Assessment of the correlation between gastric morphology, gastric emptying, post prandial GLP-1 response, and hunger scores following longitudinal sleeve gastrectomy

Summary: Longitudinal sleeve gastrectomy (LSG) is the most commonly performed bariatric operation. While the physiological mechanism by which LSG causes weight loss is unclear, early investigations indicate LSG causes augmention in the flow of nutrients through the stomach. Our preliminary investigations lead us to believe LSG accelerates gastric emptying, which augments the postprandial secretion of midgut hormones, such as glucagon like peptide-1 (GLP-1), and satiety. We hypothesize the extent to which LSG induces this physiologic effect can be predicted by the morphology of the stomach following resection.

We propose to directly test the impact of post surgical gastric morphology on gastric emptying, Glp-1 levels, and hunger/satiety, with the following specific aims:

1) Use dynamic MRI to measure stomach morphology
2) Use dynamic MRI to assess the kinetic rate of gastric emptying, the rate and amplitude of antral contraction, and presence of akinesis/hypokinesis of any segment of the gastric wall
3) Assess levels of Glp-1 in response to a mixed meal challenge
4) Assess hunger in response to a mixed meal challenge using a visual analog scale

We propose to study the above before and three months following LSG. Our hope is that the knowledge gained will allow for a) refinement of the technique of LSG to improve weight loss and/or decrease complications, b) development of novel and less invasive interventions that mimic the physiologic effect of LSG, and c) exploration of LSG as a treatment for gastroparesis.

Background: Longitudinal sleeve gastrectomy (LSG) is the most commonly performed bariatric procedure at this time. However, the physiological mechanism(s) by which LSG, and indeed all bariatric surgical procedures, induce weight loss have yet to be fully elucidated. In addition, the two most commonly accepted mechanisms for the physiologic effects of LSG are at direct odds with each other. LSG is thought to be a "restrictive" bariatric operation, whereby tubularization of the stomach may create a partial obstruction to the flow of nutrients.

However, most of the studies that examined gastric emptying after LSG (Burgerhart et al,[1] Bauman et al[2], Michalsky et al,[3] Bragettho et al,[4] and Melissas et al,[5],[6] Shah et al,[7] and Fallatah et al[8]) documented an increased rate of gastric emptying postoperatively. Only Bernstine et al[9] demonstrated no change in gastric emptying. The technique for LSG varies widely, with no accepted physiologic outcome for surgeons to target. The size of Bougie used to calibrate the gastrectomy ranges from 32F to 48F, with some surgeons imbricating the staple line, further narrowing the stomach tube. The point on the antrum at which resection of the greater curvature of the stomach begins varies from 2 cm to 7 cm proximal to the pylorus; Fallatah et al[8] showed more aggressive resection of the antrum led to a decreased rate of gastric emptying, with the majority of these patients complaining of significant nausea refractory to metoclopramide and domperidone. The lack of standardization was underscored by Toro et al, who studied upper gastrointestinal series after LSG and identified four distinct morphologies of the stomach tube in the same group of surgeons (tubularized vs antral pouch vs fundic pouch vs dumbbell); furthermore, these morphologies were associated with differing physiologic outcomes, as they led to different hunger scores and reflux scores.[10]

Augmentation of nutrient flow through the upper gastrointestinal tract can lead to satiety and impact caloric intake through the ileal brake.[11] According to the ileal brake hypothesis, hormones secreted by the ileum in response to a meal feed back on central nervous system targets to induce satiety, and on the proximal gastrointestinal tract to slow motility. Hormones identified to be involved in this mechanism include GLP-1[12],[13] and peptide YY.[14],[15] GLP-1 has been shown to reduce of caloric intake in humans.[16]

Bariatric procedures that retard the flow of nutrients have been utilized; this was the aim of procedures such as vertical banded gastroplasty (VBG) and adjustable silicon gastric banding (ASGB). These procedures that restrict the flow of nutrients do not lead to augmentation of ileal brake hormones.[17] In addition, the partial obstruction associated with these procedures leads to dysfunction of the proximal gastrointestinal tract, manifesting as gastroesophageal reflux (GERD) disease[18] and as pseudoachalasia.[19],[20] LSG performed over narrower bougie is associated with increased incidence of adverse outcomes, such as staple line leaks and postoperative nausea and emesis (Hawasli et al[21], Parikh et al[22]).

Our prior explorations into this field include the presentation of cases to elucidate the beneficial impact of LSG on gastric emptying in individuals with gastroparesis; we also documented the worsening of nausea and regurgitation when LSG was performed after truncal vagotomy and pyloroplasty (in whom the antral pump was presumptively inactive).[23] For these studies, we utilized nuclear scintigraphy to measure gastric emptying. We plan to utilize dynamic MRI in this study. Dynamic MRI can provide kinetic measures of the emptying of solids and liquds. It is superior to nuclear scintigraphy in that it also can provide sensitive information gastric morphology, as well as the amplitude and rate of peristaltic waves. Dynamic MRI was utilized to assess gastric emptying following LSG by Bauman et al.2 This showed lack of any peristaltic acitivity in the "sleeved" portion of the stomach, but increased propulsion in the antrum, leading to overall decrease in the t ½ for emptying. However, the investigators used only a liquid meal. We hope to carry out a pilot study utilizing liquid and solid meal, with correlation of the rate of gastric emptying with post-prandial GLP-1 levels and visual analog scales of hunger. If we are able to correlate gastric emptying with post prandial GLP-1 level and hunger scores, we can then study the impact of subtle morphological differences in post surgical anatomy.

