

Durable Remission of Diabetes After Bariatric Surgery: What Is the Underlying Pathway?

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ABSTRACT

Background: In the past, type 2 diabetes mellitus (DM) was regarded as a progressive, incurable disease for which palliative therapy could not, over the long term, prevent the associated amputations, blindness, renal failure, and early mortality. This is no longer true. Full and durable remission of type 2 DM, with major decreases in morbidity and mortality, is now achieved regularly with several types of surgery that reduce contact between food and the foregut.

Objectives: The aims of this article are to review the impact of bariatric surgery on obesity, remission of DM, and obesity-related morbidity and mortality, and the possible mechanisms for this advance.

Methods: This article is based on our 2 meta-analyses of the literature published through April 30, 2006, as well as the most significant reports in the bariatric surgical literature that have been published in English since April 30, 2006. The studies included in our second meta-analysis provided the details of the methodology for the present literature review, including the levels of evidence.

Results: Results of our 2 meta-analyses were published previously. Briefly, the analyses revealed that the clinical and laboratory manifestations of type 2 DM resolved or improved in most of the patients who underwent bariatric surgery; the responses were greatest in the patients who lost the most excess body weight; and the improvements were maintained for ≥ 2 years. The studies reported that intestinal operations such as gastric bypass reduced contact between food and the foregut, produced full and durable remission of DM, reduced mortality, and reversed other comorbidities associated with severe obesity (eg, asthma, gastroesophageal reflux, hypertension, stress incontinence). Insulin levels decreased markedly after surgery, as did glycosylated hemoglobin (A1C) and fasting blood glucose levels. Although these effects were initially attributed to weight loss, the rapid reversal of DM within a matter of days after surgery suggest that bariatric surgery changes the signaling mechanism of the gut with pancreatic islet cells, muscles, fat, the liver, and other organs.

Conclusions: Bariatric surgery has opened new vistas, producing durable full remission of type 2 DM—a breakthrough previously considered impossible—with normalization of A1C levels over time and discontinuation of all antidiabetes medication for many patients. These advances create new opportunities for exploring the mechanisms of type 2 DM and its control through pharmaceutical approaches. DM is no longer an irreversible, incurable, or hopeless disease. (*Insulin*. 2010;5:46–55) © 2010 Excerpta Medica Inc.

Key words: diabetes, bariatric surgery, gastric bypass, obesity, gastric banding, biliopancreatic diversion.

INTRODUCTION

Type 2 diabetes mellitus (DM) has become a worldwide epidemic with overwhelming human, social, and economic burdens. According to the Centers for Disease Control and Prevention (CDC),¹ in the United States, the number of adults with DM has tripled since 1980, resulting in ~71,000 lower-limb amputations unrelated to trauma in 2004 and making DM the leading cause of nontraumatic lower-limb amputations. In 2005, DM was the leading cause of kidney failure, accounting for 44% of new cases. Furthermore, ~180,000 people in the United States and Puerto Rico required chronic dialysis or needed a kidney transplant because of end-stage kidney disease related to

DM. In 2007, in the United States, 23.5 million people aged ≥ 20 years (10.7% of this population) were estimated to have diagnosed or undiagnosed DM—with 1.6 million new cases reported in this group that year. DM is also the leading cause of retinopathy, resulting in 12,000 to 24,000 new cases of blindness each year in adults 20 to 74 years of age.

Despite the availability of various antidiabetes medications, preventive care practices, and widespread educational programs that emphasize diet, exercise, and behavioral modification, DM remains one of the 4 most expensive diseases in the United States.² The total cost of DM in 2007 was \$174 billion (USD; \$116 billion direct medical costs and \$58 billion indirect costs [ie, disability, work loss, premature

mortality)). DM also costs lives. According to death certificate reports in the United States, DM was the seventh leading cause of death in 2006, even though it is likely to be underreported as the underlying cause of death.¹ Furthermore, the risk of death among patients with DM is about twice that of people of similar age without DM.¹

DM and its complications are not limited to the United States. The disease can be found in almost every population in the world. According to the International Diabetes Federation,³ DM is expected to cause close to 4 million deaths worldwide in people aged 20 to 79 years in 2010, representing 6.8% of total global mortality and rivaling the mortality rates for several infectious diseases (eg, HIV/AIDS). In addition, 70% of the 285 million people with DM live in low- and middle-income countries³; whether this can be attributed to increased urbanization, westernization, and economic development in developing countries, as many maintain, is not clear. Data regarding the epidemiology and cost of type 2 DM in the United States change almost daily; for the most current information, readers are referred to 2 CDC Web sites.^{1,4}

The discovery in 1980 that gastric bypass induces complete and durable remission of type 2 DM in a matter of days was initially so startling that we did not report it for 2 years, until we had sufficient numbers of cases to be certain that this observation was correct.⁵ Our fifth patient, for example, was a severely obese woman who was admitted on the day of surgery with a blood glucose level of 495 mg/dL despite administration of 90 units of insulin earlier that day. We operated on the patient with an infusion of insulin. On the day after surgery, her insulin requirement decreased to 8 units. Six days after surgery (the last day she required insulin), she was discharged without any antidiabetes medication. We (and practitioners in most major hospitals) now see such results routinely. In our practice, we have followed patients for >20 years after their gastric bypass; they are still euglycemic and off all antidiabetes medication, without evidence of retinal, renal, or peripheral vascular pathology.

This article reviews the impact of bariatric surgery on obesity, remission of DM, and obesity-related morbidity and mortality, and the possible mechanisms for this advance.

