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Histopathologic and Immunohistochemical Sequelae of Bariatric Embolization in a Porcine Model

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Abstract

Purpose—To evaluate the histopathologic sequelae of bariatric embolization on the gastric mucosa and to correlate with immunohistochemical evaluation of the gastric fundus, antrum, and duodenum.

Materials and Methods—This study was performed on 12 swine stomach and duodenum specimens after necropsy. Of the 12 swine, 6 had previously undergone bariatric embolization of the gastric fundus, and the 6 control swine had undergone a sham procedure with saline. Gross pathologic, histopathologic, and immunohistochemical examinations of the stomach and duodenum were performed. Specifically, mucosal integrity, fibrosis, ghrelin-expressing cells, and gastrin-expressing cells were assessed.

Results—Gross and histopathologic evaluation of treatment animals showed healing or healed mucosal ulcers in 50% of animals, with gastritis in 100% of treatment animals and in five of six control animals. The ghrelin-immunoreactive mean cell density was significantly lower in the gastric fundus in the treated animals compared with control animals (15.3 vs 22.0, $P < .01$) but similar in the gastric antrum (9.3 vs 14.3, $P = .08$) and duodenum (8.5 vs 8.6, $P = .89$). The gastrin-expressing cell density was significantly lower in the antrum of treated animals compared with control animals (82.2 vs 126.4, $P = .03$). A trend toward increased fibrosis was suggested in the gastric fundus of treated animals compared with controls ($P = .07$).

Conclusions—Bariatric embolization resulted in a significant reduction in ghrelin-expressing cells in the gastric fundus without evidence of upregulation of ghrelin-expressing cells in the duodenum. Healing ulcerations in half of treated animals underscores the need for additional refinement of this procedure.

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Ghrelin is the only hormone known to stimulate appetite and is referred to as the “hunger hormone” (1–4). By stimulating food intake, ghrelin induces positive energy balance, resulting in weight gain (5,6). Morbidly obese patients have been shown to have a higher expression of ghrelin-producing cells in the gastric mucosa (7). The unique nature of this hormone and its effect on appetite have led to attempts of multiple approaches to modulate ghrelin production, but no feasible direct clinical technique has yet been achieved (8–12).

A catheter-based procedure, termed “bariatric embolization,” has been introduced more recently; this technique directly targets the gastric fundus, owing to the fact that it contains the highest concentration of ghrelin-secreting cells in the body (13–16). In the investigations of this technique, calibrated spheres were delivered into the arterial vasculature of the gastric fundus to induce localized ischemia. The investigations have shown that bariatric embolization results in suppression of systemic ghrelin levels and has a significant impact on weight gain. However, the histologic sequelae of bariatric embolization on the gastric mucosa have not yet been reported. Also, ghrelin homeostasis is complex, and the potential impact of bariatric embolization on ghrelin-expressing cell upregulation is difficult to predict. The purpose of the present study was to evaluate the histopathologic sequelae of bariatric embolization on the gastric mucosa and to correlate with immunohistochemical evaluation of mucosal ghrelin and gastrin expression in the gastric fundus, antrum, and duodenum.

MATERIALS AND METHODS

Animal Model

The Institutional Animal Care and Use Committee approved this study, which was performed on swine stomach and duodenum specimens after necropsy. Juvenile female animals had previously been randomly assigned to undergo either bariatric embolization or a sham procedure (16). Treated swine (n = 6) had previously undergone particle embolization of arteries supplying the gastric fundus, whereas control animals (n = 6) underwent a sham embolization with 5 mL of saline. The detailed technique was reported previously (16). Briefly, all four gastric arteries supplying the fundus received embolization to stasis with 4–6 mL of diluted 40- μ m calibrated microspheres (Embozene; CeloNova BioSciences, Inc, San Antonio, Texas) using a 3-F microcatheter system (Fig 1). All animals were euthanized at 8 weeks after the procedure with Euthasol 1 mL/10 lb (Lloyd Laboratories, Shenandoah, Iowa).

Gross Pathology

Following euthanasia, a ventral midline incision was made from the neck to the lower abdomen. The skin and soft tissues were reflected laterally to reveal the chest and abdominal cavities. The stomach was separated from the surrounding soft tissue and vasculature and removed from the abdominal cavity by transecting the proximal esophagus and third part of the duodenum. The excised stomach was opened along the greater curvature and placed in formalin for tissue fixation. After fixation, the gastric mucosa was examined to evaluate for evidence of mucosal ulceration or injury. Tissue sections were taken from areas of mucosal ulceration and erythema. Additionally, representative sections of the gastroesophageal

junction, gastric fundus, body and antrum, and duodenum were taken in the six treatment animals and five control animals. Histopathologic evaluation of one control animal was not performed because of desiccation of the specimen.

