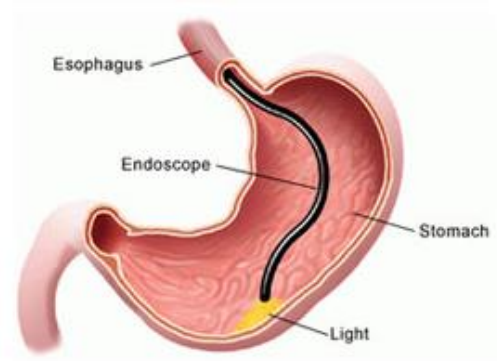
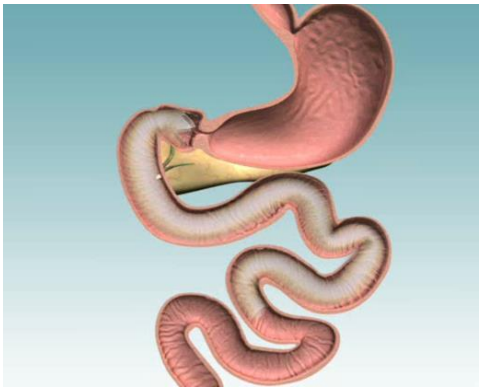
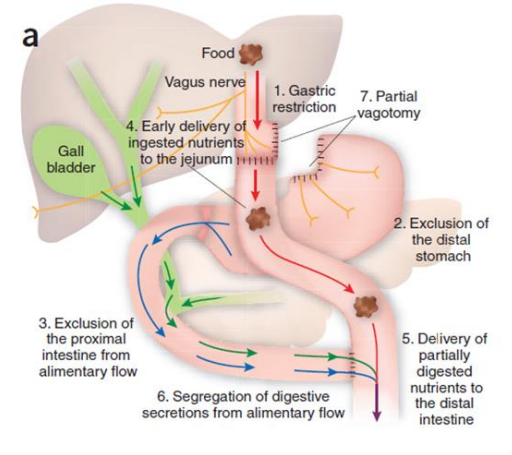
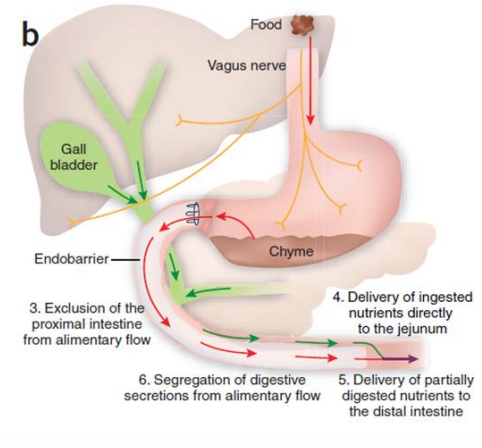
Endoluminal therapies for weight loss and the treatment of obesity-related metabolic diseases









Internal Medicine Grand Rounds – January 10, 2014

Vincent Aguirre, M.D., Ph.D.
UT Southwestern Medical Center
Assistant Professor, Department of Medicine
Division of Digestive and Liver Disease
Center for Hypothalamic Research

This is to acknowledge that Dr. Aguirre has disclosed that he does not have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Aguirre will not be discussing off-label uses in her presentation.

Biography:
Vincent Aguirre, M.D., Ph.D., is a graduate of the Harvard-MIT Medical Scientist Training program. After internship and residency at the Brigham and Women's Hospital, he completed sub-specialty training in Gastroenterology at the Massachusetts General Hospital. His laboratory investigates the regulation of body weight and metabolism by the gastrointestinal tract using Roux-en-Y gastric bypass (RYGB) as a model system. An additional focus of the lab is to implement an understanding of the mechanisms of gastric bypass for the development and evaluation of pre-clinical and clinical indwelling gastrointestinal devices for the therapy of obesity and related metabolic diseases.

The purpose of this presentation:
(1) To highlight the magnitude of the problem of obesity as well as obesity-related co-morbid conditions;
(2) to discuss the clinical efficacy of bariatric surgery and how an understanding of its anatomic and physiological mechanisms will facilitate the development of less-invasive, endoscopic devices for obesity and obesity-related conditions that can be applied more broadly than surgery; and,
(3) to present early pre-clinical and clinical data involving the implementation of the Endobarrier, an indwelling, endoscopically-placed device currently undergoing phase 2 evaluation for efficacy versus standard-of-care diabetes management.

