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EDITORIAL

## Will Gastroenterologists Be Successful as Metabolic Physicians?

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### ABSTRACT

As the result of incomplete treatments, obesity continues to be a worldwide origin for multiple medical problems, including metabolic disorders. With the worldwide rise in obesity, the prevalence of type 2 diabetes mellitus has increased in both men and women. Effective treatments for obesity can improve the treatment of

metabolic disorders. The adjustable gastric band and the vertical sleeve gastrectomy are less complex gastric surgeries utilized by bariatric surgeons for the treatment of metabolic disorders. Studies have supported the utility of both of these gastric surgeries for the treatment of subgroups of individuals with diabetes mellitus. The field of gastroenterology has mainly been examining four major endoscopic procedures for the treatment of obesity: intragastric balloons, intragastric aspiration systems, intraluminal gastric suturing, and intraluminal barriers deployed within the upper small intestine. Ongoing studies are examining the ability of these endoscopic procedures to treat metabolic disorders, which includes reduction in the blood levels of hemoglobin A1C in individuals with diabetes mellitus. Ongoing issues are discussed that should be addressed prior to the wide spread utilization of endoscopic procedures for the treatment of this metabolic disorder.

**Key words:** Obesity; Type 2 Diabetes Mellitus; Adjustable Gastric Band; Sleeve Gastrectomy; Intragastric Balloon; Endoscopic Gastroplasty; Aspiration; Intraluminal Barrier

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### EDITORIAL

Obesity continues to be a worldwide origin for multiple medical problems, including metabolic disorders. A study of 195 countries found that since 1980, the prevalence of obesity doubled in more than 70 countries<sup>[1]</sup>. This finding supports the belief that interventions designed to reduce the prevalence of obesity have not been effective.

The development of major metabolic disorders, including type 2 diabetes mellitus, are related to the clinical presence of obesity<sup>[2]</sup>. As the result of the worldwide rise in obesity, Figure 1 summarizes the world wide rise in the prevalence of type 2 diabetes mellitus from 1980 to 2014<sup>[3]</sup>. By 2014, the rise in the prevalence of diabetes mellitus in men had outpaced the rise in women. Unfortunately, low-income and middle-income countries had faster increases in the number of individuals with diabetes mellitus. Newer interventions

to control obesity must be proposed, studied, and introduced into clinical practice in order to slow the growth of this major, potentially disabling metabolic disorder.

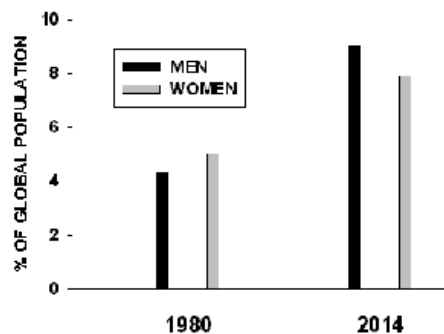
The last decade has seen a dramatic shift in the worldwide landscape of surgical and endoscopic operations for medically complicated obesity. The total number of bariatric procedures has continued to rise. A worldwide survey from 2016 revealed that 634,897 primary bariatric surgical procedures as well as 25,359 endoluminal procedures were performed<sup>[4]</sup>. Among the bariatric surgical procedures, a higher percentage of individuals are now undergoing vertical sleeve gastrectomy (VSG) and a lower percentage of individuals undergoing adjustable gastric banding (AGB).

Individuals with diabetes mellitus considered in diabetes guidelines<sup>[5]</sup> as candidates for bariatric surgery have: a body mass index 30-34.9 kg/m<sup>2</sup> with inadequate control of hyperglycemia during the use of oral or injectable medications (an indication that is not consistent with present National Institutes of Health guidelines for bariatric surgery), a body mass index 35-39.9 kg/m<sup>2</sup> with inadequate control of hyperglycemia during optimal medical therapy, or a body mass index  $\geq 40$  kg/m<sup>2</sup>. Bariatric surgeons favor Roux Y gastric bypass for those diabetic individuals with significant chronic gastroesophageal reflux or with insulin-dependent type 2 diabetes mellitus<sup>[6]</sup>. Their concern in those individuals with chronic gastroesophageal reflux is based upon VSG being a refluxogenic procedure. A large amount of the parietal cell mass is removed during a VSG. However, increased pressure in the tabularized stomach allows contents to reflux from the gastric sleeve and into the distal esophagus. VSG slows egress into the stomach, increasing the length of time that the esophagus is exposed to gastric contents.

