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## Current and future impact of clinical gastrointestinal research on patient care in diabetes mellitus

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### Abstract

The worldwide rise in the prevalence of obesity supports the need for an increased interaction between ongoing clinical research in the allied fields of gastrointestinal medicine/surgery and diabetes mellitus. There have been a number of clinically-relevant advances in diabetes, obesity, and metabolic syndrome emanating from gastroenterological research. Gastric emptying is a significant factor in the development of upper gastrointestinal symptoms. However, it is not the only mechanism whereby such symptoms occur in patients with diabetes. Disorders of intrinsic pacing are involved in the control of stomach motility in patients with gastroparesis; on the other hand, there is limited impact of glycemic control on gastric emptying in patients with established diabetic gastroparesis. Upper gastrointestinal functions related to emptying and satiations are significantly associated with weight gain in obesity. Medications used in the treatment of diabetes or metabolic syndrome, particularly those related to pancreatic hormones and incretins affect upper gastrointestinal tract function and reduce hyperglycemia and facilitate weight loss. The degree of gastric emptying delay is significantly correlated with the weight loss in response to liraglutide, a glucagon-like peptide-1 analog. Network meta-analysis shows that liraglutide is one of the two most efficacious medical treatments of obesity, the other being the combination treatment phentermine-topiramate. Interventional therapies for the joint management of obesity and diabetes mellitus include newer endoscopic procedures, which require long-term follow-up and bariatric surgical

procedure for which long-term follow up shows advantages for individuals with diabetes. Newer bariatric procedures are presently undergoing clinical evaluation. On the horizon, combination therapies, in part directed at gastrointestinal functions, appear promising for these indications. Ongoing and future gastroenterological research when translated to care of individuals with diabetes mellitus should provide additional options to improve their clinical outcomes.

**Key words:** Obesity; Gastric emptying; Diabetes mellitus; Gastric bypass; Bariatric surgery; Weight loss

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**Core tip:** The worldwide prevalence of obesity continues to rise. Delayed gastric emptying and impaired gastric accommodation result in upper gastrointestinal symptoms, through intrinsic nerve and pacemaker dysfunction. Glycemic control has a limited effect on gastric emptying in diabetic gastroparesis. Treatment of diabetes with pancreatic hormones and incretins inhibits gastric emptying, reduces hyperglycemia, and facilitates weight loss. Meta-analysis shows that glucagon-like peptide-1 analog, liraglutide, is one of the two most efficacious treatments of obesity. Bariatric surgery and endoscopic interventions are efficacious in diabetes and obesity, but long term follow-up is required for endoscopic interventions as well as for newer bariatric procedures. On the horizon, combination therapies directed at gastrointestinal function appear promising for these indications.

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## INTRODUCTION

In a recent international study of 195 countries, the prevalence of obesity doubled in more than 70 countries since 1980<sup>[1]</sup>. This worldwide rise in the prevalence of obesity supports the need for an increased interaction between ongoing clinical research in fields of gastrointestinal medicine/surgery and diabetes mellitus. There have been a number of clinically-relevant advances in diabetes, obesity and metabolic syndrome, emanating from gastrointestinal research. These advances include newer information in pharmacological or medical care, endoscopic procedures, and bariatric surgical procedures.

The most exciting gastrointestinal research areas relevant to diabetes are focused on the stomach and on weight loss, with the goals of resolution of hyperglycemia and/or prevention of secondary complications of diabetes mellitus. Ongoing studies have focused on the

stomach because patients with diabetes develop upper gastrointestinal symptoms, including the syndrome of gastroparesis. In addition, pharmacological treatments and bariatric procedures directed to the stomach have been the most efficacious treatments of obesity. Some of these clinical gastrointestinal research observations are considered likely to impact patient care in diabetes mellitus and/or obesity and may thus lead to improved patient outcomes.