Educational Objectives:
1. Understand the scope of the problem of overweight and obesity and how body weight is related to the risk of developing obesity-related co-morbid conditions.
2. Understand the clinical use and efficacy of bariatric surgery for obesity and obesity-related conditions.
3. Understand how knowledge of the physiological mechanisms of RYGB will facilitate the development of less-invasive, endoscopic therapeutic options for obesity and obesity-related conditions.
4. Understand the current state of bariatric endoscopy, both procedures that are used as primary therapy for weight loss as well as those procedures performed in patients who have previously undergone bariatric surgery. This latter group includes revisional techniques that have shown efficacy for weight loss in RYGB patients with weight regain and gastro-jejunostomy stomal dilation.

Protocol:

1. Obesity and the risk of developing related co-morbidity

A staggering 36% of U.S. adults, approximately 72 million people, are obese (i.e., have a BMI > 30). Obesity is associated with myriad conditions that confer significant morbidity and

reduce mortality. These include type 2 diabetes, large and small vessel cardiovascular disease, hypertension, osteoarthritis, sleep apnea, and a host of others. While the prevalence of obesity in the U.S. adult population has plateaued recently (1), 18% of adolescents (age 12-19) are also obese, defined as being over the 85th percentile on the 2000 CDC pediatric growth charts (2). Thus, obesity will remain a large-scale public health problem for years to come.

2. Bariatric surgery is the most efficacious and durable therapy for weight loss and resolution of obesity-related co-morbidity

Even modest weight loss (<5-10%) improves obesity-related co-morbid conditions, improves quality-of-life and sense of well-being, and reduces mortality. However, non-surgical therapeutic options for weight loss (i.e., lifestyle, behavioral, and pharmacologic) are rarely substantial and seldom durable, even in the research setting (3). On the other hand, bariatric surgery has emerged as the most efficacious therapy for sustained weight loss. There are several bariatric procedures that vary in their degree and manner of gastric restriction and intestinal bypass (Figure 1). Numerous observational studies report sustained excess weight loss (EWL) of 40-70%, improved obesity-related co-morbidity in excess of 70-80% of surgical patients (Table at top of next page), reduced cancer incidence and reduced mortality observed after these procedures (4). Importantly, these effects of bariatric surgery on body weight and glycemic control have been substantiated in recent RCTs (4-6).

3. The need for less-invasive therapeutic options for weight loss and obesity-related disease

The complication and mortality rates of bariatric surgery have improved with their wide-spread clinical application over the past 20 years, rivaling even that observed for elective laparoscopic cholecystectomy (4). However, candidacy for surgery has strict BMI requirements. These include class 2 obesity (BMI 35-40) in the setting of severe obesity-related co-morbidity