METHODS

This article is based on our 2 meta-analyses of the literature published through April 30, 2006,^{6,7} as well as the most significant reports in the bariatric surgical literature that have been published in English since April 30, 2006. The studies included in our second meta-analysis provided the details of the methodology for the present literature review, including the levels of evidence. In addition, because this is such a rapidly exploding field, we have incorporated our extensive personal experience in bariatric surgery, as well as information from recent international meetings in Rome and New York.⁸⁻¹⁰

RESULTS

Detailed results of our 2 meta-analyses^{6,7} were published previously. The latter meta-analysis⁷ included 621 studies

with 888 treatment arms and 135,246 patients; 103 treatment arms with 3188 patients reported on the resolution of the clinical and laboratory manifestations of DM. Nineteen studies, including 43 treatment arms and 11,175 patients, reported both weight loss and DM resolution separately for the 4070 patients with DM. Mean weight loss was 38.5 kg, or 55.9% excess body weight loss. Overall, 78.1% of patients with DM had complete resolution, and DM was improved or resolved in 86.6% of patients. Weight loss and DM resolution were greatest for patients undergoing biliopancreatic diversion/duodenal switch, followed by gastric bypass; responses were lowest with banding procedures.

Intestinal operations such as gastric bypass reduced contact between food and the foregut, produced full and durable remission of DM, reduced mortality, and reversed other comorbidities associated with severe obesity (eg, asthma, gastroesophageal reflux, hypertension, stress incontinence). Insulin levels decreased markedly after surgery, as did glycosylated hemoglobin (A1C) and fasting blood glucose levels. Although these effects were initially attributed to weight loss, the rapid reversal of DM within a matter of days after surgery suggested that bariatric surgery changes the signaling mechanism of the gut with pancreatic islet cells, muscles, fat, the liver, and other organs.

Bariatric Surgery: Effects on Obesity

The Greenville version of the Roux-en-Y gastric bypass (RYGB) (**Figure 1**) was created in 1978 as an adaptation of the procedure developed in 1967 by Mason and Ito¹¹ to produce weight loss in severely obese patients. The procedure consisted of a gastric partition drained by a loop gastroenterostomy with the proximal duodenum. We found that this operation, which is no longer used, led to biliary reflux into the stomach and esophagus. We therefore added a Roux-en-Y limb to produce unidirectional flow out of the gastric pouch, which we also reduced sharply in size.¹² The Greenville version of the RYGB, now widely adopted throughout the world but modified in the length of the jejunal limb, is designed to limit food intake to the 30-mL proximal gastric pouch, delay emptying of that pouch with a 10-mm gastroenterostomy, and interfere with digestion through the exclusion of the remaining stomach, duodenum, and 60- to 150-cm jejunal limbs beyond the ligament of Treitz. Although we independently developed this procedure, Griffen et al¹³ reported use of the Roux-en-Y modification 2 years before we did.

The gastric bypass is not the only effective operation that has been developed to produce weight loss in severely obese individuals. **Figure 2** includes drawings of 4 other bariatric operations currently being performed. The adjustable gastric band was designed to only interfere with food intake,¹⁴ whereas the gastric bypass, the gastric sleeve,¹⁵ and the duodenal switch not only limit food intake but also interfere with digestion by excluding part of the gut and mixing food with biliopancreatic secretions more distally.¹⁶ The duodenojejunal bypass differs from the other procedures by pre-

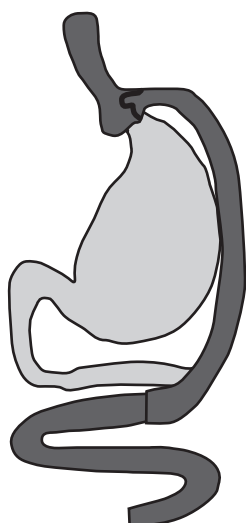


Figure 1. The Greenville gastric bypass. This procedure, an adaptation of the procedure developed by Mason and Ito,¹¹ creates a proximal pouch about 30 mL in size by segmentation of the stomach with staples. The pouch is drained by a Roux-en-Y created by dividing the proximal jejunum about 30 cm below the ligament of Treitz.

servicing the volume of the stomach and, allegedly, permitting a full and unrestricted diet.¹⁷

Access to a variety of procedures has helped considerably in our understanding of their potential mechanisms of action. However, except for the adjustable gastric band, bariatric operations have not been standardized. For example,

the gastric bypass, performed by surgeons around the world, can vary in terms of pouch size, orientation of the pouch (vertical vs horizontal), partition versus division of the stomach, size of the gastrojejunostomy, use of a “Fobi band”¹⁸ (GaBP Ring AutoLock™ System, Bente Medical Products, Woodland, California), techniques used for anastomosis (circular vs linear staples vs hand sewn), length of the biliary limb, length of the alimentary limb, antecolic versus retrocolic location of the Roux-en-Y limb, methods used to create the jejunajejunostomy (stapled vs hand sewn), size of the jejunajejunostomy, and use of an open versus a laparoscopic approach for the procedure. Accordingly, >1000 operations have been referred to as a “gastric bypass”; the wide variety of procedures should soon allow us to determine the best approaches, but also will limit our comparisons and interpretations of results across studies.

The number of bariatric operations performed in the United States is not known, but was estimated by the ASMBS to be >200,000 in 2007 and >220,000 in 2008 (personal communication with Georgeann Malloray, Executive Director of ASMBS, fall 2009). Of these, ~100,000 were performed in 364 Centers of Excellence certified by the ASMBS or the American College of Surgery (personal communication with Gary Pratt, President of the Surgical Review Corporation, which manages the ASMBS program, fall 2009). This effort at quality control has produced significant improvement in outcomes with a sharp reduction in complications. Among the patients who have undergone bariatric surgery in ASMBS-certified hospitals, the operative and 90-day mortality rates were 0.14% and 0.35%, respectively,¹⁹ similar to rates that have been reported for cholecystectomy,^{19,20} despite the fact that these patients are burdened by multiple comorbidities and represent major operative risks preceding the operation.