## OBSERVATIONS RELATED TO UPPER GASTROINTESTINAL SYMPTOMS AND GLYCEMIC CONTROL IN DIABETES MELLITUS

### *Delayed stomach emptying is associated with upper gastrointestinal symptoms*

Based on a systematic review of the literature, including 92 gastric emptying studies (26 breath test, 62 scintigraphy, 1 ultrasound, and 3 wireless motility capsule) there is an association between optimally measured delayed gastric emptying and upper gastrointestinal symptoms<sup>[2]</sup>. Twenty-five of these studies provided quantitative data for meta-analysis (15 scintigraphy studies enrolling 4056 participants and 10 breath test studies enrolling 2231 participants). Evaluating the studies that used optimal gastric emptying test methodology, there were significant associations between gastric emptying and nausea, vomiting, abdominal pain, and early satiety/fullness in patients with upper gastrointestinal symptoms; gastric emptying and early satiety/fullness in patients with diabetes; and gastric emptying and nausea in patients with gastroparesis.

### *Gastric motor functions and other features in referred patients with diabetes with upper gastrointestinal symptoms*

Among 108 adult patients with diabetes mellitus (60.2% females; median age 49.0 years; 71.3% with type 2 diabetes mellitus; one-third insulin dependent with median hemoglobin A1C 6.7%) presenting with upper gastrointestinal symptoms, the manifestations of diabetic triopathy (peripheral neuropathy, nephropathy, and retinopathy) were uncommon at the time of presentation<sup>[3]</sup>. Nausea was the most common symptom (80.6%). Gastric emptying was rapid in 37% and slow in 19%. Gastric accommodation was abnormal in 39%. There was normal gastric accommodation and gastric emptying in 28% and 40.3% of the patients with type 2 diabetes mellitus had accelerated gastric emptying at one hour. These observations emphasize the importance of measuring these functions in patients with upper gastrointestinal symptoms in order to individualize treatment, such as with a dopamine D<sub>2</sub> antagonist or a 5-hydroxytryptamine receptor (5-HT<sub>4</sub>) agonist for patients with delayed gastric emptying and a 5-HT<sub>1A</sub> agonist in patients with impaired gastric accommodation.



### **Histopathological features and expression in the intrinsic mechanisms involved in gastric motor functions**

In different morphological studies based on light microscopy examination of full-thickness gastric biopsies and immunofluorescence, there is evidence of reduction in the pacemaker cell repertoire (interstitial cells of Cajal<sup>[4,5]</sup> and fibroblast-like cells positive for platelet-derived growth factor alpha<sup>[6]</sup>), reduced numbers of neurons expressing nNOS<sup>[4]</sup>, and reduced numbers of M2 macrophages, which normally express the mannose receptors (CD206) and heme oxygenase-1, mediate cell repair, and have anti-inflammatory roles<sup>[5]</sup>. Other studies show increase in CD68 immunocytes, suggesting immune-mediated damage to these pacing mechanisms<sup>[6]</sup>, and this may be aggravated in the presence of vagal denervation, a common sequel of longstanding type 1 diabetes mellitus. Normally, the efferent vagus nerve signals release of norepinephrine from splenic nerves, activating the  $\beta$ 2-adrenergic receptor expressed on T cells, and macrophages and other immune cells, suppressing the release of pro-inflammatory cytokines<sup>[7]</sup>. In summary, the interplay of vagal neuropathy, intrinsic neuropathy and immune modulation are considered combination factors leading to the gastric motility disorder.

### **Role of hyperglycemia in diabetic gastroparesis**

The role of hyperglycemia in diabetic gastroparesis is unclear. On the one hand, there is epidemiological evidence of association of glycemia with upper gastrointestinal symptoms<sup>[8]</sup>, documentation of poor glycemic control in 36% patients admitted to the hospital for exacerbations of diabetic gastroparesis<sup>[9]</sup>, kidney and pancreas transplants improve gastric emptying and associated gastrointestinal symptoms<sup>[10]</sup>. Conversely, hemoglobin A1C was not a statistically significant predictor of abnormal (compared to normal) gastric emptying of solids in a study of 129 patients<sup>[11]</sup>, and long-term blood glucose control had no significant effect on gastric emptying in type 2 diabetes mellitus<sup>[12]</sup>.