Figure 1. Various bariatric procedures

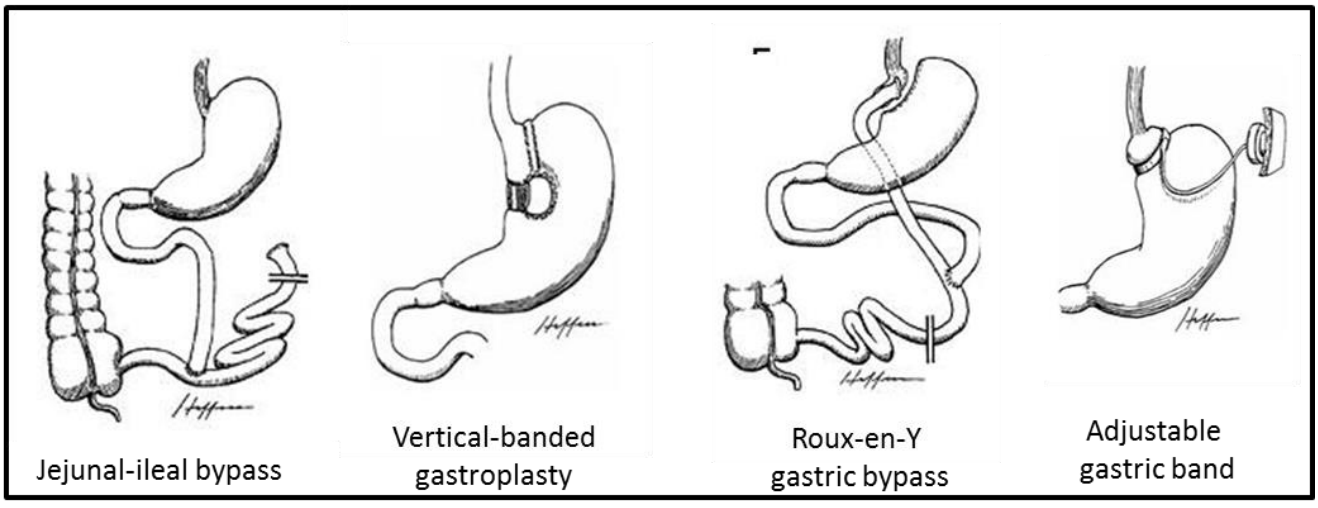


Table 8 Overview of Weight Loss, Surgical Procedure, and Diabetes Resolution

	Total	Gastric Banding	Gastroplasty	Gastric Bypass
% EBWL	55.9	46.2	55.5	59.7
% Resolved overall	78.1	56.7	79.7	80.3
% Resolved <2 y	80.3	55.0	81.4	81.6
% Resolved ≥2 y	74.6	58.3	77.5	70.9

%EBWL – percent excess body weight loss; BPD/DS – biliopancreatic diversion/duodenal switch.

or class 3 obesity (BMI > 40) (7). Under these guidelines, bariatric surgery is being performed for approximately 113,000 patients per year (2006 data) at a cost of ~$1.5 billion (8). However, surgical therapy for obesity is underutilized and less than 0.1% of those eligible ever undergoes a weight loss procedure and realizes their substantial benefits.

In addition, the risk of developing obesity-related co-morbid conditions increases with BMI from a value as low as 21 reported in some studies. As more than 72% of the U.S. adult population has a BMI >25, a majority of the population is at risk of developing obesity-related co-morbidity with limited therapeutic options. Therefore, less-invasive therapies for weight loss and related diseases are vitally needed. The improved safety profile of such therapies will allow more broad clinical application for those at risk. Such options include behavioral, pharmacologic, less-invasive surgeries, as well as the potential for endoluminal/endoscopic therapies, which are the topic of this presentation.

4. Bariatric endoscopy

a. Endoscopy in patients after bariatric surgery

Bariatric endoscopy includes procedures performed after bariatric surgery for diagnostic and therapeutic purposes in patients presenting with complaints such as with abdominal pain, GI bleeding, biliary colic, iron-deficiency anemia, dysphagia, nausea/vomiting, and band-slippage. There is also an emerging body of literature investigating the use of endoscopic suturing devices for stomal revision (9). For example, a recent report demonstrates modest weight loss induced by reduction of gastro-jejunal stomal size in patients presenting with a dilated post-surgical stoma and weight regain (10)(Figure 2). There are a number of devices with patents pending and/or in various stages of development that are exclusively investigational, the majority of which have yet to be presented publically or published.

b. Primary bariatric endoscopy

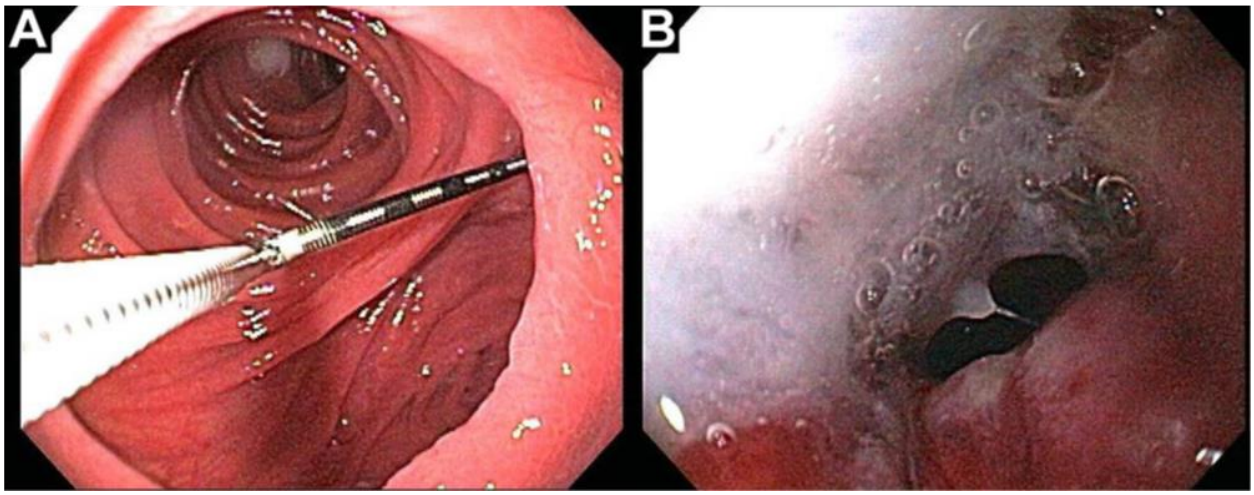
Endoscopic devices intended for primary therapy of weight loss are also an area of intensive research and development (See Figure 3 below). The gastrointestinal tract has been targeted from the oral cavity to the small intestine. For example, oral retainers, including the DDS Retainer, have been designed to restrict the ability to consume food. The esophagus/gastro-esophageal junction has been targeted with devices intended to restrict inlet, thereby limiting intake and, possibly, enhancing satiety. An example is the Full Sense Bariatric Device.