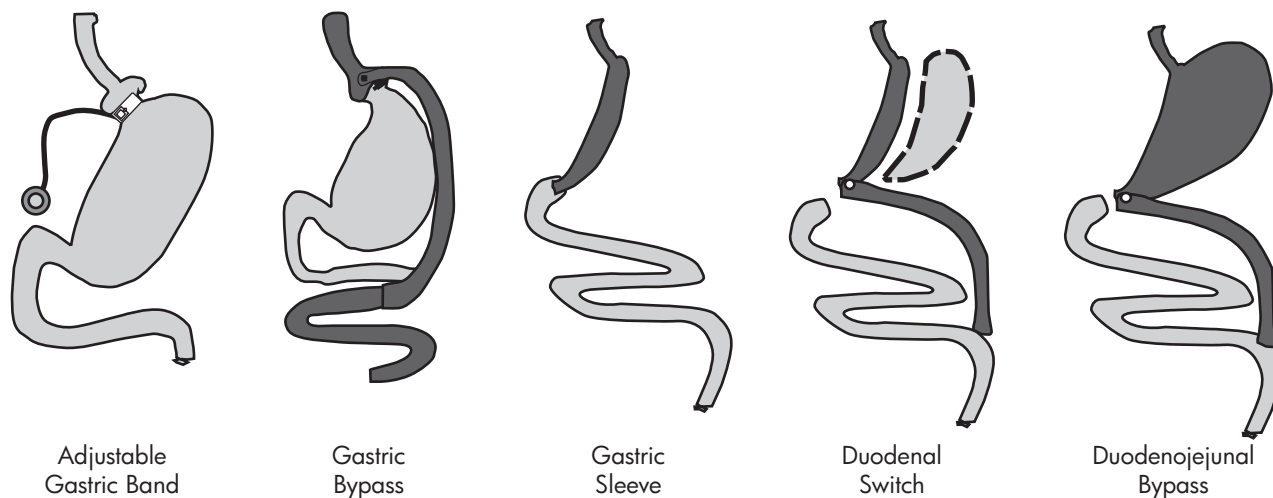


Figure 2. Comparison of the 5 bariatric operations currently being performed for type 2 diabetes mellitus.

Bariatric surgery is currently the only effective treatment for severe obesity that produces long-lasting weight loss.²¹⁻²³ In 1995, our study of 608 morbidly obese patients who were followed for up to 16 years (follow-up rate, 95%) reported that gastric bypass resulted in a durable mean weight loss of 106 lb (48.2 kg), from 317 to 211 lb (144.1–95.9 kg).^{12,24} In 2003, this result was confirmed by Schauer et al,²⁵ who reported a mean weight loss of 97 lb and mean excess weight loss of 60%.

Weight loss varies according to the operation performed and the patient's age, sex, physical activity, maintenance of vitamin/mineral supplementation, race, and possibly other factors. In general, weight loss is greatest with biliopancreatic bypass and least with gastric banding. Also in general, females tend to lose more weight than do males, younger individuals lose more than do their older counterparts, patients who exercise and maintain good nutrition lose more than do those who do not, and white patients tend to lose more weight than do black patients. Again, these are impressions; to our knowledge, no reliable data exist regarding the effects of age, sex, or race on the different bariatric procedures.

We conducted a meta-analysis⁶ of 136 studies (22,094 patients) that used the 3 most frequently performed operations: gastric banding, gastric bypass, and the duodenal switch. The mean percentage of excess weight loss was 47.5%, 61.6%, and 70.1%, respectively; and the operative mortality rate was 0.1%, 0.5%, and 1.1%, respectively. These 2004 figures should be considered in context, however. Operative and 90-day mortality rates for these procedures have decreased dramatically over the past 5 years.

Similarly, and again this is a generalization, the safest procedure in terms of mortality, complications, and long-term nutritional deficits appear to be gastric banding, followed by gastric bypass. Biliopancreatic bypass appears to be associated with the most complications.^{6,7} In terms of resolution of comorbidities, the biliopancreatic procedure produces the highest levels of resolution, whereas gastric banding produces the lowest levels. Unfortunately, banding procedures have the highest failure rates, requiring revision or conversion to other procedures in 5% of cases per year.

In short, no bariatric operation is perfect. However, based on the studies included in our meta-analyses^{6,7} and personal communications, it appears that bariatric surgeons around the world favor the gastric bypass by far over the other choices because of its excellent results, safety profile, and low rate of short- and long-term complications.

Gastric Bypass: Unexpected Remission of DM

To our knowledge, the first glimpse of a permanent treatment for DM was seen by our group in 1980, when we were surprised to find full and rapid remission of DM in patients within days after undergoing the Greenville gastric bypass.²⁶ Instead of an increased need for insulin to cover the stress of surgery, patients returned to euglycemia and normal levels of insulin before they left the hospital; 4 of every 5 patients were able to go home without any antidiabetes medication.

The long-term outcomes of 608 severely obese patients who underwent gastric bypass are presented in the **table**.¹² These patients were followed for up to 16 years (follow-up rate, 95%; mean duration of follow-up, 9.4 years).²⁷ The group included 165 patients with DM (27%) and 165 patients with impaired glucose tolerance (27%). After a minimum of 6 months of follow-up, of the 146 evaluated patients with DM, 121 (83%) maintained full remission. Of the 152 evaluated patients with impaired glucose tolerance, 150 (99%) returned to normal glucose levels. In a 5-year study of 1160 patients, Schauer et al²⁵ also reported an 83% remission rate for patients with DM after gastric bypass surgery. Finally, our meta-analysis⁶ found complete resolution of DM in 76.8% of patients and partial resolution or improvement in 86.0% of patients. This meta-analysis also reported resolution of DM in 48% of patients after laparoscopic gastric banding, in 84% of patients after RYGB, and in >95% of patients after biliopancreatic bypass or duodenal switch.

