The role of bariatric surgery in the treatment of diabetes

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***Abstract*:** The obesity epidemic contributes to approximately 44% of the world's type 2 diabetes burden. Bariatric surgery is an effective treatment for type 2 diabetes mellitus in patients with morbid obesity as it improves glycaemia, blood pressure, lipids and inflammation. This review describes the evidence supporting the addition of bariatric surgery to the treatment algorithms used by diabetologists. We emphasize the need to view bariatric surgery as an adjuvant therapy which should not be used instead of but rather together with best medical therapy.

Keywords: bariatric surgery, diabetes mellitus, obesity

Introduction

Epidemiology of diabetes as driven by obesity

Obesity is a growing pandemic responsible for significant health and socioeconomic consequences. Its prevalence has doubled since 1980 with up to 500 million adults being classified as obese in 2008 [WHO, 2011]. Obesity is a result of deranged energy homeostasis which is often the consequence of dysfunction in multiple neuroenteric systems [Pournaras and le Roux, 2009]. Type 2 diabetes (T2DM) rates are increasing alongside obesity with an estimated 170 million people worldwide affected by diabetes mellitus in 2000 [Ginter and Simko, 2010].

Bariatric surgery combined with optimal medical therapy is more effective than a combination of lifestyle and medication interventions for weight loss [Mingrone *et al.* 2012; Schauer *et al.* 2012]. Bariatric surgery results in sustained weight loss for up to 20 years, with a reduction in mortality compared with medical care with diets, exercise and medication [Sjöström, 2013; Sjöström *et al.* 2007]. Further advances in T2DM management must be obtained in order to manage the existing diabetic pandemic and to curb its progress.

This review briefly describes the evidence that supports the addition of bariatric surgery to existing treatment algorithms used by diabetologists.

Surgical technique

Roux-en-Y gastric bypass

The Roux-en-Y gastric bypass (RYGB) consists of creating a gastric pouch of 20–30 ml in volume that is anastomosed with the distal jejunum. To create this, the jejunum is transected approximately 50 cm from the duodenojejunal junction [Higa *et al.* 2000; Welbourn *et al.* 2010]; the proximal end of the transected jejunum is anastomosed to the distal portion at approximately 100 cm from the transection point and the distal end to the gastric pouch [Higa *et al.* 2000]. The newly formed gastrojejunal anastomosis up to the jejunojejunal anastomosis is named the alimentary limb, the gastric remnant to the jejunojejunal anastomosis, the biliopancreatic limb and the remaining portion of the small bowel the common limb. Current accepted configurations are placing the small bowel antecolic or retrocolic with an antegastric reconstruction [Edwards *et al.* 2007; Müller *et al.* 2007]. Multiple techniques of performing the gastrojejunal anastomosis have been described with no clear consensus on which is best [Bendewald *et al.* 2011; Giordano *et al.* 2011].

Vertical sleeve gastrectomy

Vertical sleeve gastrectomy (VSG) involves a left partial gastrectomy to leave a thin cylindrical portion of stomach connecting the oesophagus to the pylorus along the lesser curve [ASMBS Clinical Issues Committee, 2012]. Sizing of the sleeve is

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Table 1. Comparison of medical *versus* LRYGB in weight, glycated haemoglobin and high-density lipoprotein in randomized controlled trials.

		Weight (kg)	Absolute change in postoperative glycated haemoglobin (%)	High-density lipoprotein*
Schauer *et al.* [2012]	Medical	−5.4 ± 8.0	−1.4	11.3 ± 25.7
	LRYGB	−29.4 ± 8.9	−2.9	28.4 ± 21.9
***p* value**		<0.001	<0.001	0.001
Mingrone *et al.* [2012]	Medical	−4.7 ± 6.4	−0.8	6.0 ± 6.3
	LRYGB	−33.3 ± 7.9	−2.2	29.7 ± 18.2
***p*-value**		<0.001	0.003	0.031

LRYGB, laparoscopic Roux-en-Y gastric bypass.

based on a 32–36 French sized bougie, resulting in approximately 100 ml volume [Rosenthal *et al.* 2012]. It may be performed as a definitive operation or as a stepping stone to a RYGB or a biliopancreatic diversion with or without a duodenal switch.

Adjustable gastric band

A silicone band is placed around the stomach at the level of the cardia through the pars flaccida [Brown *et al.* 2008] with an adjustment port placed in the subcutaneous tissue, usually in the epigastric region, connected to the band via silicone tubing. The port contains a silicone diaphragm, which allows repeated punctures with a noncoring needle to alter the volume of the band. The absence of any anatomical changes makes it possible to easily reverse or revise.