The stomach has been the most frequently targeted area of the gut for weight loss purposes. The best known of the gastric devices include various iterations of space-filling balloons. By filling up the gastric space with inert, immovable, and space-filling material, the intended outcome was early space-filling and exhausted gastric accommodation/enhanced satiety at a smaller volume of ingested food resulting in an overall reduction of intake. While the earliest balloons, such as the Garren-Edwards balloon, demonstrated limited, if any, success and moderate to severe adverse effects (9, 11), more recent iterations, such as the ReShape Duo (depicted in Figure 3), are demonstrating early promise in patients and portend possible future success (9).

Other gastric devices have been developed to deliver various bio-polymers into the stomach, which expand and intend to mimic the same mechanism and effect of the intra-gastric balloons. Intensive investigation has also focused on the use of gastric pacing to enhance satiety and reduce intake (9, 12). However, meta-analyses of gastric pacing studies report limited utility of this approach for weight loss as well (13). Finally, aspiration therapy (percutaneous gastrostomy) using the Aspire Assist Siphon Assembly (Aspire Bariatrics, King of Prussia, PA) has recently been reported to have improved efficacy versus lifestyle therapy for EWL (49% versus 15%, device versus lifestyle) (14).

Various devices have been developed for gastric plication or apposition of opposing mucosal surfaces via the placement of adjacent sutures (See TOGA depicted in Figure 3). Sutures introduced using these devices can be introduced trans-mural/serosal or not (i.e., mucosal or sub-mucosal). In observational studies with small subject number, these devices have demonstrated modest efficacy (9). However, these studies have been confounded by frequent, early staple-line break-down and failure of intended plication. Work in this area is on-

Figure 2. (A) Pre-reduction and (B) post-reduction endoluminal images of gasto-jejunostomy.



going.

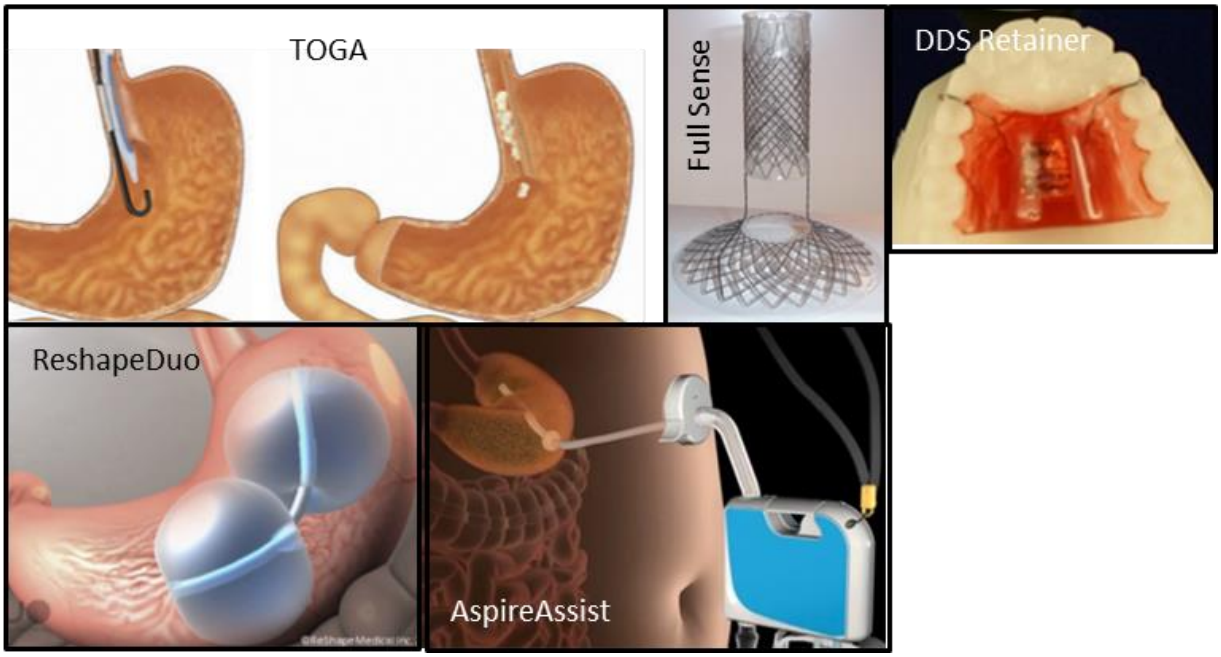
The small intestine has not been the focus of much development as related to the placement of indwelling devices, surprisingly. A search for U.S. patents does, however, reveal that intestinal devices may be entering into the investigational (clinical and pre-clinical) stage in the near future.