Histopathology and Immunohistochemistry

Hematoxylin-eosin–stained sections were prepared using standard techniques. Trichrome-stained sections from the gastric fundus were scanned (Aperio, Vista, California) and analyzed using the color deconvolution algorithm (ImageScope; Aperio) to determine the amount of fibrosis.

For immunohistochemical detection of ghrelin, mouse antighrelin immunoglobulin G in a ratio of 1:4,000 (No. MAB10404; Millipore, Billerica, Massachusetts) was used. The bound ghrelin antibody was detected with Bond Refine HRP-labeled ready-to-use detection system on the Bond III automated immunohistochemical slide staining system (Leica Microsystems, Bannockburn, Illinois). Immunohistochemical analysis was performed using light microscopy (Olympus BH-2; Olympus, Center Valley, Pennsylvania). Ghrelin-immunoreactive cell density was expressed as the average number of positive cells per high-power field (400 $\times$, 0.49 mm field diameter).

Gastrin staining was performed as follows with standard immunohistochemical techniques. The XT iVIEW DAB system (Ventana Medical Systems, Tucson, Arizona) was used with a rabbit antigastrin polyclonal antibody (Cell Marque, Rocklin, California). This antibody stains the G cells of human antral and pyloric mucosa and cells producing gastrin. Formalin-fixed, paraffin-embedded tissue was placed on positively charged slides and dried by warming to 100°C. Slides, antibody, and iVIEW detection kit dispensers were loaded onto a Benchmark instrument (Ventana Medical Systems, Tucson, Arizona). Antibody incubation was set for 32 minutes at 37°C. The automated run included reaction with iVIEW biotin, horseradish peroxidase, 3,3'-Diaminobenzidine tetrahydrochloride (DAB), and copper reagents. When the run was completed, slides were rinsed with wash buffer and counterstained with hematoxylin, and a coverslip was applied.

Statistical Analysis

Ghrelin-immunoreactive cell density was expressed as the average number of positive cells per high-power field (400 $\times$, 0.49 mm field diameter) for samples of the fundus, antrum, and duodenum of treatment and control animals. Gastrin-positive cell density was reported as the average number of positive cells per high-power field (20 $\times$). Cell densities were compared using the Wilcoxon rank sum test. A *P* value $\leq .05$ was considered statistically significant. Statistical analysis was performed using Stata Statistical Software: Release 11 (StataCorp LP, College Station, Texas).

RESULTS

Gross Pathology

Gross evidence of gastric mucosal abnormalities was identified in four of six treatment animals. One treated animal had a large ulcer with surrounding erythema measuring 7.9 cm

× 5.5 cm that was located within the gastric body on the anterior surface of the stomach. Another treatment animal had a 2.9 cm × 1.7 cm ulcer with surrounding erythema located in the gastric body on the posterior surface of the stomach. A third treatment animal showed a well-circumscribed 2.1 cm × 1.7 cm area of mucosal flattening consistent with a healed ulcer within the gastric body along the greater curvature. A fourth treatment animal had a 1.2 cm × 1.0 cm area of erythema in the gastric body along the greater curvature without frank ulceration. No control animals showed any gross evidence of gastric mucosal injury.

Histopathology

Histopathologic evaluation of treatment animals confirmed the presence of embolic particles within the gastric fundus, with a lesser concentration in the gastric body and antrum. All treated animals showed minimal to mild sequelae of ischemia in the gastric fundus, as evidenced by fibrosis with some fibrotic strands traveling up into the lamina propria mucosae. As observed on gross pathology, histopathology confirmed mucosal ulceration in two of six (33%) treatment animals. Both animals showed fibrinopurulent debris and granulation tissue at the ulcer surface overlying extensive mucosal and submucosal fibrosis with surrounding ischemic changes, without acute ulcer exudate, consistent with a healing ulcer. No full-thickness ulceration or perforation was identified. A third treatment animal showed reepithelialized mucosa demonstrating reactive foveolar hyperplasia overlying extensive mucosal and submucosal fibrosis consistent with a well-healed gastric ulcer.

Tissue sections from the fourth treatment animal with a 1.2 cm × 1.0 cm area of erythema in the gastric body along the greater curvature showed evidence of ischemic damage in the body and antrum, including fibrosis of the mucosa and muscularis mucosae without frank ulceration. The remaining two treatment animals also showed some histologic sequelae of ischemia, primarily within the gastric body and antrum but did not show evidence of mucosal ulceration. All treatment and control animals showed mild to moderate gastritis with varying numbers of plasma cells in the lamina propria mucosae. The control animals showed no evidence of ulceration or ischemic damage.