Table. Full and durable remission of type 2 diabetes mellitus (DM) in 608 patients after gastric bypass surgery (follow-up, 6 months–16 years).¹²

	Type 2 DM	Impaired Glucose Tolerance
Total no. of patients	165	165
No. of patients evaluated	146	152
Resolution of type 2 DM	121 (83%)	150 (99%)

Dixon et al²⁸ recently reported better outcomes with gastric banding. Of the 60 enrolled patients who were randomized to surgery (n = 30) or to conventional treatment (n = 30), 55 (92%) completed the 2-year follow-up. Remission of DM was achieved in 22 patients (73%) in the surgical group and in 4 patients (13%) in the conventional-therapy group ($P < 0.001$). The relative risk (RR) of remission for the surgical group was 5.5 (95% CI, 2.2–14.0). The mean (SD) weight loss was 20.7% (8.6%) in the surgical group and 1.7% (5.2%) in the conventional-therapy group at 2 years ($P < 0.001$). Remission of DM was related to weight loss ($R^2 = 0.46$, $P < 0.001$) and lower baseline A1C levels (combined $R^2 = 0.52$, $P < 0.001$). No serious complications were reported in either group.

Gastric Bypass: Effects on Morbidity and Mortality of Severely Obese Patients

Bariatric surgery does not merely normalize glucose levels. The intervention has been found to correct lipid abnormalities²⁹ and pulmonary function³⁰; reduce fatty infiltration³¹ in the heart, liver, and muscle; stabilize intracranial pressure in cases of pseudotumor cerebri³²; decrease intra-abdominal

pressure, with reversal of urinary stress incontinence^{33,34}, alleviate the endocrine abnormalities associated with obesity, with return to normal menses, fertility, and improvement of polycystic ovary disease^{35,36}; and reduce DM-related mortality.²⁷ MacDonald et al²⁷ retrospectively compared our group of 154 morbidly obese patients with DM who underwent a gastric bypass and a group of 78 patients who were scheduled for bypass surgery but did not undergo the procedure. The 2 groups were not randomized but were well matched, with no significant differences in age, sex, weight, body mass index (BMI), or comorbidities. The mortality rate was 9% (14 of 154 patients over a mean follow-up period of 9 years, or 1% per year) in the surgical group and 28% (22 of 78 patients over a mean follow-up period of 6.2 years, or 4.5% per year) in the control group ($P < 0.0003$). Similar reductions in the mortality rate of severely obese patients (with or without DM) after bariatric surgery have been reported by Sjöström et al³⁷ and Adams et al.³⁸ An observational study by Christou et al,³⁹ also in patients with or without DM, revealed substantial risk reductions for development of cardiovascular disorders and cancer, as well as reductions in endocrine, infectious, psychiatric, and mental disorders among patients who underwent bariatric surgery compared with controls who did not undergo surgery. A 78% reduction in the incidence of cancer was reported in the gastric bypass patients compared with the controls, with an 89% reduction in the RR of death over 5 years.

Weight Loss and Reduced Intake Alone Are Not Responsible for Remission of DM

Initially, remission of DM after gastric bypass was attributed to weight loss and decreased food intake. That was a logical conclusion, because 2 fundamental elements of the medical management of DM are weight loss and dietary restriction. Patients who underwent gastric bypass surgery lost weight, and in the first 3 days after surgery, they were restricted to 30 mL of a high-protein supplement every 4 hours, supplemented by water. These conclusions were challenged, however, after further consideration. Compared with diabetic patients who develop hyperglycemia and need additional insulin during the postoperative period for other operations (eg, colectomies), most patients who underwent bariatric surgery returned to euglycemia in a matter of days and left the hospital without any antidiabetes medication.¹²

More convincing was the return to full euglycemia before substantial weight loss occurred and the maintenance of normal plasma glucose and A1C levels even when patients returned to a normal diet and, although no longer severely obese, generally continued to be obese or overweight. In our 16-year study of 608 morbidly obese patients,¹² the mean weight dropped from 317 lb (144.0 kg) to 211 lb (95.9 kg),²⁷ which was still considered obese. However, these data must be interpreted with caution. We do not know whether these patients maintained their obesity by eating more than normal individuals with smaller meals or whether there were profound differences in the utilization of food. The litera-

ture, including animal studies, remains confusing. However, DM did not return in 4 of every 5 individuals.

The study by Dixon et al²⁸ also confirmed the role of the gut. The effect of gastric banding, in contrast to that of gastric bypass, is related solely to a reduction in food intake. The patients progressed from an early postoperative euglycemia rate of ~40% to 73% after 3 years, and the investigator deduced that the improvement over time was related to weight loss.

Whether there is really a direct cause-and-effect relationship between obesity and DM also must be considered. It is true that obesity is a well-known risk factor for DM and improves in patients with hyperglycemia, insulin resistance, and hyperinsulinemia when weight-loss and exercise programs are implemented successfully.⁴⁰ However, it is also true that 10% of patients with DM are lean, and only ~33% of the severely obese patients in our practice have DM.

Based on these data, it is appropriate to conclude that although DM and obesity are related, it is not a cause-and-effect relationship. Another conclusion might be that DM is not just a single disease with multiple variations. This is not a new idea, but one that the response to bariatric surgery might help us dissect in the future.

Is Remission of DM Related to Weight Loss or to Bypassing the Gut?

Whether the remission of DM after bariatric surgery is due solely to weight loss or whether the gut also plays a role remains a contentious issue. It is an important question. If exclusion of a section of the gut can produce remission, then it follows that the foregut is involved in the pathogenesis of the disease and that an understanding of the role of the gut could lead to new approaches to the treatment of this expensive disease.

Those who claim that the effect of bariatric surgery is due solely to weight loss cite the classic response of diabetic patients to dietary regimens. They also cite the 40% to 60% rate of DM remission after gastric banding,²⁸ an operation designed to reduce food intake. Others, however, argue that the higher remission rate after gastric bypass (83%)^{25,27} and biliopancreatic bypass or duodenal switch (>95%),⁶ 2 operations that prevent contact between food and the foregut, clearly suggests that the gut plays a role. It has also been suggested that, with gastric banding, gastric bypass, and the duodenal switch, the rate of remission after exclusion of the gut is related to the degree of reduction of contact between food and the gut.