5. Bariatric Surgery as a model system to investigate mechanisms by which the gut causes weight loss

a. Inadequacy of current bariatric endoscopy approaches

Despite intensive investigation into the design and development of indwelling endoscopic devices for weight loss, the majority of these devices is either in the infancy of its development or has been largely unsuccessful (such as the oral retainer DDS, Full Sense esophageal inlet restrictor, intra-gastric balloons, early gastric placating devices). I propose that the reason for this is a lack of understanding of the mechanisms by which the gut regulates body weight and improves obesity-related metabolic diseases. For example, if restriction of gastric size and accommodation play no role in the effect of bariatric surgery to induce weight loss, endoscopic devices aimed at inducing gastric restriction are unlikely to succeed for their intended purpose (discussed below). Bariatric surgery therefore provides a unique translational research opportunity to investigate the physiologic mechanisms by which the gut (after bariatric surgery) induces sustained weight loss and improves obesity-related co-morbid conditions, particularly type 2 diabetes.

Figure 3. Primary bariatric endoscopy



b. Patients after RYGB fail to manifest a compensatory anabolic response to resist weight loss and promote weight regain

Even modest weight loss induces a compensatory response characterized by changes in feeding behavior, decreased energy expenditure, decreased thyroid function, and decreased sympathetic tone. These responses function coordinately to resist further weight loss and promote weight re-gain (15). These responses are the reason for the high recidivism observed after diet-induced weight loss. The cause of this compensatory response is a fall in plasma leptin that occurs with weight loss and reduced adipose tissue. In support of this hypothesis, leptin replacement to pre-weight loss levels reverses these biological responses (16, 17). Despite experiencing substantial weight loss, patients after bariatric surgery, particularly those undergoing procedures involving intestinal bypass, fail to mount such a compensatory response. This occurs despite a substantial reduction in plasma leptin that occurs after bariatric surgery, most notably, Roux-en-Y gastric bypass (RYGB). Why patients after RYGB fail to exhibit this compensatory response despite weight reduction and a fall in plasma leptin is unknown but the focus of intensive investigation.

Despite substantial weight loss after RYGB, which is far greater in magnitude than that required to induce the compensatory response discussed above, feeding behavior is reduced (hunger is reduced and satiety is enhanced), rather than increased, and food preference switches from high fat to low fat items. As anyone who has ever been on a diet knows, diet-induced weight loss has the opposite effect on hunger and food choice. In addition, functional MRI in patients after RYGB demonstrates a reduced effect of high calorie food items to activate rewards areas of the cerebral cortex (18-22). This lack of a compensatory response to RYGB-induced weight loss is likely the reason for the durability of weight reduction observed after RYGB as well as its profound clinical efficacy as a therapy for obesity and related metabolic disease.