Immunohistochemistry

Analysis of the density of ghrelin-expressing cells within the gastric fundus revealed a significantly lower ghrelin-immunoreactive mean cell density in the treatment animals versus control animals (15.3 vs 22.0, $P = .001$) (Figs 2, 3). However, the ghrelin-immunoreactive mean cell density in the gastric antrum was similar in treatment animals versus control animals (9.3 vs 14.3, $P = .075$). Similarly, in the duodenum, the ghrelin-immunoreactive mean cell density was similar in treatment animals versus control animals (8.5 vs 8.6, $P = .89$) (Fig 4).

Gastrin-positive cells were decreased in the treated animals (82.2 ± 21 bariatric embolization vs 126.4 ± 36 sham, $P < .03$, Wilcoxon rank sum test) (Fig 5). Animals treated with bariatric embolization showed a trend toward an increase in fibrosis in the gastric fundus ($6.58\% \pm 6.5$ sham vs $18.34\% \pm 13.2$ bariatric embolization, $P < .07$) primarily infiltrating the crypts (Fig 6).

DISCUSSION

Of all the hormones implicated in appetite regulation, ghrelin is not only the most potent but also is the only orexigenic (appetite-stimulating) hormone, which counteracts the effect of the remaining appetite-inhibiting hormones (4,17,18). Although ghrelin-producing cells are present throughout the gastrointestinal tract, the highest density is in the gastric fundus, with 10–20 times more ghrelin per gram of tissue than the duodenum, the next richest source, with cell density decreasing caudally (5,6,19,20). Bariatric embolization of the fundus with particles has previously been shown to result in significant depression of serum ghrelin levels with a corresponding impact on weight in both porcine and canine models (15,16). Given the complexity of ghrelin regulation, the actual etiology for serum depression of ghrelin was previously unknown. In this study, we showed that bariatric embolization causes a reduction of ghrelin-producing cells in the fundus, which is the likely mechanism for serum ghrelin depression.

Numerous mechanisms have been implicated in the regulation of circulating ghrelin levels, involving insulin, glucose, somatostatin, growth hormone, leptin, melatonin, and the parasympathetic nervous system (21,22). Given the homeostatic nature of the endocrine system, efforts to decrease circulating ghrelin levels may be counteracted by compensatory upregulation of ghrelin secretion from the ghrelin-producing tissues in the gastrointestinal tract. The duodenum is an important sites of ghrelin production with an anatomically discrete arterial supply from the gastric fundus and is a likely candidate for ghrelin upregulation. At 8 weeks after treatment, we found no evidence of upregulation of ghrelin-expressing cells in the duodenum. Although the limited duration of this study precludes analysis of long-term changes, the possibility of a long-term suppression of serum ghrelin levels is also potentially supported by studies performed after sleeve gastrectomy, in which a large portion of the gastric fundus and body is removed. In these patients, serum ghrelin levels are significantly lower in the immediate postoperative period and at 5 years compared with preoperative levels (23). It has been proposed that a long-term reduction in serum ghrelin levels by resection of ghrelin-producing cells is a contributory mechanism for weight loss in patients undergoing sleeve gastrectomy (24).

Although the gastric fundus was the target for embolization, there was no evidence of mucosal ulceration of the gastric fundus in any treatment animal; however, sequela of ischemia (ie, fibrosis) was present. Histologically, the infused particles were observed throughout the fundus, body, and antrum of the analyzed stomachs. This lack of fundal ulceration may be due to the rich collateral vascular supply to the fundus from multiple sources. However, healed or healing ulcers were identified in the gastric body in three treated animals, without evidence of perforation or necrosis. Ulceration of the gastric body has been previously described in a canine model of particle embolization of the stomach, occurring in 4 of 11 treated animals (25). Although embolization was performed until stasis was achieved, there may be some variability in the actual degree of embolization, given the extensive collateral network of the gastric arteries. Alternatively, perhaps the gastric body may be more sensitive to ischemia, possibly from being a “watershed” territory. Gastritis was observed in five of six control animals, suggesting that the stress of the procedure, new

environment, or general anesthesia induced inflammation or ischemia that may have further predisposed treated animals to ulcer formation.

Although mucosal ulceration is an unwanted effect, the finding that the ulcers encountered in this study had healed or were healing in the absence of antiulcer therapy is promising. In contrast, gastric and duodenal ulcers that result from nontarget delivery during radioembolization of hepatic malignancies are typically indolent and refractory to antiulcer treatments (26). Further modification of technique, such as particle size, embolization endpoint, and number and distribution of arteries receiving embolization may reduce the likelihood of developing such gastric ulceration patterns. Finally, considering the critical importance of proton pump inhibitors in the management of gastric and duodenal ulcers, which have ischemia as a component of their pathophysiology, acid reduction may serve a role for minimization of ulcer development with bariatric embolization (27,28).