### **Role of stomach emptying on glycemic control**

The available literature suggests that the stomach emptying does have an impact on glycemic control, and not only in patients with gastroparesis. Some published reports confirm the notion that gastroparesis impacts glycemic control: (1) patients with gastroparesis as documented in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort, gastroparesis was associated with relatively worse glycemic control, as assessed by glycosylated hemoglobin<sup>[13]</sup>; (2) there is poor glycemic control in 36% patients admitted to the hospital for exacerbations of diabetic gastroparesis<sup>[9]</sup>; and (3) in insulin-treated patients with gastroparesis, delayed gastric emptying may increase the potential for a mismatch the timing of exogenous, preprandial, insulin

and the actual delivery of nutrients such as glucose from the stomach to be absorbed from in the small intestine. In a study involving 11 type 1 patients, less insulin was required to achieve euglycemia during the first 120 min after a meal in the 5 with gastroparesis, and more between 180-240 min<sup>[14]</sup>. In addition, there is also evidence that the rate of gastric emptying has a major impact on the glycemic response to carbohydrate-containing meals in health and diabetes, particularly the initial postprandial increment<sup>[15]</sup>. Therefore, it is now appreciated that postprandial glycemic excursions make a major contribution to "overall" glycemic control as assessed by hemoglobin A1C. Delayed gastric emptying in type 1 diabetes has recently been reported to be associated with an overall increase in blood glucose during the day; this may reflect the mismatch between the preprandial insulin and the later absorption of food due to the delayed gastric emptying<sup>[16]</sup>.

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## **OBSERVATIONS RELATED TO GASTROINTESTINAL HORMONES IN OBESITY**

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### **Role of gastric emptying in the beneficial effects of GLP-1 analogs**

Liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, is approved for treatment of obesity; however, the mechanisms of action of liraglutide are incompletely understood and include increase in satiety, increase in resting energy expenditure, and direct effects on appetite centers in the brain<sup>[17]</sup>. In a randomized, double-blind, placebo-controlled trial of subcutaneous liraglutide (3.0 mg) in 40 patients at Mayo Clinic, liraglutide delayed gastric emptying of solids at 5 wk and 16 wk, and there was significantly greater weight loss and lower volume of a nutrient drink to reach the maximum tolerated volume in the liraglutide group than in the placebo group. The effects of liraglutide on weight loss are associated with delay in gastric emptying of solids, and the measurement of gastric emptying (e.g., at 5 wk of treatment) may be a biomarker of responsiveness and may help to select individuals for prolonged treatment with this class of drug<sup>[18]</sup>.

The effect of GLP-1 receptor agonist on weight loss does not appear to be impacted by the presence of metabolic derangements such as type 2 diabetes. However, there is evidence of a significant correlation in the weight loss induced by liraglutide and delay of gastric emptying<sup>[18]</sup>.

### **Incretin combinations for obesity**

Incretin and pancreatic hormones [e.g., amylin, glucagon, glucose-stimulated insulinotropic peptide (GIP), GLP-1 and peptide tyrosine tyrosine (PYY)] generally inhibit upper gastrointestinal motor function<sup>[19]</sup> or secretion (e.g., oxyntomodulin). Moreover, many of these hormones also exert central effects that reduce appetite<sup>[20]</sup>, and some

**Table 1 Bariatric endoscopic procedure**

Intraluminal devices
Intragastric balloon
Orbera <sup>a</sup>
ReShape <sup>a</sup>
Obalon <sup>a</sup>
Duodeno-jejunal bypass sleeve (EndoBarrier)
Aspiration therapy (AspireAssist)
Intraluminal suturing
Endoscopic sleeve gastropasty
Transoral gastropasty

<sup>a</sup>In order of date approved by United States Food and Drug Administration.

(e.g., GLP-1 analogs or GLP-1 receptor agonists) are efficacious in the treatment of obesity<sup>[21]</sup>.

Several combined incretin hormones have been tested in the context of obesity. Co-administration of GLP-1 with glucagon in humans increased energy expenditure and reduced food intake<sup>[22,23]</sup>. A unimolecular dual incretin consisting of PEGylated GLP-1 and GIP co-agonist maximized metabolic benefits in rodents, monkeys, and humans<sup>[24]</sup>.

The combination of GLP-1 and PYY<sub>3-36</sub> also exerts synergistic effects with a reduction of 30.4% of food intake compared to placebo and more than the sum of each hormone independently, suggesting a synergistic effect<sup>[25]</sup>. Acute, continuous, subcutaneous infusion for 10.5 h/d of GLP-1, PYY, and oxyntomodulin (summarized as GOP) was administered at doses that replicate postprandial levels observed after Roux-en-Y gastric bypass in a placebo-controlled, crossover study. GOP reduced food intake with a mean reduction of 32% without significantly altering resting energy expenditure<sup>[26]</sup>.