c. Animal model of RYGB to investigate mechanism

The goal of our laboratory effort is to understand the physiologic mechanisms of bariatric surgery using RYGB as our research model. We have developed a mouse model of RYGB that recapitulates all of the effects of the human procedure (23, 24). Using this model, we have determined a neurologic basis by which RYGB reduces body weight (sympathetically-mediated increase in energy expenditure) and improves glucose homeostasis (parasympathetic effect on hepatic insulin sensitivity). Mice after RYGB also exhibit sustained weight loss despite reduced plasma leptin. This is because the gut-derived efferent mechanisms induced by RYGB engage hypothalamic neuro-circuitry directly involved in body weight regulation and energy homeostasis, the melanocortin-4 receptor pathway (24). In support of this hypothesis, melanocortin-4 receptor null mice fail to respond to the effects of RYGB on body weight and glucose homeostasis (24).

d. 7-component model of RYGB

A significant focus of the lab is to determine which anatomic rearrangement(s) occurring during RYGB induce these physiologic mechanisms. This information will, in turn, focus efforts to a particular gut manipulation that, if induced endoscopically, can manifest a comparable clinical effect.

To this end, we conceptually think of RYGB as being comprised of 7 independent surgical manipulations or "components":

1. Gastric restriction
2. Exclusion of the distal stomach
3. Exclusion of the proximal intestine from alimentary flow
4. Early delivery of ingested nutrients to the jejunum
5. Delivery of partially digested nutrients to the distal intestine
6. Segregation of digestive secretions from alimentary flow
7. Partial vagotomy

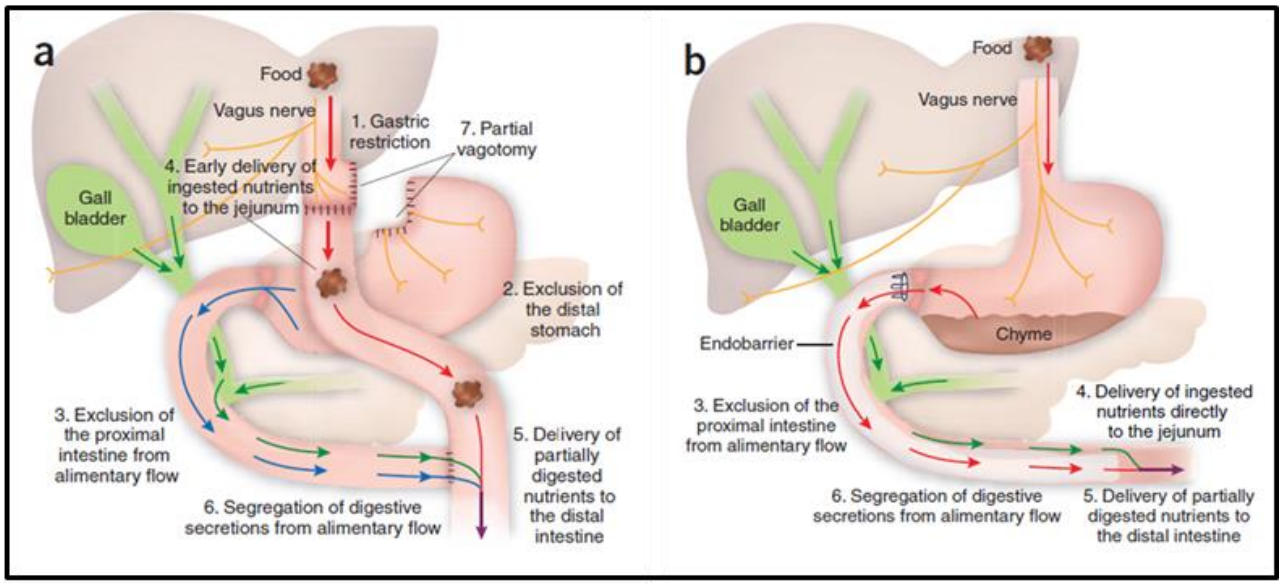
Presumably, one of these components, or subset of components, is responsible for distinct effects of RYGB (Figure 3). It would be impossible to mimic all of the surgical manipulations occurring during RYGB (Figure 3a) with a single endoscopic device. Therefore, knowing which component or components is/are responsible for distinct effects of RYGB will facilitate the development of endoscopic therapies with similar efficacy to RYGB as it would be more feasible to endoscopically mimic one component (or a subset of components) rather than the entire procedure.