The stomach has multiple endocrine functions, which also may be affected by bariatric embolization. For example, gastrin, a peptide hormone produced by the G cells in the antrum, stimulates secretion of gastric acid (hydrochloric acid) and augments gastric motility (29). Our results showed that bariatric embolization reduced the population of gastrin-secreting cells in the antrum, which, along with increasing fibrosis in the gastric fundus, may suggest alterations in gastric motility and absorption. Bariatric embolization may induce additional hormonal and functional changes that work synergistically to promote weight loss.

In our study, several important limitations are notable. First, animals did not have baseline analysis of the gastric mucosa. The presence of gastritis in all control animals suggests that some degree of mucosal inflammation or ulceration could have been present in these animals before our intervention. Second, hormonal regulation occurs on a dynamic and continuous basis. Because necropsy tissue was procured at a single time point, it is impossible to determine whether some degree of repopulation of ghrelin-expressing cells has already occurred in the gastric fundus at 8 weeks. Ghrelin-expressing cells may be upregulated in the duodenum or elsewhere in a more delayed fashion. Third, embolization of all arteries to the gastric fundus to stasis was performed to maximize ischemic insult to the gastric fundus, which may be responsible for the development of ulcers. In a different study, embolization solely of the left gastric artery was adequate to induce a depression in serum ghrelin levels but without producing ulcers (15). Although ghrelin is an important hormone that promotes hunger, numerous other hormones can affect hunger, and the impact of bariatric embolization on these hormones was not studied. Finally, owing to an improperly stored specimen and subsequent tissue autolysis, one of the control animals did not undergo pathologic analysis.

In conclusion, bariatric embolization resulted in significant decreases of ghrelin-expressing cells in the gastric fundus, without compensatory upregulation of ghrelin-expressing cells in the duodenum of treated animals at 8 weeks. Gastrin-producing cells were diminished in the antrum, and a trend toward fibrosis of the gastric fundus was shown. Bariatric embolization not only may affect hormonal production but also possibly may affect gastric motility and absorption. However, healing ulcerations in the gastric body of two of six animals

underscores the need for continued refinement of this procedure. With the concomitant use of gastroprotective agents, modification of embolization techniques, and improved understanding of the gastric vascular anatomy to minimize nontarget injury, clinical translation of this procedure should be feasible.

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Figure 1.

Selected images from the bariatric embolization procedure. **(a)** Initial celiac arteriogram shows the gastric fundus arterial supply, which include analogues of the main left gastric artery (long arrow), accessory left gastric artery (arrowhead), a gastric fundal branch arising from the splenic artery (short arrow), and a right gastric artery arising from the left hepatic artery (curved arrow). **(b)** Follow-up celiac arteriogram after superselective embolization was performed on all four fundal branches showing stasis of flow.

Figure 2.

Section of gastric fundus (hematoxylin-eosin, $\times 100$). **(a)** Control animal with preservation of the mucosa (*M*) and no evidence of ischemic damage. The submucosa (*SM*; bracket) and muscularis propria (*MP*) are normal. **(b)** Treatment animal showing well-preserved mucosa with ischemic damage as evidenced by dense confluent fibrosis involving the muscularis propria and submucosa (bracket) with fibrotic strands extending through the mucosa (arrowheads). Two microspheres (arrows) are present in the mucosa. (Available in color online at www.jvir.org.)

Figure 3. Immunohistochemical staining of the gastric fundus for ghrelin-expressing cells ($\times 100$). **(a)** Control animal shows multiple dark foci that represent ghrelin positivity. **(b)** Treatment animal shows decreased numbers of ghrelin-expressing cells. (Available in color online at www.jvir.org.)

Figure 4.

Immunohistochemical staining of the gastric fundi ($\times 100$) and duodena confirms a significant reduction in the ghrelin-immunoreactive cell density in the gastric fundus after embolization. There is no compensatory upregulation of ghrelin-expressing cells in the duodena of treated animals.

Figure 5.

Immunohistochemical staining of the gastric fundi for gastrin-immunoreactive cell density of the gastric antrum. **(a)** Control animal shows numerous punctate dark foci that represent stained gastrin. **(b)** Treated animal shows a substantial reduction in the gastrin-immunoreactive cell density. (Available in color online at www.jvir.org.)

Figure 6.

Trichrome-stained sections from the gastric fundus show a trend toward an increase in fibrosis in the gastric fundus ($6.58\% \pm 6.5$ sham vs $18.34\% \pm 13.2$ treatment, $P = .07$) primarily infiltrating the crypts.