### Combined bariatric endoscopy with pharmacotherapy

One study compared the effects of an intragastric balloon in 64 patients compared to a combination of balloon plus liraglutide, up to 1.8 mg/d, in 44 patients matched for body mass index (BMI) at baseline<sup>[27]</sup>. The mean weight loss after balloon removal was 8.3 kg greater in the balloon plus liraglutide group than in the balloon alone group, and the advantage persisted 6 mo post-balloon removal in the group receiving liraglutide<sup>[27]</sup>.

## BARIATRIC ENDOSCOPIC PROCEDURES

The development of endoscopic interventions for treatment of obesity and diabetes mellitus has focused on two areas (Table 1), the placement of intraluminal devices and intraluminal suturing<sup>[28,29]</sup>.

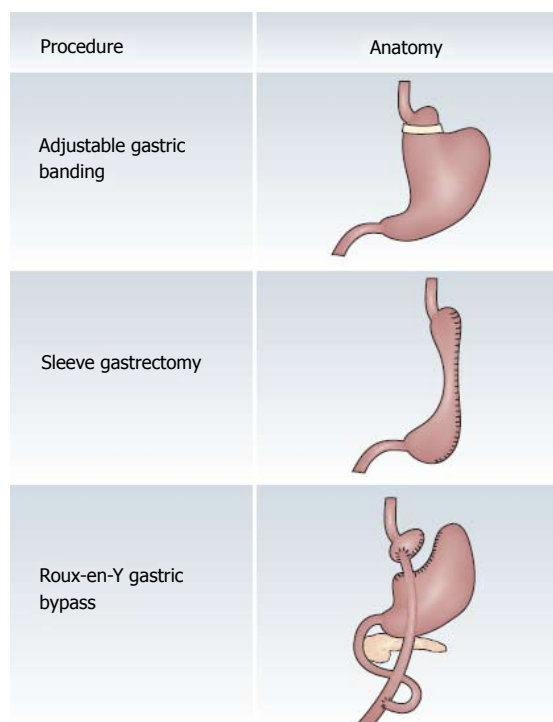
### Intraluminal devices

The first intragastric balloon, the Garren-Edwards bubble, was approved by the United States Food and Drug Administration in 1985. The United States Food and Drug Administration has now approved 3 separate intragastric

balloon systems in the past 3 years: The Orbera balloon, the ReShape balloon, and the Obalon balloon. Delayed gastric emptying has been identified as a mechanism for weight loss in individuals who have undergone insertion of a fluid-filled intragastric balloon<sup>[29]</sup>, which raises the question of their utility in individuals with diabetic gut autonomic neuropathy. After the intraluminal balloons are removed, individuals required a maintenance program (which has not yet been standardized) to prevent weight regain. Our previous concern<sup>[29]</sup> that specialized training is needed for the use of these devices appears to be supported by three warnings (in February 2017, August 2017, and June 2018) from the United States Food and Drug Administration with regards to issues related to intragastric balloons including multiple deaths related to intragastric balloons. Two major reviews in the past two years examined the 30+ year experience with intragastric balloons<sup>[30,31]</sup>. Brethauer *et al.*<sup>[30]</sup> concluded that more study was required in patients with type 2 diabetes mellitus. Popov *et al.*<sup>[31]</sup> concluded that intragastric balloons were more effective than diet alone for an initial improvement of metabolic risk factors, but that their conclusions are limited by the small number of participants and the lack of long-term follow-up data.