These recent studies in animals and humans support the hypothesis that the gut plays a critical role in the remission of DM. Rubino and Marescaux⁴¹ performed a series of 3 experiments in Goto-Kakizaki rats, a lean animal model of DM (Figure 3). The first experiment revealed that an operation in which the stomach was spared permitted normal food intake but excluded food from the duodenum and upper jejunum and induced full remission of DM without weight loss. In the second experiment, the investigators

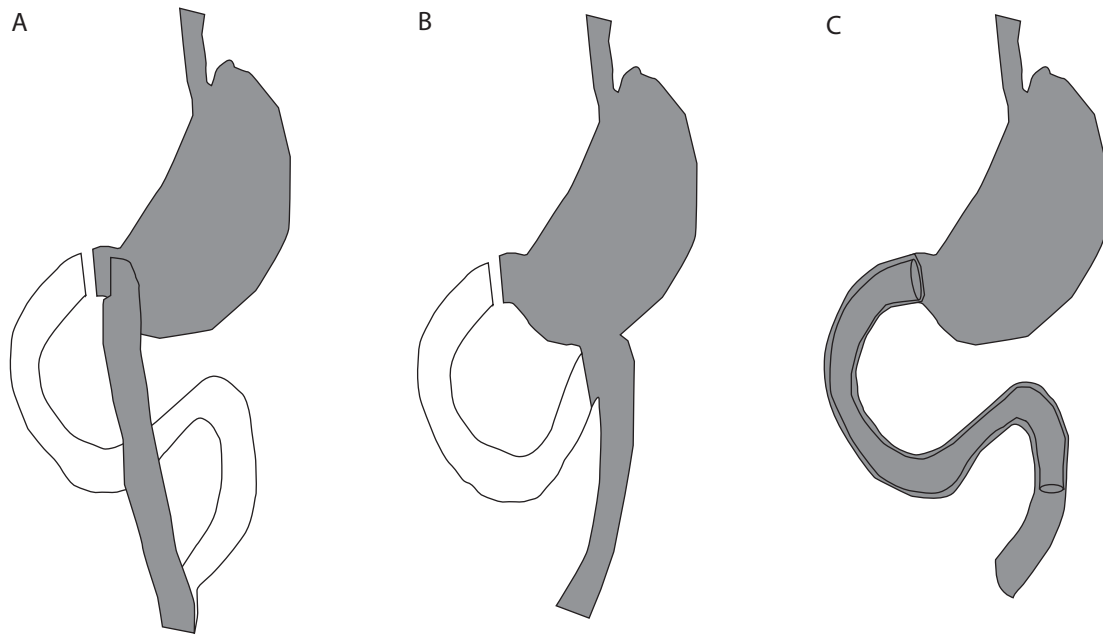


Figure 3. The 3 classic experiments performed by Rubino and Marescaux⁴¹ in the spontaneous nonobese animal model of type 2 diabetes mellitus. (A) Stomach-sparing duodenojejunal bypass. (B) Gastroenterostomy with division of the pylorus, preventing food from entering the duodenum. (C) Silastic® (Dow Corning Corporation, Midland, Michigan) sleeves placed in the duodenum and jejunum, preventing contact between food and the mucosa. Euglycemia was restored in all 3 experiments without any weight loss.

reported that a gastroenterostomy that allowed food to flow in 2 directions did not reduce hyperglycemia. However, when the pylorus was divided to exclude the duodenum and upper jejunum, the rats became euglycemic. The third experiment involved lining the duodenum and upper jejunum with Silastic® (Dow Corning Corporation, Midland, Michigan) sleeves, which prevented contact between food and the mucosa and restored euglycemia. When the sleeves were perforated to restore food–mucosa contact, DM returned. The findings of these investigators and others⁴² led to disagreements regarding whether the DM remission was related to the exclusion of food from the foregut or to the dumping of undigested food into the “hindgut.” Those disagreements have subsided with the recognition that both effects are probable and that the gut is much more likely a continuum with varying degrees of response along its tract rather than 2 separate organs.

The study conducted by Rubino and Marescaux⁴¹ led to 3 clinical trials in Mexico, Brazil, and India that examined the effects of a “Rubino Procedure,” known as the duodenal-jejunal bypass (DJB), a stomach-sparing exclusion of the duodenum and upper jejunum in lean patients with DM. The first study, conducted in Mexico by Arguelles et al (personal communication with J.A. Arguelles, fall 2009), was not well controlled, but 5 patients appeared to experience resolution of DM without weight loss. The 2 other studies

were performed using clearly defined prospective protocols. In Brazil, Cohen et al⁴³ initially reported full remission in 2 overweight patients with DM after undergoing the DJB procedure. The patients had normal plasma glucose and A1C levels after the procedure without significant changes in body weight or BMI. A current study by these investigators, which now includes >40 patients (some of whom are lean), has confirmed these early results, but the findings from this study have not yet been published (personal communication with A.R. Ramos, fall 2008). Similarly, in India, Lakdawalla et al reported 3 well-studied lean patients whose DM appeared to resolve fully after undergoing the DJB (personal communication with M.A. Lakdawalla, fall 2008). Cohen et al and Lakdawalla et al reported larger studies at a surgical meeting in 2007,⁸ but these results have not yet been reported in the literature. RYGB and biliopancreatic bypass have also been reported to resolve DM in nonobese patients.^{44–46}

The Role of the Intestine

Early studies reported that exclusion of part of the foregut produced remission of DM even in lean animals and humans.^{44–46} Therefore, it would seem reasonable to conclude that the gastrointestinal tract plays a critical role in glucose homeostasis and insulin action. That role may be best expressed through neuroendocrine cells in the crypts,

which may communicate through paracrine and endocrine hormones secreted into the portal circulation, as well as neural signals communicating through parasympathetic, sympathetic, and vagal fibers. The gut hormones, also known as incretins because of their stimulation of insulin secretion, are under vigorous investigation. However, the major focus is currently on glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide (GIP), ghrelin, and peptide YY3–36.⁴⁷ Also under investigation are hormones from the adipocytes, including leptin and adiponectin.⁴⁸ The list will certainly grow larger in the next few years.