Intraluminal gastrointestinal exclusion device

The use of a device which excludes the duodenum from contact with food in patients with obesity was first described in 2007 [Gersin *et al.* 2007]. The duodenal–jejunal bypass liner (e.g. Endobarrier, GI Dynamics, Lexington, MA, USA) is placed endoscopically and deployed to cover the proximal 60 cm of the small bowel. The exclusion of the duodenum results in weight loss and improvement in glycaemia while the device is in place [Escalona *et al.* 2012]. The device may need to be replaced after 1 year so long-term benefit remains to be quantified. As with the VSG, more long-term data are required to ascertain its value as a standalone procedure.

Surgery as an 'add-on' procedure for diabetes

The first-line treatment for newly diagnosed T2DM is usually lifestyle modification combined with pharmacotherapy. Surgical procedures have only recently been considered as a potential adjunct therapy for T2DM. Yet, we have known about the favourable effects on weight and glycaemia in patients with obesity and T2DM undergoing RYGB since 1978 [Mason *et al.* 1978]. Moreover in randomized controlled trials, after 2 years, patients who undergo a bariatric surgical procedure compared with medical management maintain better glycated haemoglobin levels and require less medication (Table 1) [Mingrone *et al.* 2012; Schauer *et al.* 2012].

In the longer term, blood pressure, glucose and lipids show more favourable results in patients who have had bariatric surgery compared with medical treatment, along with a significant survival improvement [Sjöström *et al.* 2007]. Although most of the patients who go into early remission of diabetes relapse, there are more patients in T2DM remission in the surgical group after 15 years of follow up [Sjöström, 2013]. Surgery has also been shown to prevent the progression from impaired glucose tolerance to T2DM [Sjöström, 2013], raising the question of whether surgery should also be offered to patients with impaired glucose tolerance and a BMI of less than 40kg/m^2.

Efficacy of bariatric surgery as a treatment modality for patients with type 2 diabetes mellitus

Changes in weight

Weight loss after bariatric surgery is multifactorial. Metabolic, anatomical and lifestyle changes all play important roles; the contribution of each varies from procedure to procedure. For example, in RYGB, there are thought to be at least three

main mechanisms: speed of transit of food from the oesophagus into the small bowel, gut hormone responses and delayed mixing of bile in the distal small bowel.

RYGB leads to rapid contact of ingested nutrients with the mid gut after a meal stimulating both hormonal responses and the vagus nerve. The neural input to the brain alters meal size and possibly food preference in the postoperative period. Rat models exhibit reduced food intake [Bueter *et al.* 2010] and an avoidance of high-fat diets [le Roux *et al.* 2011]. In humans, RYGB results in a selective reduction of the reward value of sweet and fatty tastes [Miras *et al.* 2012b]. Visual analogue scores showed enhanced postprandial satiation postoperatively, which was associated with exaggerated satiety gut hormone responses [glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY)] [Borg *et al.* 2006]. Inhibition of GLP-1 and PYY using the somatostatin analogue octreotide after RYGB increases appetite [le Roux *et al.* 2007]. The reduction in hunger and increase in satiety coupled with a shift in preference for lower glycaemic index foods are most likely the major factors for long-term sustained weight loss.

Twenty-four hour energy expenditure is paradoxically increased in patients after RYGB compared with patients who have lost the same amount of weight with vertical banded gastroplasty [Werling *et al.* 2013]. An explanation for the increased energy expenditure and sustained lower body weight in the postoperative period in human and animal models of bypass surgery may be derived from the presence of bile in the ileum rather than duodenum [Pournaras *et al.* 2012]. Bile plays a role in the regulation of cellular function by modulating nuclear transcription that increases cellular metabolism [Makishima *et al.* 1999]. This produces an increase in basal metabolic rate, which changes the energy homeostasis, resulting in weight loss. The weight loss as a result of RYGB compared with medical therapy is shown in Table 1.