Some countries have the availability of a duodeno-jejunal bypass sleeve, termed the EndoBarrier. This impermeable fluoropolymer sleeve with a nitinol anchor is deployed from the duodenal bulb and into the jejunum under fluoroscopic and endoscopic guidance. A clinical trial of this device in the United States in individuals with diabetes mellitus was halted early due to the development of liver infections. Three studies involving the EndoBarrier in individuals with type 2 diabetes mellitus have been published in the past one year. Betzel *et al.*<sup>[32]</sup> were able to implant the device in 185 out of 198 participants. Sixty-nine percent of the participants were able to complete a one year program prior to removal of the device. Hemoglobin A1C levels declined by a mean of 9%, but no long term data was available. Forner *et al.*<sup>[33]</sup> reported their findings in 114 individuals who maintained an EndoBarrier for a mean of 51.1 wk after its placement; the authors reported that mean Hemoglobin A1C was not significantly improved but that 6 subjects developed device obstructions, 5 individuals had gastrointestinal hemorrhage, 2 individuals developed liver abscesses, and 1 individual developed acute pancreatitis. Patel *et al.*<sup>[34]</sup> reported a multicenter trial involved EndoBarrier Placement in 45 individuals with type 2 diabetes. Thirty-one individuals (69%) completed the 12 mo study. The mean hemoglobin A1C reduction at 12 mo was 0.8% below baseline. After explant, these subjects were only followed for an additional 6 mo.

The AspireAssist (Aspire Bariatrics, King of Prussia, Pennsylvania, United States) was approved by the United States Food and Drug Administration in 2016. A specialized aspiration tube (with both an intragastric portion with holes to permit aspiration as well as a skin port) is placed percutaneously at upper endoscopy into an individual's stomach. Stomach contents are then



**Figure 1 Comparison between bariatric surgical procedures.** The top cartoon depicts the adjustable gastric band which limits the types of food consumed postoperatively by patients. The middle cartoon depicts the vertical sleeve gastrectomy which limits the volume of food consumed postoperatively by patients. The lower cartoon depicts the Roux-en-Y gastric bypass which limits volume of food consumed, may alter absorption of macronutrients, and alters release of intestinal incretins (Reproduced with the permission of Nature Publishing Group from Bal *et al.* *Nature Rev Endocrinol* 2012; 8: 544-556).

aspirated 20 min after a meal containing more than 200 kcal. A recent European trial examining the aspiration tube described a decrease in Hemoglobin A1C from 7.8% at baseline to 6.8% at only 1 year post-placement and mean percent weight loss of 19.2% at 4 years post-placement<sup>[35]</sup>.

As described above, long-term weight loss and metabolic results are not available for these endoscopic devices. Therefore their role in the treatment of obese individuals with diabetes mellitus remains to be defined.

### Intraluminal suturing

Formation of an endoscopic sleeve gastropasty or a transoral gastropasty has been described by using intraluminal suturing devices during upper endoscopy. The Mayo Clinic, Rochester, Minnesota United States reported a method in 2013 for an endoscopic sleeve gastropasty. This procedure involves the use of a commercially available suturing device (OverStitch, Apollo Endosurgery, Austin, Texas United States), and the endoscopic sleeve gastrectomy is the predominant intraluminal technique presently described in the literature. Development of an endoscopic procedure to mimic the surgical vertical sleeve gastrectomy could reduce the risks of a gastric leak or perforation and of general anesthesia. However, results from the surgical literature support the importance of obtaining long-

term weight loss data. When the Mayo Clinic, Rochester, Minnesota, United States reported their results from the surgical non-banded vertical gastropasty, only 31% of patients were judged to have persistent excess weight lost after 4 years<sup>[36]</sup>. A proposed mechanism for weight loss after the endoscopic sleeve gastrectomy is slowing of gastric emptying, which raises the question of its utility in individuals with diabetic gut autonomic neuropathy. Further research should better define the potential long-term role of intraluminal suturing in weight loss and the treatment of obese individuals with diabetes mellitus.

