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Bariatric Surgery and Type 2 Diabetes Mellitus: Surgically Induced Remission

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Abstract

The relationship between obesity and type 2 diabetes mellitus (T2DM) is well known. Morbidly obese patients with T2DM who undergo bariatric surgery have improvement or remission of their diabetes. Different types of bariatric operations offer varying degrees of T2DM remission. These operations are classified as restrictive, malabsorptive, or a combination of both. The gold-standard operation, known as the Roux-en-Y gastric bypass, is a combination operation.

Most often, improvement of the diabetes is seen within days of the operation. Various theories to explain this rapid change include calorie restriction and hormonal changes from exclusion of the upper gastrointestinal tract. Weight loss accounts for the sustained improvements in glucose control. The patients who benefit the most are those who are early in their disease course.

Having a single treatment for both obesity and T2DM is ideal. As bariatric surgery has become a safe operation when performed by experienced surgeons, it should be considered a treatment for these diseases. The impact it can have on the lives of individual patients and society as a whole is tremendous.

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Background

The close relationship between type 2 diabetes mellitus (T2DM) and obesity is well documented.[1] All obese patients have some level of insulin resistance and the risk of developing T2DM grows with increasing weight.[2-4] Both glucose intolerance and diabetes can improve or resolve with early, intensive therapy. Lifestyle changes will often improve diabetes; however the changes are usually not sustained.[5,6] Most non-surgical treatments can control hyperglycemia, but they cannot induce the remission of diabetes.[7]

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Abbreviations: (BMI) body mass index, (BPD) biliopancreatic diversion, (GIP) gastric inhibitory peptide, (GLP-1) glucagon-like-peptide-1, (HbA1c) hemoglobin A1c, (JIB) jejunoileal bypass, (LAGB) laparoscopic adjustable gastric band, (RYGB) Roux-en-Y gastric bypass, (T2DM) type 2 diabetes mellitus, (VBG) vertical banded gastroplasty

Keywords: bariatric, gastric bypass, remission, type 2 diabetes

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The distinctions between overweight, obesity, morbid obesity, or super morbid obesity are based on body mass index (BMI). The BMI is calculated as a ratio of weight in kilograms to the square of the height in meters. (A BMI calculator can be found at http://www.nhlbisupport.com/bmi/.) Because BMI is a simple ratio of weight to height squared, it has limitations in accuracy as an estimation of excess body fat; for example, a short muscular man may have a high BMI, but not have true obesity. For most individuals, BMI is a helpful indicator of excess weight, and therefore has become the standard indicator to describe the degree of excess weight in obese patients.[8] A BMI greater than 30 is considered an indication of obesity. According to the National Center for Health Statistics, 32% of non-institutionalized adults 20 years or older are considered obese.[9] At this time the guidelines for performing bariatric surgery on patients includes a BMI > 40, or a BMI between 35 and 39.[9] with an obesity-related health problem, such as diabetes.[10]

Improvement and remission of T2DM after bariatric surgery has been recognized for several years.[11] Restrictive versus malabsorptive operations offer different degrees of resolution of T2DM or insulin resistance.[1-7,11-51] The greatest benefit occurs in those who are early in the course of T2DM, before beta-cell function is severely damaged.[11-14,22]

Types of Bariatric Surgical Procedures

Bariatric operations are classified as either restrictive, malabsorptive, or a combination of both. Purely restrictive operations include the laparoscopic adjustable gastric band (LAGB) and the vertical banded gastroplasty (VBG). These operations involve placement of a band made out of foreign material around the upper portion of the stomach to restrict the amount of food that can be ingested.[7] Although the VBG is no longer commonly performed, the LAGB has been gaining popularity. Another purely restrictive operation that has recently emerged is the vertical sleeve gastrectomy. In this procedure, the capacity of the stomach's reservoir is greatly reduced by removing the fundus and body along the greater curvature, resulting in a long narrow tube formed by the remaining lesser curvature down to the preserved antrum and pylorus.[15] (**Figure 1**)

The initial goal of a malabsorptive operation is to reduce the area of intestine that contacts the food, to decrease absorption. The jejunoileal bypass (JIB) was the first operation performed for this purpose, but was subsequently abandoned because of severe malnutrition.