Gastric banding was initially thought to work through the reduced stomach size above the band [Dixon *et al.* 2005]. Achieving the optimal intraluminal pressure within the gastric band is key to achieving reduced food intake secondary to attenuated hunger prior to, and increased satiety after, a meal without dysphagia [Burton *et al.* 2010, 2011]. One mechanism proposed suggested that satiation was felt when food boluses, and not liquids, were squeezed between the gastric band and gastric mucosa [Burton *et al.* 2010, 2011; O'Brien, 2010]. This causes the intraganglionic laminar endings to be stimulated and produce satiety feedback to the brain [O'Brien, 2010], probably through the vagus nerve. The reduction in hunger may also be mediated through the same physiological processes [Dixon *et al.* 2005]. No gut hormone profile changes occurs after gastric banding, suggesting that resolution of the metabolic syndrome occurs with time as weight is lost [O'Brien, 2010]. Weight loss as a result of gastric band compared with medical therapy is about 15% [Sjöström, 2013].

The VSG was initially thought to be a restrictive procedure [Yehoshua *et al.* 2008]. More recent studies have proposed that removal of the fundus may have a hormonal mechanism as it contains ghrelin-producing cells [Goitein *et al.* 2012; Langer *et al.* 2005]. Ghrelin levels fall significantly in the postoperative period with permanent attenuation [Peterli *et al.* 2012]. Patients who have had VSG compared with those with RYGB or gastric band have a more exaggerated fall in ghrelin levels [Peterli *et al.* 2012; Ramón *et al.* 2012]. However, the role of ghrelin as a hunger hormone remains unclear as postoperative results are mixed [Goitein *et al.* 2012; Langer *et al.* 2005]. Scintigraphy examination post VSG shows that the mechanism of action may be associated with the increased gastrointestinal transit time due to a smaller gastric component resulting in earlier satiety and improved metabolic profile [Shah *et al.* 2010]. GLP-1 and PYY hormones follow a similar trend to patients who have had RYGB [Jiménez *et al.* 2012]. The enhanced sensation of satiety may be secondary to this increased gastrointestinal transit, triggering neural signals from the proximal small bowel [Bjorklund *et al.* 2010] or altering responses of hormones involved with appetite, similar to the RYGB. Patients who have had VSG lose significantly more weight compared with those on optimal medical therapy: weight loss 25.1 ± 8.5 compared with 5.4 ± 8.0, respectively [Schauer *et al.* 2012].

Despite their short-term use, the duodenal–jejunal bypass liner is emerging as a potentially interesting procedure with an additional reduction in haemoglobin A1c (HbA1c) of 1.4% combined with 10–15% weight loss at 1 year [Escalona *et al.* 2012; Schouten *et al.* 2010]. Since the risk of an endoscopic procedure is lower compared with

surgery, the duodenal–jejunal bypass liner can be used to focus on patients with T2DM who are not eligible or do not want bariatric surgery. The mechanism of action is yet to be determined [Gersin *et al.* 2007].

Weight loss maintenance after all the surgical procedures remains a challenge for some patients. The combination of a high-protein and low-glycaemic-index diet with surgery may thus yield better results in the longer term. The role of pharmacotherapy and specifically the addition of GLP-1 analogue therapy to those with suboptimal endogenous GLP-1 [le Roux *et al.* 2007] appears feasible in rats [Fenske *et al.* 2013] but needs to be tested in humans.

Changes in glycaemia

As shown in Table 1, when RYGB is combined with optimal medicine the glycated haemoglobin (HbA1c) improves significantly postoperatively [Mingrone *et al.* 2012; Schauer *et al.* 2012]. At 2 years fasting glucose levels were lower in patients who had RYGB compared with those who only received medical therapy [Mingrone *et al.* 2012]; similar findings have been noted in patients who have had VSG [Schauer *et al.* 2012]. In patients with T2DM of 2 years or less in duration, more than 70% of those with a gastric band achieved a fasting blood glucose level of less than 7.0 mmol/liter compared with those receiving medical therapy [Dixon *et al.* 2008]. At 6 months post implantation of the duodenal–jejunal bypass liner, de Jonge and colleagues demonstrated a mean improvement in HbA1c from 8.4 ± 0.2 to 7.0 ± 0.2% and fasting glucose improved from 11.6 ± 0.5 to 8.6 ± 0.5 mmol/liter [de Jonge *et al.* 2013]. In an observational study by de Moura and colleagues, at 1-year follow up, 72.7% of patients with endoscopic duodenal–jejunal bypass liner had an improvement in their T2DM [de Moura *et al.* 2012]. The exclusion of the duodenum from contact with nutrients appears to have a profound metabolic effect that is yet to be fully understood. It is likely to have a similar mechanism of action as the duodenal–jejunal bypass surgical procedure performed on animal models [Breen *et al.* 2012] or indeed the biliopancreatic limb of the RYGB. Combining surgery with metformin appears to have very few problems and given the proven advantages of metformin as regards long-term morbidity and mortality, clinicians should think carefully before discontinuing the drug after surgery.