## BARIATRIC SURGERY

### Bariatric surgical procedures

The well described and worldwide utilized bariatric surgical procedures<sup>[37]</sup> include the adjustable gastric band, the vertical sleeve gastrectomy, and the Roux-en-Y gastric bypass (Figure 1). By 2014, there were 579000 yearly bariatric surgical procedures of which 45.9% were the vertical sleeve gastrectomy, 39.6% were the Roux-en-Y gastric bypass, and 7.4% were the adjustable gastric band<sup>[38]</sup>. The adjustable gastric band systems now use a soft, silicone ring which is placed around the upper part of the stomach approximately 4 cm below the gastroesophageal junction and is connected to an access port by tubing to adjust the band volume. Restriction of the proximal stomach is altered by addition or removal of sterile saline through the access port and there is no cutting or stapling of the stomach or bypass of small intestine. The vertical sleeve gastrectomy or gastric sleeve resection can be completed with a single step restrictive operation. By resection of 60% to 80% of the stomach along the greater curvature, multiple staplers can produce a tubular gastric pouch. Weight loss after vertical sleeve gastrectomy appears to involve several potential mechanisms in addition to restriction in the size of meal portions<sup>[39]</sup>. In the Roux-en-Y gastric bypass, there is complete division of native stomach with production of a gastric pouch of less than 30 mL. The surgeon divides the jejunum 30 to 70 cm distal to the junction of the duodenum with the jejunum. The location of the jejuno-enteric anastomosis determines the lengths of the Roux limb (*e.g.*, the gastric pouch to the jejuno-enteric anastomosis) and the common channel (*e.g.*, the jejuno-enteric anastomosis to the ileocecal valve). A common channel that is shorter than 120 cm can induce a severe malabsorptive disorder. The mechanisms of weight loss after gastric bypass are complex and can include upper gut bacterial overgrowth, a common intestinal disorder in individuals with diabetes mellitus, as well as glucose malabsorption<sup>[40]</sup>. Studies of glucose malabsorption after gastric bypass are of interest because jejunal administration of glucose appears to suppress plasma levels of the orexigenic hormone, acyl ghrelin<sup>[41]</sup>. Further studies of the mechanisms of weight loss after bariatric surgery are clearly important since a proportion of individuals have poor long-term weight loss<sup>[42]</sup>.



**Table 2 Long term weight loss after bariatric surgery**

Ref.	Study <sup>a</sup>	Type of surgery <sup>b</sup>	Follow up	Result (%) <sup>1</sup>
[52]	MA	AGB	≥ 10 yr	EWL: 47.4
[52]	MA	VSG	≥ 5 yr	EWL: 53.2
[52]	MA	RYGB	≥ 10 yr	EWL: 63.5
[44]	MCS	AGB	15 yr	MWL: 13.0
[44]	MCS	RYGB	15 yr	MWL: 27.0
[53]	SCS	VSG	8 yr	EWL: 67.0
[54]	SCS	VSG	8 yr	EWL: 51.1
[55]	MCS	VSG	10 yr	EWL: 70.5
[56]	SR	AGB	3-5 yr	EWL: 45.0
[56]	SR	VSG	3-5 yr	EWL: 64.5
[56]	SR	RYGB	3-5 yr	EWL: 65.7

<sup>a</sup>MA: Meta-analysis; MCS: Multi-center study; SCS: Single-center study; SR: Systematic review; <sup>b</sup>AGB: Adjustable gastric band; VSG: Vertical sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; <sup>1</sup>EWL: Mean percentage excess weight loss; MWL: Mean weight loss.

### Long term mortality after bariatric surgery

The potential importance of bariatric surgery in individuals with diabetes mellitus was well publicized following a 2007 report that after a mean follow up of 7.1 years, individuals who underwent gastric bypass surgery had a 40% decrease in their adjusted long-term mortality (but by 92% for diabetes) compared to the control group<sup>[43]</sup>. This landmark study has been supported by a report of decreased mortality compared to usual care at 16 years in the Swedish Obese Subjects trial<sup>[44]</sup>. In a national study from Israel, bariatric surgery at a mean follow up of 4.5 years was shown to lower all-cause mortality compared to usual care obesity management<sup>[45]</sup>. Finally, in a recent examination of the American National Health and Nutrition Examination Survey, it was reported that bariatric surgery can result in a relevant reduction of mortality in the United States obese population<sup>[46]</sup>.

### Long term weight loss after bariatric surgery

Evaluation of the results reported for the different major bariatric surgical procedures may vary dependent upon whether single center data or multicenter data is examined. The largest discrepancy appears in reports concerning the adjustable gastric band, which may in part explain its decreased worldwide utilization. Several major reports in the past one year have supported major weaknesses of the adjustable band. In a single center report from Switzerland, after over 10 years of follow up, 71% of patients had lost their gastric band and only 15% of patients had good to excellent results<sup>[47]</sup>. In a French national study of 52868 patients up to 7 years after adjustable gastric banding, the band removal rate was about 6% per year<sup>[48]</sup>. In a study from the state of New York, among 16444 patients who underwent adjustable gastric banding, with at least four years of follow up the rate of revisions/conversions was 26.0%<sup>[49]</sup>. An early meta-analysis reported that bariatric surgery does result in a weight loss of 20 to 30 kg, which is maintained for