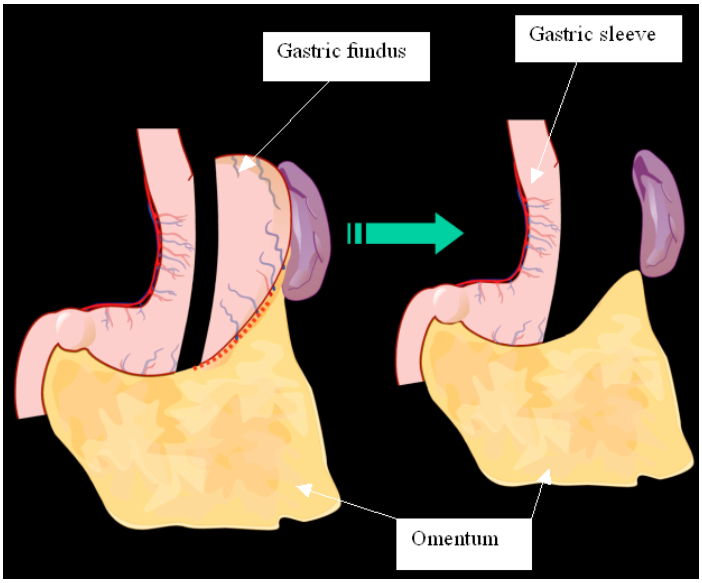

Figure 1. Vertical sleeve gastrectomy

More and more studies are now suggesting that it is the diversion of food away from the duodenum that causes a rapid change in the gastrointestinal hormonal milieu, resulting in a significant change in the way ingested food is processed in terms of energy extraction and storage.[16] Currently there is also an investigational device called the EndoBarrier™ (GI Dynamics™, Lexington, MA) which is a duodenal-jejunal bypass sleeve placed endoscopically. (For additional information, see http://www.gidynamics.com/endobarrier_technology). The product is not yet commercially available.

Two types of operations exist that are a combination of restriction and malabsorption. The first is the biliopancreatic diversion (BPD), whereby a vertical sleeve gastrectomy is performed, and most of the small intestine is bypassed by disconnecting the duodenum and attaching the ileum to the remaining stomach.[7] The operation is still performed, however with ever-decreasing frequency, because the malabsorptive effect is so great that the patient needs to be very vigilant about nutrient, vitamin, and protein supplementation. Very high compliance is required, and lifetime steatorrhea is the anticipated result. The second operation in this category is considered the surgical gold standard for treating morbid obesity. This operation, known as the Roux-en-Y gastric bypass (RYGB), involves creating a small, 15–30-ml gastric pouch that is attached to the jejunum in a Roux-en-Y fashion (as a defunctionalized limb). Then downstream, about 75–150 cm distal to this gastrojejunostomy, the distal small intestine in this area is attached to the proximal small intestine that drains the

biliopancreatic secretions from the duodenum, achieving intestinal continuity.[7] This results in a very small gastric reservoir and bypass of most of the stomach, the entire duodenum, and part of the jejunum. (**Figure 2**)