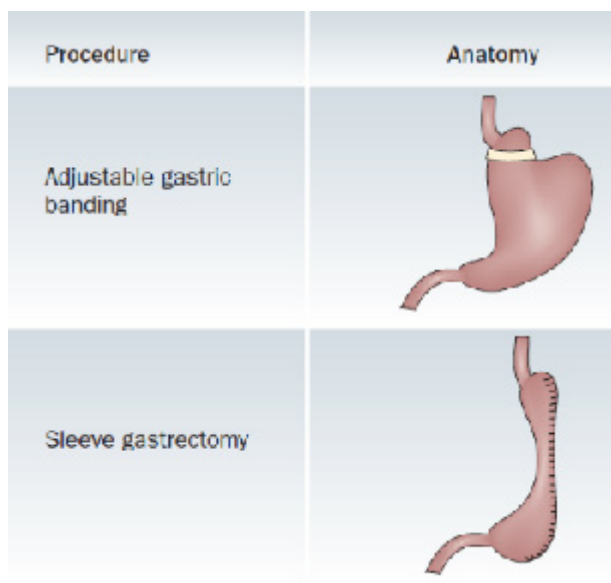
Two less complex bariatric surgical procedures that involve only surgery on the stomach, AGB and VSG, are shown in Figure 2. In present AGB systems, there is no cutting or stapling of the stomach or bypass of small intestine. Rather, a soft, silicone ring with an adjustable bladder is placed just below the gastroesophageal junction around the upper part of the stomach. The AGB is then connected with tubing to a subcutaneous access port to permit adjustment of the band volume. Addition or removal of sterile fluid through the access port can decrease or increase the flow of fluids and solids through the proximal stomach<sup>[7]</sup>.

The VSG was initially described as the first step of a two stage operation for the “super obese”, but has since become a standalone procedure that has durable long term weight loss. It has been suggested that the relative technical ease, shorter learning curve, faster operating time, and fewer metabolic side effects coupled with similar outcomes led to the adoption of and rapid expansion of the VSG. The initial step is locating the pylorus and measuring a distance on the greater curvature of 2 to 6 cm proximally (to reduce bleeding rates<sup>[8]</sup>). The greater omentum is removed in a step wise fashion to avoid a retained fundus. Once the stomach is fully mobilized, a 36 to 40 French bougie is passed transorally along the lesser curve of the stomach towards the pylorus. The greater curve of the stomach is transected with a series of staple cartridges along the bougie. A VSG will restrict the size of meals, but weight loss may result from other mechanisms including blockade of ghrelin (“hunger” hormone) release<sup>[9]</sup>, or bacterial overgrowth in the upper gut with glucose malabsorption<sup>[10]</sup>.

In evaluation of postoperative weight loss, the larger discrepancies in individuals who have undergone AGB, when compared to individuals who underwent VSG, may in part be dependent upon whether single center data or multicenter data is examined. Table



**Figure 1** Temporal Trends in Global Prevalence of Diabetes Mellitus. The findings parallel the rise in the global prevalence of obesity. Note that by 2014 the rise in the prevalence of diabetes mellitus in men outpaced the rise in women.



**Figure 2** Laparoscopic Bariatric Surgical Procedures Involving Only Gastric Surgery. The upper cartoon depicts the adjustable gastric band which limits the types of foods and the volume of food consumed. The lower cartoon depicts the vertical sleeve gastrectomy which limits the volume of consumed food (Reproduced with the permission of Nature Publishing Group from Bal BS, et al. Nature Rev Endocrinol 2012; 8: 544-556).

1 summarized long term weight loss reported after gastric bariatric surgical procedures. The AGB is less effective than VSG in long term studies of weight loss<sup>[11-13]</sup>, but a meta-analysis did report that for  $\geq 10$  years, individuals can lose a mean of 47% of their excess weight (excess weight is defined by: total body weight – ideal body weight). As shown in Table 1, individuals after VSG can lose a mean of up to 70% of their excess weight at 10 years after surgery. Between these two gastric bariatric surgeries, major long-term weaknesses of the AGB have been described. A major problem with the AGB is consideration of removal of the AGB. Removal of the AGB has been reported in 71% of individuals after 10 years in a single center in Switzerland<sup>[19]</sup>, 26% in a four year study of 16,444 individuals in New York state<sup>[20]</sup>, and 6% yearly in a 7 year French national study that involved 52,868 patients<sup>[21]</sup>.