The recognition of GLP-1 has already affected the medical treatment of DM, with exenatide,* a GLP-1 analogue (39-amino-acid peptide, insulin secretagogue) with glucoregulatory effects that is now in clinical use for patients whose DM is not well controlled on other oral medications.⁴⁷ Exenatide enhances glucose-dependent insulin secretion via the pancreatic β -cells, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying, although the mechanism of action remains unclear. This agent is injected subcutaneously twice daily using a pre-filled pen device. GIP⁴⁹ and GLP-1 are known incretins, which promote β -cell growth, enhance glucose-stimulated insulin secretion, and improve insulin action.^{50–52}

In a study of obese patients with a BMI ≥ 35 kg/m², conducted by Laferrère et al,⁵³ 9 women with DM, who were examined before and 1 month after gastric bypass surgery, were compared with 10 matched controls before and after they achieved an equivalent amount of diet-induced weight loss. The study revealed that total GLP-1 levels after oral glucose increased 6 times and the incretin effect increased 5 times. According to the investigators, “The data suggest that the greater GLP-1 and GIP release and improvement in incretin effect are related not to weight loss but rather to the surgical procedure.”

It is also possible that the abnormalities seen in DM may not be caused by incretins, but might instead be due to “anti-incretins,” signals that interfere with insulin action and glucose metabolism at the cellular level, especially in muscle mitochondria, small organelles that are hampered by the accumulation of fat in patients with DM.⁵² In fact, the pathophysiology of DM may involve an inappropriate balance of both incretins and anti-incretins related to increased production of anti-incretins on stimulation of the gut mucosa by the passage of food. The anti-incretin factor has not been clearly determined, but continued research on the duodenum and proximal jejunum may elucidate potential causes of DM.

In all likelihood, there are multiple unidentified gut and peripherally secreted peptides that regulate upward and downward the metabolic pathways that lead to DM. One gut signal may overstimulate pancreatic β -cells and cause insulin resistance at the mitochondrial level in muscle, concurrently

causing the liver to induce excessive gluconeogenesis, producing hyperglycemia and end-organ damage over time.

A New Horizon for Research

How can these exciting findings be applied to clinical practice? The current guidelines adopted by Medicare and most insurance carriers seem appropriate at this time. Currently, bariatric surgery is indicated for patients who:

- have a BMI ≥ 40 kg/m² or a BMI ≥ 35 kg/m² with substantial comorbidities;
- fully understand the selected operation and its short- and long-term outcomes;
- agree to long-term follow-up;
- do not have unresolved emotional problems, including substance abuse or alcoholism;
- are 18 to 65 years of age.

However, several serious challenges are associated with these guidelines. There is increasing evidence that patients with DM and a BMI ≥ 30 kg/m² should also be considered candidates for bariatric surgery, especially Asian and black Americans, who have levels of comorbidity at a BMI of 32 kg/m² similar to those of white Americans with a BMI of 35 kg/m². Several ongoing studies have been designed to determine whether bariatric surgery is an appropriate therapy for severely obese children and adolescents, a group for whom no other satisfactory treatments exist. Finally, given the seriousness of DM, sleep apnea, polycystic ovary disease, and other comorbidities, is the BMI an appropriate measure for determining suitability of bariatric surgery?

Six operations have been shown to produce full remission of type 2 DM with varying degrees of success. The first 3 are: the adjustable gastric band (45% success, with claims up to 70% after 3 years of weight loss), gastric bypass (84%), and biliopancreatic bypass with duodenal switch (>95%).^{6,7} Data regarding the remaining 3 procedures (ie, the gastric sleeve, duodenojejunal bypass, and ileal transposition) are still fragmentary. Each of the procedures provides not only excellent, ethical models for studying DM, but also opportunities to explore the mechanisms of action and new approaches to the treatment of previously resistant diseases such as sleep apnea, asthma, cardiac failure, cirrhosis, and immune suppression. The choice of operation is also not well defined, but there seems to be increasing agreement that patients with significant comorbidities fare better with the gastric bypass or the duodenal switch. Among the restrictive procedures, the gastric sleeve, with its removal of the ghrelin-producing fundus and no need for insertion of a foreign body or adjustments, is gradually gaining popularity over gastric banding.

The bariatric procedures cause a still poorly understood triad of effects that interplay in the resolution of DM: dietary changes, weight loss, and exclusion of the gut. Little is known about the intake and utilization of food after surgery. Weight loss is a known component of DM management, but the surgical patients experience antidiabetes effects long before any weight loss occurs. DM resolution has also been reported

*Trademark: Byetta® (Eli Lilly and Company, Indianapolis, Indiana).

in lean patients who have undergone gastric bypass surgery and maintained stable weight.⁵⁴

Gut exclusion appears to be a major factor in DM resolution in obese and lean patients. The exact mechanism for this result is unclear, but molecular signaling from the gut via the portal system to the liver and pancreas appears to regulate insulin and glucose levels responsible for the disease. Other unknown factors include the roles of the brain and nervous system, especially parasympathetic and sympathetic nerves; the role of nutrient exposures at different levels of the gut; the interactions between the upper and lower gut (the foregut/hindgut controversy is named inappropriately, because the entire small bowel is part of the foregut); changes in bacterial flora; and viral and other ecologic causes of DM. It is time for diabetologists, surgeons, and other investigators to join forces, to consider exploration of the role of the gut in chronic disease, and to undertake the badly needed prospective, randomized, national studies comparing medical and surgical therapies.

