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Original article

The association between sleeve gastrectomy and histopathologic changes consistent with esophagitis in a rodent model

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Abstract

Background: As the association between sleeve gastrectomy (SG) and gastroesophageal reflux disease remains unclear, the aim of this study was to evaluate whether performance of SG impacts the development and severity of esophagitis in a rodent model. Setting: University Hospital.

Methods: Wistar rats (Charles River Institute, Wilmington, MA) were fed a high fat diet (HFD) for 4 months and then were divided into 3 cohorts of nearly equal mean weight: HFD only (n = 25), sham operation + HFD (n = 29), and SG + HFD (n = 19). Animals were euthanized at 12 weeks. The esophagus was harvested en-bloc and processed for histologic assessment by a board certified pathologist, blinded to the animal treatment group. Reflux was graded by severity and defined as the presence of inflammation in the esophageal squamous mucosa.

Results: Rats who underwent SG had significantly increased reflux severity, compared with sham and HFD alone (21.1% versus 0% versus 4.5%, $P = .02$), respectively. No difference was demonstrated in negative, mild, or moderate esophagitis between the control, sham, and sleeve groups. Using nonparametric ANOVA, the mean severity score for severe esophagitis was significantly increased in the SG group versus sham or HFD group (1.5 versus .81 versus 1.36, $P = .0202$) respectively. Following multinomial logistic regression to assess for confounding variables to the severity scores, final weight, and change in weight, had no effect on severity of esophagitis between the 3 groups ($P > .373$).

Conclusions: SG is independently associated with histopathologic changes consistent with severe esophagitis in an animal model, likely secondary to gastroesophageal reflux. (Surg Obes Relat Dis 2015;■:00–00.) © 2015 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords: GERD; Esophagitis; Reflux; Sleeve gastrectomy

Obesity has reached epidemic proportions in the United States and around the world. Recent reports cite that up to 35% of adults in the United States are considered obese [1]. The association between obesity, gastroesophageal reflux disease (GERD), and its sequelae, such as erosive esophagitis, is well established [2]. Several studies have shown

that between 39%–61% of obese patients have concurrent gastroesophageal reflux disease [3–5].

Bariatric surgery has emerged as the only effective treatment for obesity and its complications [6]. In recent years, laparoscopic sleeve gastrectomy (LSG) is gaining popularity as a single-stage bariatric procedure and is positioned to surpass or has already surpassed Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding (AGB) as the most frequent procedure performed [7]. Although LSG has been reported to be effective in weight

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reduction as well as improving or resolving weight related co-morbid conditions, the available data regarding its effect on GERD is disparate. Whereas some studies demonstrate improvement in symptoms of reflux, others cite worsening of symptoms resulting in conversion to RYGB in the most extreme cases [8–9]. There was a lack of consensus regarding the effect of sleeve gastrectomy on GERD during the International Sleeve Gastrectomy Expert Panel Consensus Statement, with only 57% of experts considering GERD as a relative contraindication for LSG [10].

Currently, the majority of studies have examined symptomatology, endoscopic findings, and pH monitoring. To date, little is known about esophageal histologic findings in the face of GERD symptomatology following LSG. Delineating a clear association between LSG and GERD and its complications, such as esophagitis, is imperative, as it has important implications in terms of procedure selection and expected outcome. The purpose of our study was to determine and characterize the impact of sleeve gastrectomy on the development and severity of esophagitis through the use of an animal model.

Methods

A diet induced obesity rodent model was selected based on previous validated sleeve gastrectomy models [11]. Following an Institutional Animal Care and Use Committee (IUCUC) approval (Protocol 450722-7), healthy 10 week old Wistar Rats (Charles River Institute, Wilmington, MA) (initial weights of 187.81 ± 29.5 g) were fed ad libitum a high fat diet (HFD) consisting of 59% fat, 27% carbohydrate, and 14% protein (diet F3282, Bio-Serv, Frenchtown, NJ). At 4 months, animals had reached their target weight, which was double their initial weight. At this time, they were divided into 3 groups based on equal total weights among the groups by using MATLAB 8.0 and Statistics Toolbox 8.1 (The Mathworks, Inc., Natick, MA). The program was used to sort the rats into different groups according to their weights such that the mean of each group is nearly identical with similar coefficients of variation. The 3 groups were:

1. High fat diet (HFD) alone (n = 25): Animals were fed a HFD ad libitum without undergoing operative intervention. Animals were measured at the time of randomization and before sacrifice;
2. HFD and sham operation (HFD + S) (n = 29): Animals were fed a HFD and underwent a sham operation;
3. HFD and sleeve gastrectomy (HFD + SG) (n = 38): Animals were fed a HFD and underwent a sleeve gastrectomy.

All animals were fasted 8–16 hours before procedure (for operative technique see later). General anesthesia was induced with 4% vaporized isoflurane administered in an

oxygen mixture. Following induction, the abdomen was shaved and disinfected with 70% ethanol and betadine and weight-based antibiotic prophylaxis was administered. Anesthetized animals were placed in the supine position with anesthesia maintenance of 2.5% vaporized isoflurane provided via a nosecone. All operations were performed utilizing sterile technique.

Sham surgery

An upper midline laparotomy was performed, the stomach exposed, eviscerated, and replaced. Once this was completed, the peritoneum and aponeurotic muscle planes of the laparotomy incision were closed with a running 2-0 Polydioxanone (PDS) suture (Ethicon Endosurgery, Cincinnati, OH). Overlying skin was sutured with 4-0 Monocryl suture (Ethicon Endosurgery, Cincinnati, OH).

Sleeve gastrectomy

Sleeve gastrectomy was performed as previously established in rodent models [12]. Following an upper midline laparotomy, the splenic and hepatic connections to the stomach were released along the greater curvature. The greater omentum was ligated and divided to the level of the pylorus to adequately expose the stomach. Following mobilization of the stomach, a sleeve gastrectomy was performed with the goal of gastric volume reduction of 70%. The thoracoabdominal (TA) linear stapler (Proximate Reloadable® Stapler (product code TX 60 B) with 3.5 mm cartridge (Ethicon, Endosurgery, Cincinnati, OH) was used to construct the gastric tube. Stapling was started 3–4 mm from the pylorus. Following gastric resection, the staple line was reinforced with hand sewn, running 4-0 Vicryl suture (Ethicon Endosurgery, Cincinnati, OH). The midline laparotomy incision was closed in a similar fashion to the sham surgery using a running 2-0 Polydioxanone (PDS) suture (Ethicon Endosurgery, Cincinnati, Ohio) for the peritoneum and aponeurotic muscle planes and 4-0 Monocryl suture (Ethicon Endosurgery, Cincinnati, OH) for the skin.

Following surgery, animal weights and food intake were recorded on a weekly basis (Figs. 1 and 2). Animals were sacrificed 12 weeks following the surgery. This time period was based on reflux rodent models in which esophagojejunostomy leads to Barrett's esophagus within this time frame [12]. Necropsy was performed, assessing integrity, morphology, and volume of the gastric tube in animals, as well as the gross appearance of the esophagus. The esophagus was harvested en-bloc and preserved for histopathologic analysis. Following hematoxylin and eosin (H & E) staining, longitudinal cross-sections were performed to visualize the gastroesophageal (GE) junction. Analysis was performed, blinded to the animal treatment group. Reflux was characterized as esophagitis defined by the presence of inflammation of the squamous mucosa at the

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