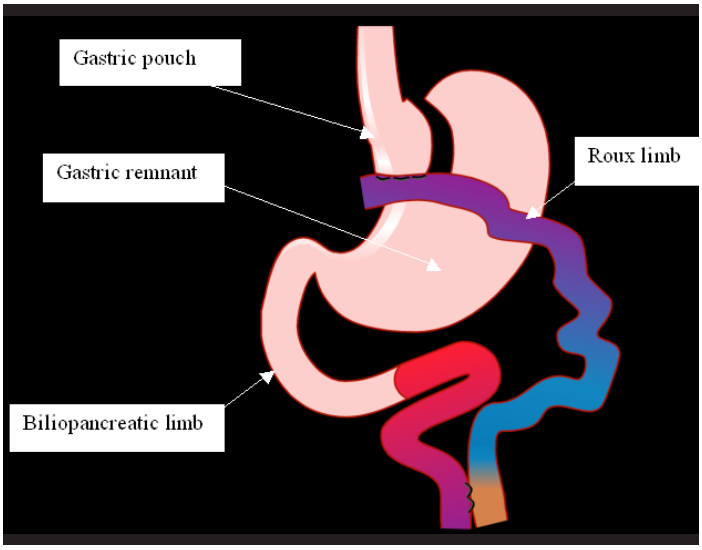

Figure 2. Roux-en-Y gastric bypass

Effects of Bariatric Surgery

Weight Loss

Weight loss has been documented after all types of bariatric surgery. Generally, greater weight loss is achieved by malabsorptive or combination operations versus the restrictive-only operations. After RYGB, patients lose 60-70% of their excess body weight.[17-19] In one large prospective, controlled study, maximal weight loss was seen 1–2 years after the operation. This mean weight loss, reported as a percentage of total body weight after gastric bypass, was 32% for RYGB, 25% for VBG, and 20% for LAGB.[20] Patients often experience a small amount of partial weight regain followed by weight stabilization. The durable and sustainable weight loss seen with bariatric surgery, especially RYGB and BPD, indicate that these are the only such reliable therapies for obesity available at present. A well-done study shows the long-term failure of diet and exercise with or without medical therapy.[20]

Control of Glucose Levels

Bariatric surgery improves glucose control. In a meta-analysis compiling data on 22,094 patients who underwent bariatric surgery, 76.8% had complete resolution of their diabetes.[21] What is surprising and interesting is not only the successful normalization of glucose, but the speed at which it occurs.[4,22]

Acute Improvement in Glucose Control

The rapid improvement and resolution of glucose intolerance and T2DM was noted early in the literature among patients who underwent gastric bypass.[11] These improvements were noted to occur before the onset of significant weight loss; therefore, factors other than simple weight loss were needed to explain this phenomenon.[23,51] One study that documented the time course of improvement of insulin resistance after RYGB found that it improved within six days of the operation, and the improvement lasted throughout the 12-month study period.[4] Several theories have been put forth to explain these findings, including calorie restriction, hormonal changes, and exclusion of the upper gastrointestinal tract.

Proponents of the theory that calorie restriction improves glucose control cite numerous sources that illustrate the impact of a low-calorie diet.[2] An early study showed that obese, non-insulin requiring T2DM patients who ate a very low calorie diet dramatically improved their fasting glucose levels from an average of 297 mg/dl down to 138 mg/dl. Interestingly, 87% of this improvement occurred in the first 10 days of the diet when the average weight loss was only 4.6 kg.[24] Several studies have shown similar results.[2]

Further evidence supporting this theory is the early improvement in glucose control after purely restrictive operations. Caloric restrictions are placed in the early postoperative period on all patients who undergo bariatric operations. Several years ago when VBG was a more popular operation, many reports noted early improvement in glucose control after the operation but before significant weight loss had occurred.[25,26] The more recent increase in vertical sleeve gastrectomies has resulted in reports of early improvement of glucose control with this restrictive operation as well. A short-term study looking at the effects of surgery on T2DM showed similar rates of resolution four months after sleeve gastrectomy and RYGB (51.4% vs 62%).[15] It is unclear whether this similarity is due to stringent calorie restriction or removal of a significant portion of the stomach, thus affecting the hormonal milieu of the gastrointestinal tract.

Nevertheless, the fact remains that RYGB and BPD result in higher rates of resolution of T2DM than restriction-only operations, such as LAGB and VBG.[11,21,23] Studies have shown that both of these operations result in long-term normalization of levels of glucose, insulin, and hemoglobin A1c (HbA1c).[11,23,27] Buchwald *et al*. performed

a meta-analysis and found differences in the rates of resolution of T2DM after different types of bariatric surgery: 98.9% after BPD, 83.7% after RYBG, 71.6% after VBG, and 47.9% after LAGB.[21]

One popular explanation for postoperative resolution of diabetes involves the gastrointestinal hormonal changes that accompany these operations. The main point of this hypothesis is that incretins (hormones that stimulate insulin secretion after the gastrointestinal tract has contact with nutrients) are produced in excess in patients with diabetes. These incretins include glucagon-like-peptide-1 (GLP-1), gastric inhibitory peptide (GIP), ghrelin and leptin.[28-33,51] Normally GLP-1 is made in the terminal ileum and colon, and GIP is made in the duodenum. Together, they are responsible for about half of the insulin that is secreted after a meal.[34] GLP-1 also increases insulin sensitivity, reduces hepatic gluconeogenesis, and reduces pancreatic glucagon secretion.[33] Ghrelin is secreted by the stomach before a meal and stimulates appetite and intestinal motility. It also inhibits insulin secretion and increases insulin sensitivity.[3]