It is impossible for the millions of people with DM worldwide to receive surgery to “cure” their illness. Therefore, it is necessary to uncover the responsible pathways to establish medically effective therapy to reduce the personal suffering and economic burden that grow with this epidemic.

The cost of bariatric surgery is now amortized in ~2 to 3 years.^{55,56} Even so, the application of this new approach remains to be defined. We are receiving an increasing number of requests for surgery from patients with DM and their

physicians, even though the patients do not meet the weight requirements. We even have patients who are trying to gain weight to become eligible for the procedures that will free them of the disease—at their own expense. It is time to reexamine the guidelines.

Perhaps the most exciting aspect of bariatric surgery is that it opens new and exciting horizons for research into DM, inflammatory diseases such as arthritis, and even cancer. We need research at all levels—molecular, pharmaceutical, clinical best practices, quality control, health care economics, and public policy. We surgeons need all the help we can get.

CONCLUSIONS

Bariatric surgery has opened new vistas, producing durable full remission of type 2 DM—a breakthrough previously considered impossible—with normalization of A1C levels over time and discontinuation of all antidiabetes medication for many patients. These advances create new opportunities for exploring the mechanisms of type 2 DM and its control through pharmaceutical approaches. DM is no longer an irreversible, incurable, or hopeless disease.

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REFERENCES

- Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2007. General Information. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed October 26, 2009.
- Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. WorkLife Initiative, June 2009. <http://www.cdc.gov/niosh/worklife/pdfs/worklifefsummary8.pdf>. Accessed October 27, 2009.
- International Diabetes Federation. Diabetes Atlas. Global Burden. <http://www.diabetesatlas.org/>. Accessed October 27, 2009.
- Centers for Disease Control and Prevention. Diabetes Data & Trends. <http://apps.nccd.cdc.gov/DDTSTRS/FactSheet.aspx>. Accessed October 26, 2009.
- Pories WJ, Flickinger EG, Meelheim D, et al. The effectiveness of gastric bypass over gastric partition in morbid obesity: Consequence of distal gastric and duodenal exclusion. *Ann Surg*. 1982;196:389–399.
- Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: A systematic review and meta-analysis [published correction appears in *JAMA*. 2005;293:1728]. *JAMA*. 2004;292:1724–1737.
- Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: Systematic review and meta-analysis. *Am J Med*. 2009;122:248–256.e5.
- New York-Presbyterian Hospital/Weill Cornell Medical Center/Weill Cornell Medical College. Diabetes Surgery Summit consensus lays foundation for new field of medicine (First International Conference on Gastrointestinal Surgery to Treat Type 2 Diabetes; Rome, Italy; March 29–31, 2007). <http://www.sciencedaily.com/releases/2009/11/091123193111.htm>. Accessed November 30, 2009.
- New York-Presbyterian Hospital/Weill Cornell Medical Center/Weill Cornell Medical College. Diabetes congress brings experts from around the world (First World Congress on Interventional Therapies for Type 2 Diabetes; New York, NY; September 15–16, 2008). http://weill.cornell.edu/deans/2008/09_22_08/article_01-09_22-2.shtml. Accessed November 30, 2009.
- Rubino F, Kaplan L, Schauer PR, Cummings DE, on behalf of the Diabetes Surgery Summit Delegates. The Diabetes Surgery Summit consensus conference: Recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. *Ann Surg*. November 23, 2009. http://journals.lww.com/annalsurgery/Abstract/publishahead/The_Diabetes_Surgery_Summit_Consensus_Conference_.99667.aspx. Accessed November 30, 2009.
- Mason EE, Ito C. Gastric bypass in obesity. 1967. *Obes Res*. 1996;4:316–319.
- Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg*. 1995;222:339–350; discussion 350–352.