Changes in hepatic insulin resistance and peripheral insulin resistance

Serum bile acid levels are increased and maintained in the postoperative state after RYGB, and are associated with improvements in glucose profiles [Makishima *et al.* 1999; Nakatani *et al.* 2009; Patti *et al.* 2009]. Bile also improves glycaemia by stimulating incretin hormones GLP-1 and PYY [Pournaras *et al.* 2012]. Additionally, RYGB leads to rapid contact of ingested nutrients with jejunal mucosa after a meal, which may stimulate mechanoreceptors. Rapid direct contact of long-chain fatty acid (LCFA) with bowel mucosa stimulates incretin responses via a neuroenteric circuit [Wang *et al.* 2008]. LCFA trigger impulses via the vagus to the hindbrain, which then produce a feedback impulse to the liver. Vagal stimulation may also increase incretin secretion and reduces endogenous glucose production by the liver [Wang *et al.* 2008]. Animal models with the duodenal–jejunal bypass surgery confirmed the presence of jejunal nutrient sensing and its incretin effect in normalizing serum glucose levels [Breen *et al.* 2012]. Breen and colleagues also found that infusing glucose directly into the jejunum produced a similar effect to LCFA [Breen *et al.* 2012], likely to also involve the vagus nerve.

In VSG, insulin sensitivity improves, but to a lesser degree than in RYGB [Kashyap *et al.* 2013]. After RYGB, hepatic insulin resistance improves with increased insulin-stimulated glucose uptake [Promintzer-Schifferl *et al.* 2011]. In rodent models with VSG, Zucker diabetic fatty rats had significantly lower serum glucose levels over time compared with controls, suggesting decreased insulin resistance [Kadera *et al.* 2013].

In the use of duodenal–jejunal bypass liners, improved insulin sensitivity can be observed as early as 1 week postoperatively without change in insulin levels [de Jonge *et al.* 2013]. The speed of change in insulin resistance suggests that weight loss or calorie restriction may not be causal, especially as increased insulin resistance is the norm in patients on medical therapy or those who are calorie restricted.

Changes in insulin secretion

At 2 years, pancreatic β-cell function improves in patients with RYGB but not in those who have had VSG [Kashyap *et al.* 2013]. Postoperatively, plasma concentration levels of insulin are reduced but the postprandial response is exaggerated

[Promintzer-Schifferl *et al.* 2011]. These changes occur within days of the procedure and are associated with a rise in GLP-1 [Pournaras *et al.* 2010]. Similar observations are seen in VSG with a rise in GLP-1, PYY, reduced fasting insulin levels and increased insulin sensitivity [Papamargaritis *et al.* 2013], but to a lesser extent than in RYGB. These differences may account for the superior glycaemic control in patients with RYGB.

In patients with a gastric band, no significant incretin or gut hormone changes occur [Pournaras *et al.* 2010]. Improvement in glycaemia, insulin secretion and insulin resistance is directly related to weight loss for this cohort. With regular and careful follow up, similar improvements in T2DM control with gastric banding and RYGB can be obtained [O'Brien and Dixon, 2003]. However, when comparing gastric banding and RYGB, improvements in T2DM are more marked in the latter [Buchwald *et al.* 2004].

In patients with longstanding T2DM who may require increasing doses of exogenous insulin, surgery may allow the patient to come off all insulin or facilitate a significant dose reduction and simplification of the regimen from basal bolus to only requiring once daily insulin analogue therapy [Fenske *et al.* 2012].

Changes in blood pressure

Blood pressure improves in 73.2% of patients who are still losing weight after bariatric surgery, with Vest and colleagues showing a mean reduction of blood pressure from 140.2/87.6 to 129.6/80.2 mmHg [Vest *et al.* 2012]. When comparing gastric band with RYGB, Buchwald demonstrated an improvement in 71.5% compared with 87.1% during or immediately after weight loss [Buchwald *et al.* 2004]. In a separate meta-analysis by Sarkhosh and colleagues, improvements in blood pressure were seen in 75% of patients who had VSG whilst they were in a negative energy balance [Sarkhosh *et al.* 2012]. A similar improvement in blood pressure is seen with the duodenal–jejunal bypass liner [Escalona *et al.* 2012]. However, blood pressure may often increase back to preoperative levels even if weight loss is maintained [Sjöström, 2004]. The mechanisms for improved blood pressure are multifactorial and may be associated with weight loss, reduced systemic inflammation, increased urinary sodium loss and restoration of metabolic homeostasis. Operations such as the RYGB may have additional urinary sodium excretion effects, which may result in longer-term superior blood pressure improvements compared with gastric banding [Hallersund *et al.* 2012]. It is common for drugs such as angiotensin-converting enzyme inhibitors (ACEis) to be stopped after surgery. This may not be as helpful as just reducing the dose and combining it with surgery in order for resistant hypertension to be addressed. Low doses of ACEi also appear to have benefits beyond the blood pressure reduction effect [Yusuf *et al.* 2000].