Remission of type 2 diabetes mellitus can be defined by the discontinuation of medications for medical treatment. As shown in Table 2, the remission rates of type 2 diabetes in obese individuals who have undergone gastric bariatric surgical procedures generally parallel the reported weight loss. Remission of type 2 diabetes mellitus can be seen up to 8 years after VSG (Table 2). Factors that may be important in understanding the remission rates after VSG

include the type of study being performed, the range of preoperative body mass index, and the length of postoperative follow up. In addition, patients are included in whom a diet and activity program, oral medications, or insulin are being used for the treatment of type 2 diabetes. The report of decreased incidences of microvascular and macrovascular complications after bariatric surgery<sup>[24]</sup> supports the important role of remission in the long-term care of individuals with type 2 diabetes.

As summarized in Table 3, placement of intraluminal devices and intraluminal suturing has been under study as endoscopic treatments for obesity. Specifically, four major endoscopic procedures for the treatment of obesity include intragastric balloons, intragastric aspiration systems, intraluminal gastric suturing, and intraluminal barriers deployed within the upper small intestine. Ongoing studies are examining the ability of these endoscopic procedures to treat metabolic disorders, which includes reduction in the blood levels of hemoglobin A1C in individuals with diabetes mellitus. The use of blood levels of hemoglobin A1C to judge clinical benefit has been a focus of national guidelines published from the American College of Physicians in the United States<sup>[28]</sup>. These national guidelines have suggested a target goal for hemoglobin A1C within the range of 7% to 8%. It was noted that more intensive treatment may increase the risk to patients with type 2 diabetes mellitus. The guidelines also noted that the absolute benefit provided by better control of hyperglycemia can be small. Finally, there was a concern raised that demonstration of the potential benefit of more intensive glycemic control may require a long time period, and so such intervention should be reserved for those individuals with type 2 diabetes who have an expected survival of greater than 15 years<sup>[28]</sup>.

The first endoscopic method for treatment of obesity began with the 1985 approval of the Garren-Edwards bubble by the United States Food and Drug Administration. Several reviews have been published in examining the 30+ year experience in the utilization of intragastric balloons. A 2016 review from the Cleveland Clinic<sup>[29]</sup> concluded that additional studies were needed with regards to the role in individuals with type 2 diabetes of intragastric balloons. A 2017 review from New York University<sup>[30]</sup> described the availability of small studies with short follow ups that made it difficult to evaluate metabolic risk factors in individuals who had undergone treatment with intragastric balloons.

Beginning in 2015, the United States Food and Drug Administration first approved the Orbera intragastric balloon, followed by the ReShape intragastric balloon (which is no longer available in the United States), and the Obalon intragastric balloon system<sup>[7]</sup>. Following reports of multiple deaths related to the use of intragastric balloons, there were then three warnings (February 2017, August 2017, and June 2018) announced by the United States Food and Drug Administration. Since then, three systemic reviews and meta-analyses<sup>[31-33]</sup> have examined weight loss after placement of intragastric balloons. The results are summarized in Table 4. Most results are focused on the use of the Orbera intragastric balloon. In these short term studies the weight loss is modest. There has been no further significant information published that addresses the question of treating type 2 diabetes by placement of intragastric balloons. The organization of a maintenance program to prevent weight regain after the removal of intragastric balloons remains to be studied.

In 2016, the United States Food and Drug Administration approved use of the AspireAssist (Aspire Bariatrics, King of Prussia, Pennsylvania, USA). This is a specialized aspiration tube that is placed into an individual's stomach at upper endoscopy using a percutaneous approach. This aspiration tube includes a skin port as

**Table 1** Long term weight loss after gastric bariatric surgery.

Procedure*	Type of Study*	Reference	Follow Up	Results**
AGB	MCS	11	15 Years	%TWL 13%
AGB	SR	12	3-5 Years	%EWL 45%
AGB	MA	13	>/= 10 Years	%EWL 47%
VSG	MCS	14	5 Years	%TWL 16.8
VSG	SCS	15	5 Years	%TWL 26
VSG	SCS	16	8 Years	%EWL 51.1
VSG	SCS	17	8 Years	%EWL 67
VSG	MCS	18	10 Years	%EWL 70.5

\*AGB: Adjustable Gastric Band; VSG: Vertical Sleeve Gastrectomy; MCS: Multi-Center Study; MA: Meta-Analysis; SR: Systemic Review; SCS: Single-Center Study; \*\*%TWL: Mean Percentage Total Weight Loss; %EWL: Mean Percentage Excess Weight Loss (Excess weight is defined as: Total Body Weight - Ideal Body Weight.)