6. The Endobarrier

Manufactured by GI Dynamics, Inc. (Lexington, MA) The Endobarrier is a 60 cm distensible, impermeable fluoropolymer with a nitinol proximal, barbed anchor. This device can be placed endoscopically in the duodenal bulb, and has been done so in more than 800 patients worldwide. When in situ in the duodenum, chime exiting the stomach through the pylorus enters the duodenum and is prevented from interacting with both the mucosa of the proximal intestine as well as the pancreatico—biliary digestive secretions. As such, it mimics components 3 (exclusion of the proximal intestine from alimentary flow), 4 (early delivery of ingested nutrients to the jejunum), 5 (delivery of partially digested nutrients to the distal intestine), and 6 (segregation of digestive secretions from alimentary flow).

The Endobarrier has been evaluated in rats, pigs, and humans (25-28). In observational studies (single arm, prospective studies lacking controls; up to 400 subjects in 13 studies), the Endobarrier has demonstrated 17 to 42% excess weight loss and reduced HbA1c of ~2% (from 7.7-8.7% to 6.5-5.5%)(29, 30). The Endobarrier has been evaluated in three randomized, sham-controlled trials including 137 patients (95 device patients, the remainder shams). Follow-up

Figure 4. 7-component model of RYGB



time in these studies was 12 weeks (as well as 24 and 52 week data in one study) in patients with an average BMI of 39-49. Seventeen to 52% of patients in the intervention groups were lost to follow-up. In these RCTs, EWL in the intervention groups was 12-22% (17% at 52 weeks in one study) versus 3-7% in placebo (sham) groups. The effect on HbA1c was presented in one study with 41 patients as -1.1% versus -0.4% in the intervention and placebo arms, respectively. The quality of this evidence has been deemed to be Low in two recent meta-analyses (27, 28, 31-33).

On the basis of this data, the Endobarrier has been approved for 12 month implantation and is presently available commercially in Chile, the Netherlands, the U.K., Germany, Austria, Australia, and Israel. In the U.S., it has been approved for a phase 2, randomized, sham-controlled, single-blind study named the Endo Trial whose goal is to determine (1) if the Endobarrier *significantly improves* glycemic control and (2) if it *can safely be used* for glycemic control. It is a prospective, single-blind, randomized, sham-controlled trial with 500 planned subjects, and randomized 2:1 versus sham, to be performed at 25 sites with one year of treatment. Sham patients will be offered cross-over to device at 52 weeks, if patients meet inclusion criteria.

We are one of the first sites to receive internal IRB approval for the Endo Trial and to begin recruiting patients. We have randomized 9 patients to the Endo Trial as of this time. This trial will determine, in a more rigorous fashion, if the Endobarrier is efficacious for diabetes therapy versus standard of care. Where this device may realize clinical application is currently unclear. This is because it has yet to demonstrate superiority to standard of care for severe obesity (bariatric surgery), diabetes management (goal of Endo Trial), pre-operative weight loss (diet), or other less efficacious primary therapies for weight reduction (lifestyle, diet, exercise, behavioral, or pharmacologic). Until these studies are performed, a clinical niche will remain undefined.

References

1. Flegal, K.M., Carroll, M.D., Ogden, C.L., and Curtin, L.R. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA.* 2010; 303:235-241.
2. Ogden, C.L., Carroll, M.D., Kit, B.K., and Flegal, K.M. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA.* 2012; 307:483-490.
3. Eckel, R.H. Clinical practice. Nonsurgical management of obesity in adults. *N Engl J Med.* 2008; 358:1941-1950.
4. Buchwald, H., et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med.* 2009; 122:248-256.
5. Schauer, P.R., et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med.* 2012; 366:1567-1576.
6. Mingrone, G., et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med.* 2012; 366:1577-1585.
7. Mechanick, J.I., et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Surg Obes Relat Dis.* 2013; 9:159-191.
8. Livingston, E.H. The incidence of bariatric surgery has plateaued in the U.S. *Am J Surg.* 2010; 200:378-385.
9. Sullivan, S. Endoscopy in the management of obesity. *Gastrointest Endosc Clin N Am.* 2013; 23:165-175.
10. Thompson, C.C., et al. Endoscopic suturing for transoral outlet reduction increases weight loss after Roux-en-Y gastric bypass surgery. *Gastroenterology.* 2013; 145:129-137 e123.
11. Imaz, I., Martinez-Cervell, C., Garcia-Alvarez, E.E., Sendra-Gutierrez, J.M., and Gonzalez-Enriquez, J. Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis. *Obes Surg.* 2008; 18:841-846.
12. Kumar, N., and Thompson, C.C. Endoscopic solutions for weight loss. *Curr Opin Gastroenterol.* 2011; 27:407-411.
13. Mizrahi, M., Ben Ya'acov, A., and Ilan, Y. Gastric stimulation for weight loss. *World J Gastroenterol.* 2012; 18:2309-2319.
14. Sullivan, S., Stein, R., Jonnalagadda, S., Mullady, D., and Edmundowicz, S. Aspiration therapy leads to weight loss in obese subjects: a pilot study. *Gastroenterology.* 2013; 145:1245-1252 e1245.
15. Leibel, R.L. Molecular physiology of weight regulation in mice and humans. *Int J Obes (Lond).* 2008; 32 Suppl 7:S98-108.
16. Rosenbaum, M., et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest.* 2005; 115:3579-3586.
17. Rosenbaum, M., Murphy, E.M., Heymsfield, S.B., Matthews, D.E., and Leibel, R.L. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab.* 2002; 87:2391-2394.