up to 10 years<sup>[50]</sup>. A follow up meta-analyses in 2013 by Gloy and associates reported in a shorter follow up that individuals allocated to bariatric surgery lost a mean of 26 kg more body weight<sup>[51]</sup>. Representative reports of long-term weight loss after bariatric surgery are summarized in Table 2. The most effective bariatric surgical procedure for weight loss at up to 15 years of post-operative follow up is the Roux-en-Y gastric bypass surgery<sup>[44,52]</sup>. The least effective major bariatric surgical procedure in long term studies of weight loss is the adjustable gastric band<sup>[44,52,56]</sup>.

### Long term control of diabetes mellitus after bariatric surgery

A joint statement by international diabetes organizations supports consideration of bariatric surgery in individuals with diabetes mellitus and: BMI ≥ 40 kg/m<sup>2</sup>, BMI 35-39.9 kg/m<sup>2</sup> and inadequate control of hyperglycemia with optimal medical therapy, or BMI 30-34.9 kg/m<sup>2</sup> and inadequate control of hyperglycemia with oral or injectable medications<sup>[59]</sup>. In the United States, individuals with diabetes mellitus considering bariatric surgery are evaluated if they fulfill National Institutes of Health criteria, which is a BMI of ≥ 35 kg/m<sup>2</sup>, while in other countries individuals with diabetes and a BMI as low as 25 kg/m<sup>2</sup> may be considered for Roux-en-Y gastric bypass. Specific bariatric surgical procedures such as the vertical sleeve gastrectomy may not be effective for treatment of individuals with type 1 diabetes mellitus<sup>[60]</sup>. A meta-analysis comparing non-surgical treatment for obesity with bariatric surgery concluded that individuals allocated to bariatric surgery had a higher remission rate of type 2 diabetes<sup>[51]</sup>. A second meta-analysis with 5 years of follow-up confirmed a significant decline in the relative risk of diabetes after bariatric surgery<sup>[61]</sup>. Representative reports of long-term control of diabetes mellitus after bariatric surgery are summarized in Table 3. The most effective bariatric surgical procedure for remission of diabetes mellitus at up to 6 years of post-operative follow up is the Roux-en-Y gastric bypass surgery<sup>[56,62]</sup>. The least effective major bariatric surgical procedure in long term studies of remission of diabetes mellitus is the adjustable gastric band<sup>[56,62]</sup>. The importance of remission of diabetes is supported by a report of decreased incidence of microvascular and macrovascular complications in post-operative bariatric patients compared to controls<sup>[58]</sup>. These published results do support the importance of ongoing development of more effective bariatric surgical procedures for the treatment of individuals with obesity and type 2 diabetes mellitus.

## BARIATRIC PROCEDURES UNDER DEVELOPMENT

Gastrointestinal surgeons who specialize in bariatrics have seen an improvement in weight related comorbidities for decades. Encouraged by mounting evidence of resolution

**Table 3** Long term control of diabetes mellitus after bariatric surgery

Ref.	Type of study <sup>a</sup>	Surgery <sup>b</sup>	Follow up	Result <sup>1</sup>
[53]	SCS	VSG	8 yr	NoRMRxDM: 43.4%
[54]	SCS	VSG	8 yr	NoRMRxDM: 37%
[56]	SR	AGB	3-5 yr	NoRMRxDM: 28.6%
[56]	SR	RYGB	3-5 yr	NoRMRxDM: 66.7%
[57]	SCS	RYGB	9 yr	NoRMRxDM: 73%
[58]	MCS	AGB	15 yr	NoRMRxDM: 38%
[58]	MCS	RYGB	15 yr	NoRMRxDM: 35%
[62]	NPBCS	AGB	6 yr	NoRMRxDM: 32%
[62]	NPBCS	VSG	6 yr	NoRMRxDM: 41%
[62]	NPBCS	RYGB	6 yr	NoRMRxDM: 58%
[63]	SCS	AGB	10 yr	NoRMRxDM: 18%