Experimental Design

Dynamic MRI assessment of gastric emptying: We plan to assess gastric emptying of a solid meal preoperatively and 3 months postoperatively utilizing dynamic MRI. MRI studies will be performed on either a wide-bore (75cm wide) 1.5T Siemens or small bore (60cm) 3T Phillips magnet. Patients who would not fit in the 3T narrower bore will be scanned on the 1.5T (open) magnet. For the purpose of these studies, magnetic field strength will not affect the measured variables and sequences will be identical on both sequences regarding spatial and temporal resolution, field of view and volumes of interest.

All studies include gastric volumetric sequences, with volume-time curves used to measure gastric emptying. Temporal resolution of these images will be chosen between 12-20 per hour (one acquisitions each 5 to 3 minute, respectively, to be determined prior to the study).

The volumetric sequences will be acquired using 3D gradient recalled echo (GRE) T1-weighted images (T1WI) with fat saturation with acceleration using parallel imaging (for example VIBE/THRIVE), with the entire volume acquired in less than 15-20 seconds, depending on patient's breath-holding capacity. Liquid or semi-solid food will be mixed with small amounts of Gadolinium-Based Contrast Agents (GBCAs), with an approximate 1/100 volumetric dilution (1/10th - 1/15th weight-based IV dose, off label use). This will distinguish the administered meal from succus entericus (bright vs dark on T1WI). The coronal view is chosen in order to account for variable gastric shapes, as well as coverage of small bowel for assessment of small bowel transit time, measured as the distance traveled by the meal by the end of the examination time, bowel as a potential metric. This sequence will have isometric voxels, allowing for reformat in any desired plane.

Interleaved between the volumetric acquisition will be the morphologic sequences for assessment of peristalsis. These will be acquired using balanced steady-state free precession (bSSFP, TRUE-FISP or balanced FFE). The plane of acquisition will be prescribed by the radiologist parallel (long axis) and perpendicular (short axis) to the lumen. Multiple images of the same location at different time points will be acquired (either with breath-hold or free-breathing), allowing assessment of peristalsis in both short and long axis (similar to cardiac MRI images. This will allow for measurement of peristalsis frequency and direction as well as any mural akinesia / dyskinesia. The volumetric-morphologic bundle will be repeated until the stomach is completely emptied or or exam time limit (30 - 45 minutes for liquid and semi-solid foods, respectively) is reached. No IV contrast will be administered.

GLP-1 response and Assessment of hunger in response to mixed meal challenge: At the same timepoints (preoperatively and 3 months postoperatively), we will conduct a mixed meal challenge test in the fasting state. Subjects will be asked to fast after midnight. We will then perform an MMT utilizing a fixed volume of nutritional supplement. We will measure levels of GLP-1 in response to this MMT; we will obtain serum levels of GLP-1 every 30 minutes (t = 0, 30, 60, 90, and 120 min).

We will also assess visual analog scales of hunger every 30 minutes. To do so, we will use an accepted standard for VAS measurement; that is, we will use anchors of words on either side of a line (e.g. "I am not hungry at all----------I have never been more hungry").[24] We will then measure the distance from the left of the line to the mark.

Statistical analysis
Continuous variables that are not normally distributed will be log-transformed in analyses. Linear regression models will used for analysis of correlation between gastric emptying and measures of GLP-1 response to MMT (maximal level, area under the curve, Maximum/Minimum ratio). Similar calculations will be used between gastric emptying and VAS assessment of hunger at each time point. Measures of GLP-1 and VAS assessments of hunger will be the dependent variables, and each will be analyzed separately. Multivariable models will be built by including other demographic factors such as body weight parameters (weight or BMI or excess body weight, individually), age and gender with entry and retention in the model set at a significant level of 0.2 and 0.05, respectively. For longitudinal data analysis, data from the two time-points will be fitted into a linear mixed model[25], with a random intercept for each subject, to examine the relationship between gastric emptying indices and GLP-1 levels and VAS scores of hunger for each time point and corresponding changes over time simultaneously. For goodness of fit, the lowest values of Akaike's information criterion (AIC) and -2 Res Log Likelihood will be employed in the model selection while accounting for within subject correlations and adjusting for potential confounders.[26,27] All analyses will be performed using SAS Software, Version 9.1.3 (SAS Institute, Cary, NC).

Schema for study:

Pre operative		
Dynamic MRI (90 minutes)	$825 x 4	$3300
Mixed meal tolerance (90 min) test to assess:		
GLP-1 response		
VAS measure of hunger		
3 months postoperative		
Dynamic MRI (90 min)	$825 x 4	$3300
Mixed meal tolerance (90 min) test to assess:		
GLP-1 response		
VAS measure of hunger		
GLP-1 ELISA plates (3)	$487 x 4	$1948
DPP4 inhibitor (1)	$92	$92
Subject reimbursement	$25 x 4 x 2	$200
Research nurse	$75/hr x 12 hrs	$900
Total		$9,740

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