18. Ochner, C.N., et al. Selective reduction in neural responses to high calorie foods following gastric bypass surgery. *Ann Surg.* 2011; 253:502-507.
19. Ochner, C.N., Laferrere, B., Afifi, L., Atalayer, D., Geliebter, A., and Teixeira, J. Neural responsivity to food cues in fasted and fed states pre and post gastric bypass surgery. *Neurosci Res.* 2012; 74:138-143.
20. Mathes, C.M., and Spector, A.C. Food selection and taste changes in humans after Roux-en-Y gastric bypass surgery: a direct-measures approach. *Physiol Behav.* 2012; 107:476-483.
21. Miras, A.D., et al. Gastric bypass surgery for obesity decreases the reward value of a sweet-fat stimulus as assessed in a progressive ratio task. *Am J Clin Nutr.* 2012; 96:467-473.
22. Seyfried, F., Miras, A.D., Bueter, M., Prechtl, C.G., Spector, A.C., and le Roux, C.W. Effects of preoperative exposure to a high-fat versus a low-fat diet on ingestive behavior after gastric bypass surgery in rats. *Surg Endosc.* 2013; 10.1007/s00464-013-3020-6.
23. Gautron, L., Zechner, J.F., and Aguirre, V. Vagal innervation patterns following Roux-en-Y gastric bypass in the mouse. *Int J Obes (Lond).* 2013; 10.1038/ijo.2013.48.
24. Zechner, J.F., et al. Weight-independent effects of roux-en-Y gastric bypass on glucose homeostasis via melanocortin-4 receptors in mice and humans. *Gastroenterology.* 2013; 144:580-590.
25. Aguirre, V., Stylopoulos, N., Grinbaum, R., and Kaplan, L.M. An endoluminal sleeve induces substantial weight loss and normalizes glucose homeostasis in rats with diet-induced obesity. *Obesity (Silver Spring).* 2008; 16:2585-2592.
26. Tarnoff, M., Shikora, S., Lembo, A., and Gersin, K. Chronic in-vivo experience with an endoscopically delivered and retrieved duodenal-jejunal bypass sleeve in a porcine model. *Surg Endosc.* 2008; 22:1023-1028.
27. Patel, S.R., Hakim, D., Mason, J., and Hakim, N. The duodenal-jejunal bypass sleeve (EndoBarrier Gastrointestinal Liner) for weight loss and treatment of type 2 diabetes. *Surg Obes Relat Dis.* 2013; 9:482-484.
28. Zechmeister-Koss, I., Huic, M., Fischer, S., and for the European Network for Health Technology, A. The Duodenal-Jejunal Bypass Liner for the Treatment of Type 2 Diabetes Mellitus and/or Obesity: a Systematic Review. *Obes Surg.* 2013; 10.1007/s11695-013-1137-2.
29. Escalona, A., et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. *Ann Surg.* 2012; 255:1080-1085.
30. de Moura, E.G., et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. *Diabetes Technol Ther.* 2012; 14:183-189.
31. Gersin, K.S., et al. Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. *Gastrointest Endosc.* 2010; 71:976-982.
32. Tarnoff, M., et al. Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. *Surg Endosc.* 2009; 23:650-656.

33. Rodriguez, L., et al. Pilot clinical study of an endoscopic, removable duodenal-jejunal bypass liner for the treatment of type 2 diabetes. *Diabetes Technol Ther.* 2009; 11:725-732.