<sup>a</sup>SCS: Single-center study; SR: Systematic review; MCS: Multi-center study; NPBCS: Nationwide population-based cohort study; <sup>b</sup>AGB: Adjustable gastric band; VSG: Vertical sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; <sup>1</sup>NoRMRxDM: No requirement for medical therapy for diabetes mellitus.

or substantial improvement in diseases such as diabetes mellitus, hyperlipidemia, and hypertension, leaders in the field created a paradigm shift by renaming the American Society of Bariatric Surgery as the American Society of Metabolic and Bariatric Surgery in 2007 (ASMBS.org; accessed on July 15, 2018). Gastrointestinal surgeons continue to manipulate the gastrointestinal tract in an effort to maximize the physiologic benefit to the individual patient. Restrictive procedures (*i.e.*, vertical sleeve gastrectomy, adjustable gastric banding, and the largely abandoned vertical banded gastroplasty) provide a benefit usually in proportion to the absolute weight loss achieved. Newer endoscopic and surgical procedures including the intragastric balloon, vBloc (described below), and aspirational therapy have more modest results.

Procedures that combine restriction with malabsorption by bypassing a portion of the foregut and midgut do provide measurable changes in comorbid conditions out of proportion to absolute weight loss. The traditional "gold standard" of surgical weight loss procedures, the Roux-en-Y gastric bypass, can provide rapid glucose control for patients. This procedure may take advantage of the "foregut hypothesis" that bypassing the foregut reduces or suppresses the secretion of anti-incretin hormones, which in turn leads to improvement of blood glucose control<sup>[64]</sup>. Proponents of the "hindgut hypothesis" feel this improvement is more likely secondary to rapid delivery of nutrients to the distal small intestine, which facilitates the release of hormones such as GLP-1<sup>[64,65]</sup>. Procedures which take advantage of this scenario include the biliopancreatic diversion/duodenal switch. Based upon these previous observations and notions, more recent modifications to this malabsorption procedure have shown favorable results in treatment of metabolic diseases, with up to 4 years of follow up<sup>[66,67]</sup>. Further refinements in these procedures will likely yield more promising results which may be able to be individualized for specific patient needs.

Another area of ongoing, active clinical research has been vagal nerve stimulation, based on the important role the vagus nerve plays in regulation pathways

involving short-term regulation of dietary intake. The therapy termed vBloc for Vagal BLOCking therapy (ReShape Lifesciences, San Clemente, California United States) uses intermittent intra-abdominal high-frequency electrical currents for vagal blocking. At laparoscopy, electrodes are placed on the two vagal trunks near the gastroesophageal junction. There is no anatomical modification and an external controller is used to program the device. Vagal nerve stimulation with vBloc in a 2 year study has shown promise for weight loss (mean of 21% of excess weight loss), but with only an marginal impact on diabetes (only a 0.3% decline in hemoglobin A1C)<sup>[68]</sup>. Further evaluation is therefore required to determine which patients with obesity and diabetes mellitus may benefit from this bariatric procedure.

## CONCLUSION

The worldwide prevalence of obesity continues to rise. This rise increases the incidence of type 2 diabetes mellitus with subsequent requirements for additional health care in countries across the world. This supports the need for an increased interaction between ongoing clinical research in the allied fields of gastrointestinal medicine/surgery and diabetes mellitus. Among the clinically-relevant advances in diabetes, obesity, and metabolic syndrome emanating from gastroenterological research, delayed gastric emptying and impaired gastric accommodation result in upper gastrointestinal symptoms, through intrinsic nerve and pacemaker dysfunction. Glycemic control has a limited effect on gastric emptying in diabetic gastroparesis. Treatment of diabetes with pancreatic hormones and incretins inhibits gastric emptying, reduces hyperglycemia, and facilitates weight loss. The GLP-1 analog, liraglutide, is one of the two most efficacious treatments of obesity. New bariatric endoscopic procedures have been developed for weight loss in individuals with obesity, but long term follow-up with regards to maintenance of weight loss and control of hyperglycemia in individuals with diabetes is required prior to mass introduction of these endoscopic interventions. Bariatric surgical procedures are efficacious

in diabetes and obesity, but a proportion of individuals have poor long-term weight loss after bariatric surgery. On the horizon, combination therapies directed at gastrointestinal function and newer bariatric surgical procedures appear promising for individuals with obesity and type 2 diabetes mellitus.

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