**Table 2** Long term control of diabetes mellitus after gastric bariatric surgery.

Procedure*	Type of Study*	Reference	Follow Up	Results**
AGB	SCS	22	10 Years	NOMRxDM 18%
AGB	NPBCS	23	6 Years	NOMRxDM 32%
AGB	MCS	24	15 Years	NOMRxDM 38%
VSG	MCS	14	6 Years	NOMRxDM 11%
VSG	MCS	25	5 Years	NOMRxDM 25%
VSG	SCS	18	8 Years	NOMRxDM 37%
VSG	NPBCS	23	6 Years	NOMRxDM 41%
VSG	SCS	16	8 Years	NOMRxDM 43%
VSG	MCS	26	5 Years	NOMRxDM 64%
VSG	SCS	15	5 Years	NOMRxDM 67%
VSG	SCS	27	5 Years	NOMRxDM 77%

\* AGB: Adjustable Gastric Band; VSG: Vertical Sleeve Gastrectomy; SCS: Single-Center Study; SR: MCS: Multi-Center Study; NPBCS: Nationwide population-based cohort study. \*\*NOMRxDM: No Medical Therapy for Diabetes Mellitus.

**Table 3** Bariatric endoscopic procedures.

Intraluminal Devices	
Intragastric Balloon	-Orbera*
	-Obalon*
Aspiration Therapy (AspireAssist)	
Duodeno-Jejunal Bypass Sleeve (EndoBarrier) †	
Intraluminal Suturing	
Endoscopic Sleeve Gastroplasty	

\*In order of date approved by the United States Food and Drug Administration; †Device is not approved by the United States Food and Drug Administration.

well as an intragastric portion with holes to permit aspiration. Twenty minutes after meals containing more than 200 kcal, stomach contents are aspirated. At 4 years after placement, a European trial reported a 19.2% mean weight loss<sup>[34]</sup>. In a more recent multicenter trial in the United States<sup>[35]</sup>, only 15 out of 111 randomized patients completed four years of follow-up.

As show in Table 5, in the European trial<sup>[35]</sup> at 1 year post placement, examination of mean hemoglobin A1C levels revealed a 1.0% decline (from 7.8% at baseline to 6.8%). One notes that the baseline mean hemoglobin A1C level of 7.8% is within the range in which intensive therapy of type 2 diabetes may provide only minor benefit<sup>[28]</sup>. In the US trial<sup>[35]</sup>, the Year 1 baseline hemoglobin A1C levels were only 5.7 +/- 0.6%.

A duodenojejunal bypass sleeve, termed the EndoBarrier (GI

Dynamics, Boston, MA), is available for placement in several countries. This device consists of an impermeable fluoropolymer sleeve with a length of 60 cm and a nitinol anchor. With the assistance of upper endoscopy and fluoroscopy, the distal end of the sleeve is passed into the jejunum. The anchor is then deployed from its introducer so that the proximal end is in the duodenal bulb.

Four major studies involving this duodeno-jejunal liner in individuals with type 2 diabetes mellitus have been reported in the past three years<sup>[36-39]</sup>. Three studies involved implantation for 12 months while one study implanted the device for up to 24 months. As summarized in Table 4, the length of these studies ranged from 12 to 48 months with total weight loss ranging from 2.2% to 12% at the completion of the trials. These trials involved 29 to 114 participants. As shown in Table 5, the mean declines in hemoglobin A1C at the completion of three trials ranging in length from 12 to 48 months was only 0.1% to 0.8%. The organization of a maintenance program to prevent weight regain after the removal of duodeno-jejunal liners remains to be studied.