Changes in lipid profile

Following surgery, serum total cholesterol, triglycerides and low-density lipid (LDL) decrease while high-density lipid increases [Vest *et al.* 2012]. Taken together with improvements in T2DM and blood pressure, the Framingham risk score for cardiac events improves [Vest *et al.* 2012]. Serum total cholesterol and triglycerides improve in patients with gastric band and RYGB [Buchwald *et al.* 2004]. In a small study comparing VSG and RYGB, there was a significant reduction in total cholesterol and LDL cholesterol at 1 year for patients who had RYGB but not VSG [Vix *et al.* 2012]. The initial changes in lipid profile seen in patients who had RYGB and not VSG may be due to changes in serum bile levels causing the alteration of cholesterol metabolism via modulation of nuclear transcription [Makishima *et al.* 1999]. Similar improvement in lipid profile is seen with the duodenal–jejunal bypass liner; however, the mechanism of action is not yet well understood [Escalona *et al.* 2012]. Although surgery often improves the lipid profile there is no clear rationale for stopping statins in patients with T2DM, especially as the effects of statins can be potentiated by surgery, thus resulting in much improved lipid profiles that may even result in a reversal of atherosclerotic plaque [Puri *et al.* 2013].

Changes in inflammation and changes in end-organ damage

The metabolic syndrome is partly driven by inflammation, which in turn is associated with end-organ damage. As patients lose weight after bariatric surgery, improvements in insulin resistance appear to correlate with improved C-reactive protein and tumour necrosis factor α [Kopp *et al.* 2003]. At 1-year follow up after bariatric surgery, serum inflammatory markers improve with reduction in

urinary and serum cytokine levels along with improved serum cystatin C levels, indicating improved renal function [Fenske *et al.* 2013]. In other studies, marked improvements in urinary sodium excretion [Hallersund *et al.* 2012] and a reduction in urinary markers of renal inflammation occur [Patle *et al.* 2012], suggesting the presence of a gut–renal axis controlling excretory function and regulating inflammation.

The development of T2DM in patients with a high percentage of body fat is often related to chronic low-grade inflammation in visceral fat [Brunetti, 2007]. Patients who develop metabolic syndrome show more low-grade chronic inflammation in their visceral adipose tissue compared with those that do not [Gauthier and Ruderman, 2010]. The oxidative stress that results from this inflammation contributes to cellular dysfunction in β-islet cells and endothelial cells.

T2DM is a systemic disease and the subsequent end-organ damage is the major cause of morbidity and mortality. Diabetic kidney disease is a result of microvascular damage to the renal glomeruli and appears for most parts to be progressive. After bariatric surgery, an improvement in kidney damage can be demonstrated with improved microalbuminuria [Miras *et al.* 2012a] and albuminuria [Iaconelli *et al.* 2011]. Halting the process of end-organ damage is vital in treating diabetes.

Combining medicine and surgery

It seems that the higher the risk of bariatric surgical procedures, the greater the improvement in comorbidities [Buchwald *et al.* 2004; Sjöström *et al.* 2007]. RYGB has fewer risks than biliopancreatic diversion and is thought to have better weight loss and metabolic improvements than adjustable gastric banding. It is hoped that newer less invasive procedures such as the duodenal–jejunal liners may help those patients with T2DM who are either not fit enough for bariatric surgery or who do not want bariatric surgery. Additionally, preoperative optimization with best medical treatment may result in better postoperative outcome [Frisch *et al.* 2010]. Currently, surgery is often proposed instead of current optimal medicine, but a subtle shift to promote surgery as adjunct therapy together with medical therapy may yield far superior results than the two modalities alone. Unsurprising, a multimodal approach to treating T2DM yields better results [Gaede *et al.* 2003]. Surgery as an add-on therapy to existing medicine could therefore be considered to be the optimal treatment for patients with T2DM and morbid obesity.

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