13. Griffen WO Jr, Young VL, Stevenson CC. A prospective comparison of gastric and jejunoileal bypass procedures for morbid obesity. *Ann Surg.* 1977;186:500–509.
14. Gagner M, Steffen R, Biertho L, Horber F. Laparoscopic adjustable gastric banding with duodenal switch for morbid obesity: Technique and preliminary results. *Obes Surg.* 2003;13:444–449.
15. Gagner M, Deitel M, Kalberer TL, et al. The Second International Consensus Summit for Sleeve Gastrectomy, March 19–21, 2009. *Surg Obes Relat Dis.* 2009;5:476–485.
16. Hess DS, Hess DW, Oakley RS. The biliopancreatic diversion with the duodenal switch: Results beyond 10 years. *Obes Surg.* 2005;15:408–416.
17. Ramos AC, Galvao Neto MP, de Souza YM, et al. Laparoscopic duodenal-jejunal exclusion in the treatment of type 2 diabetes mellitus in patients with BMI <30 kg/m² (LBM). *Obes Surg.* 2009;19:307–312.
18. Fobi MA. Placement of the GaBP ring system in the banded gastric bypass operation. *Obes Surg.* 2005;15:1196–1201.
19. Pratt GM, McLees B, Pories WJ. The ASBS Bariatric Surgery Centers of Excellence program: A blueprint for quality improvement. *Surg Obes Relat Dis.* 2006;2:497–503.
20. Girard RM, Morin M. Open cholecystectomy: Its morbidity and mortality as a reference standard. *Can J Surg.* 1993;36:75–80.
21. US Department of Health and Human Services. National Institutes of Health. Bariatric surgery: Gastrointestinal surgery for severe obesity. NIH Publication No. 01-4006, December 2001. <http://www.lapsurgery.com/BARIATRIC%20SURGERY/NIH%20SURGERY%20FOR%20OBESITY.htm>. Accessed October 30, 2009.
22. Nguyen GC, Laveist TA, Segev DL, Thuluvath PJ. Race is a predictor of in-hospital mortality after cholecystectomy, especially in those with portal hypertension. *Clin Gastroenterol Hepatol.* 2008;6:1146–1154.
23. Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. *Am J Clin Nutr.* 1992;55(Suppl):615S–619S.
24. Hickey MS, Pories WJ, MacDonald KG Jr, et al. A new paradigm for type 2 diabetes mellitus: Could it be a disease of the foregut? *Ann Surg.* 1998;227:637–644.
25. Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en-Y gastric bypass on type 2 diabetes mellitus. *Ann Surg.* 2003;238:467–484.
26. Sinha MK, Pories WJ, Flickinger EG, et al. Insulin-receptor kinase activity of adipose tissue from morbidly obese humans with and without NIDDM. *Diabetes.* 1987;36:620–625.
27. MacDonald KG Jr, Long SD, Swanson MS, et al. The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg.* 1997;1:213–220.
28. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: A randomized controlled trial. *JAMA.* 2008;299:316–323.
29. Zambon S, Romanato G, Sartore G, et al. Bariatric surgery improves atherogenic LDL profile by triglyceride reduction. *Obes Surg.* 2009;19:190–195.
30. Nguyen NT, Hinojosa MW, Smith BR, et al. Improvement of restrictive and obstructive pulmonary mechanics following laparoscopic bariatric surgery. *Surg Endosc.* 2009;23:808–812.
31. Pillai AA, Rinella ME. Non-alcoholic fatty liver disease: Is bariatric surgery the answer? *Clin Liver Dis.* 2009;13:689–710.
32. Chandra V, Dutta S, Albanese CT, et al. Clinical resolution of severely symptomatic pseudotumor cerebri after gastric bypass in an adolescent. *Surg Obes Relat Dis.* 2007;3:198–200.
33. Varela JE, Hinojosa M, Nguyen N. Correlations between intra-abdominal pressure and obesity-related co-morbidities. *Surg Obes Relat Dis.* 2009;5:524–528.
34. Laungani RG, Seleno N, Carlin AM. Effect of laparoscopic gastric bypass surgery on urinary incontinence in morbidly obese women. *Surg Obes Relat Dis.* 2009;5:334–338.
35. Kral JG, Christou NV, Flum DR, et al. Medicare and bariatric surgery. *Surg Obes Relat Dis.* 2005;1:35–63.
36. Lara MD, Kothari SN, Sugerman HJ. Surgical management of obesity: A review of the evidence relating to the health benefits and risks. *Treat Endocrinol.* 2005;4:55–64.
37. Sjöström L, Narbro K, Sjöström CD, et al, for the Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med.* 2007;357:741–752.
38. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357:753–761.
39. Christou NV, Sampalis JS, Liberman M, et al. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg.* 2004;240:416–423.
40. American Diabetes Association. The American Diabetes Association (ADA) has been actively involved in the development and dissemination of diabetes care standards, guidelines, and related documents for many years. Introduction. *Diabetes Care.* 2009;32(Suppl 1):S1–S2.
41. Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: A new perspective for an old disease. *Ann Surg.* 2004;239:1–11.
42. de Campos Martins MV, Peixoto AA, Schanaider A, et al. Glucose tolerance in the proximal versus the distal small bowel in Wistar rats. *Obes Surg.* 2009;19:202–206.
43. Cohen RV, Schiavon CA, Pinheiro JS, et al. Duodenal-jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22–34 kg/m². A report of 2 cases. *Surg Obes Relat Dis.* 2007;3:195–197.
44. Noya G, Cossu ML, Coppola M, et al. Biliopancreatic diversion preserving the stomach and pylorus in the treatment of hypercholesterolemia and diabetes type II: Results in the first 10 cases. *Obes Surg.* 1998;8:67–72.
45. Cohen R, Pinheiro JS, Correa JL, Schiavon CA. Laparoscopic Roux-en-Y gastric bypass for BMI <35 kg/m²: A tailored approach. *Surg Obes Relat Dis.* 2006;2:401–404.
46. Castagneto M, De Gaetano A, Mingrone G, et al. A surgical option for familial chylomicronemia associated with insulin-resistant diabetes mellitus. *Obes Surg.* 1998;8:191–198.
47. Holst JJ, Lasalle JR. An overview of incretin hormones. *J Fam Pract.* 2008;57(Suppl 9):S4–S9.
48. Samaras K, Botelho NK, Chisholm DJ, Lord RV. Subcutaneous and visceral adipose tissue FTO gene expression and adiposity,

- insulin action, glucose metabolism, and inflammatory adipokines in type 2 diabetes mellitus and in health [published online ahead of print September 9, 2009]. *Obes Surg*.
49. Neumiller JJ. Differential chemistry (structure), mechanism of action, and pharmacology of GLP-1 receptor agonists and DPP-4 inhibitors. *J Am Pharm Assoc*. 2009;49(Suppl 1):S16–S29.
 50. Drucker DJ. The role of gut hormones in glucose homeostasis. *J Clin Invest*. 2007;117:24–32.
 51. Drucker DJ. Glucagon-like peptide-1 and the islet beta-cell: Augmentation of cell proliferation and inhibition of apoptosis. *Endocrinology*. 2003;144:5145–5148.
 52. Lynn FC, Pamir N, Ng EH, et al. Defective glucose-dependent insulinotropic polypeptide receptor expression in diabetic fatty Zucker rats. *Diabetes*. 2001;50:1004–1011.
 53. Laferrère B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2008;93:2479–2485.
 54. Rubino F. Is type 2 diabetes an operable intestinal disease? A provocative yet reasonable hypothesis. *Diabetes Care*. 2008;31(Suppl 2):S290–S295.
 55. Kahan S. ACP Journal Club. Bariatric surgery was cost-effective at 2 years for management of type 2 diabetes in obese patients. *Ann Intern Med*. 2009;151:JC2-14, JC2-15.
 56. Nguyen NT, Slone JA, Nguyen XM, et al. A prospective randomized trial of laparoscopic gastric bypass versus laparoscopic adjustable gastric banding for the treatment of morbid obesity: Outcomes, quality of life, and costs [published online ahead of print August 27, 2009]. *Ann Surg*.

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