In 2013, Dr. Christopher Gostout’s group at the Mayo Clinic, Rochester, MN reported the development of a method for formation of an endoscopic gastroplasty that may parallel the gastric anatomy following a VSG<sup>[40]</sup>. A commercially available suturing device (OverStitch, Apollo Endosurgery, Austin, Texas USA) was used in this initial report, and multiple variations have since been reported. As shown in Table 4, consistent and similar weight loss results have been reported in individuals who have undergone endoscopic gastroplasty<sup>[41-46]</sup>. These studies however have been reported with follow ups of only 12 to 36 months. As shown in Table 5, in three studies that have evaluated the response of individuals with type 2 diabetes mellitus, there are wide ranges of responses recorded from a mean decrease in hemoglobin A1C of 1.0% to a remission rate as high as 76%. In a systematic review of endoscopic gastroplasty published by Cohen and associates<sup>[47]</sup>, the authors conclude that, due to the short follow up periods and the low scientific quality of published literature, endoscopic gastroplasty cannot be presently recommended for use in clinical practice.

To summarize, obesity continues to be a worldwide origin for multiple medical problems, including metabolic disorders. The prevalence of type 2 diabetes mellitus has indeed increased worldwide in both men and women. The adjustable gastric band and the vertical sleeve gastrectomy are less complex gastric surgeries utilized by bariatric surgeons for the treatment of metabolic disorders. Studies have supported the utility of both of these gastric surgeries for the treatment of subgroups of individuals with diabetes mellitus. Four major endoscopic procedures being examined for the treatment of obesity include intragastric balloons, intragastric aspiration systems, intraluminal gastric suturing, and intraluminal barriers deployed within the upper small intestine. Ongoing studies include only short term studies that have demonstrated that intraluminal gastric suturing to produce an endoscopic gastroplasty is the most reliable endoscopic method for inducing weight loss. There is little present evidence to support an endoscopic weight loss as a viable method for improving glycemic control in individuals with type 2 diabetes mellitus. The organization of a maintenance program to prevent weight regain after the removal of intragastric balloons or intraluminal duodeno-jejunal barriers remains to be studied.

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**Table 4** Weight loss after endoscopic procedures.

Type of procedure*	Study*	Reference	Follow up	Result**
IGB	SR	31	3-6 Months	%EWL 14%
IGB	MA	32	6 Months	%TWL 6.7%
IGB	SR	33	6 Months	%TWL 13.2%
AAT	MCS	34	4 Years	%TWL 19.2%
AAT	MCS	35	4 Years	%TWL 18.7%
DJB	MCS	36	4 Years	%TWL 2.2%
DJB	MCS	37	18 Months	%TWL 11%
DJB	MCS	38	12 Months	%TWL 11.7%
DJB	MCS	39	4 Years	%TWL 12%
EG	SCS	41	18 Months	%TWL 14.8%
EG	MCS	42	2 Years	%TWL 18.6%
EG	SR	43	2 Years	%TWL 20%
EG	MCS	44	2 Years	%TWL 20.9%
EG	SCS	45	3 Years	%EWL 41.9%
EG	SR	46	12 Months	%EWL 68.3%

\*IGB: Intragastric Balloon; AAT: Aspire Aspiration Tube; DJB: Duodeno-Jejunal Barrier; EG: Endoscopic Gastroplasty; SR: Systemic Review; MA: Meta-Analysis; MCS: Multi-Center Study; MA: Meta-Analysis; SCS: Single-Center Study; \*\*%EWL: Mean Percentage Excess Weight Loss; %TWL: Mean Percentage Total Weight Loss (Excess weight is defined as: Total Body Weight - Ideal Body Weight).

**Table 5** Control of diabetes mellitus after endoscopic procedures.

Procedure*	Type of Study*	Reference	Follow up	Result**
AAT	MCS	34	1 Year	Mean Decrease 1%
DJB	MCS	38	12 Months	Mean Decrease 0.1%
DJB	MCS	36	4 Years	Mean Decrease 0.2%
DJB	MCS	37	18 Months	Mean Decrease 0.8%
EG	MCS	44	1 Year	Mean Decrease 1.0%
EG	SCS	41	18 Months	Remission 13 / 17 Patients
EG	SCS	45	3 Years	Remission Rate: 27.8%

\*AAT: Aspire Aspiration Tube; DJB: Duodeno-Jejunal Barrier; EG: Endoscopic Gastroplasty; MCS: Multi-Center Study; SCS: Single-Center Study; NPBCS: Nationwide population-based cohort study. \*\*Mean decrease in Hemoglobin A1C after treatment.

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