Conflicts of interest

All contributing authors declare no conflicts of interest.

References