After the jejunal anatomy has been rerouted, the secretion of these hormones is altered.[7] GLP-1 changes after RYGB have been inconsistent, with some studies showing increased levels[35] and others not showing any changes.[36,37] There are studies that show that GLP-1 levels increase after RYGB and BPD and stay elevated for 20 years.[38,39] GLP-1 is secreted after meals.[33] Since GLP-1 is a hindgut hormone, one theory proposes that an expedited delivery of nutrients to the hindgut increases the amount of GLP-1 released. These studies were done following literature that emerged about increasing levels of GLP-1 in humans and rats after the intestine was bypassed to carry undigested food to the distal alimentary tract. However, these operations did not involve the bypass of nutrients around the duodenal passage, and are not the best models to use when considering RYGB.[7,40,41]

The role of GIP in the resolution of T2DM after RYGB is more questionable. Studies have shown that patients with T2DM have a defect in the GIP receptor on beta cells in the pancreas. Therefore, it is theorized that any changes in GIP levels after the operation would not have any clinical significance.[33]

Ghrelin's role in remission of diabetes after bariatric surgery has been studied. Ghrelin was found to be suppressed after weight loss from RYGB.[42] However, ghrelin changes after RYGB have also been reported to be inconsistent; results vary from decreased levels, no change, or increased levels.[43-45] If this hormone is to be credited for the remission of diabetes, the hormonal changes need to occur before the weight loss.[7] Therefore the role of ghrelin is questionable, since it seems to be tied to weight loss.

Peptide YY, just like GLP-1, is secreted from the terminal ileum and colon. In the gut, this peptide decreases pancreatic endocrine and exocrine secretion. In general, obese patients have depressed levels of peptide YY, and they require more calories to secrete the same amount of this hormone as compared to non-obese patients. Peptide YY increases after restrictive procedures, however, basal levels remain unchanged after RYGB. Yet, when stimulated by a meal, the output of peptide YY is higher in patients who have undergone an RYGB than in obese patients serving as controls.[33] Again, just as with the other gastrointestinal hormones mentioned earlier, the role of peptide YY is unclear.

The foregut hypothesis is more complex and substantiated by interesting studies. A rat model for non-obese diabetes was used to test the theory that excluding the duodenum would improve diabetes. The authors compared a gastrojejunal connection alone versus a gastrojejunal connection plus duodenal exclusion, such as the RYGB. Only the rats with the duodenal exclusion had improvement in their diabetes. This effect was nullified after reversal of the duodenal exclusion. The authors concluded that excluding a portion of the proximal intestine is important in improving diabetes.[46]

In another rodent study by the same author, a gastrojejunal bypass was performed while gastric volume was maintained. This study group was compared with three other groups: a sham-operation group, a food-restricted group, and a medically treated group. The bypassed rats had better glucose control than those in the other groups. The authors concluded that "bypass of the duodenum and jejunum can directly control type 2 diabetes, not secondarily to weight loss or treatment of obesity."[47]

This same non-obese T2DM rat model was used by another group of authors. In their study they compared a group who underwent gastrojejunal bypass to a control group. Both groups were otherwise treated the same. The intervention group had improved glucose levels after oral glucose tolerance tests one week and one month after the operations. Hormone levels were also measured. There were no changes in the levels of GIP, GLP-1, insulin, or glucagon. However, the intervention group

had a decrease in leptin levels one week and one month after surgery.[48]

Chronic Improvement in Glucose Control

The weight loss achieved by all types of bariatric surgery has been demonstrated numerous times.[1-7,11-50] Since even relatively little weight loss can significantly improve T2DM, there is little doubt that the long-term weight loss achieved through surgery would bring about improvements in insulin sensitivity and diabetes.[49,50] Any type of bariatric operation that induces significant weight loss will result in T2DM improvement.[2] Those patients with the greatest loss have the most improvement in their T2DM.[22] From a biochemical standpoint, there is improvement in the acute insulin response after weight loss surgery, showing that mild or moderate T2DM is a reversible disease.[14]

An important aspect of improvement in T2DM after bariatric surgery is the preoperative severity of T2DM. In a study by Schauer *et al*., all patients had improvement or resolution of their diabetes after RYGB, however, patients with mild cases of diabetes were more likely to achieve sustained remission.[22] Measures of increased T2DM severity included elevated HbA1c and greater insulin use. Three negative predictors were preoperative T2DM duration, elevated HbA1c, and insulin use. Patients with these negative predictors were less likely to achieve resolution. In contrast, important parameters that increased the chances of remission were the preoperative use of oral medications instead of insulin and a less than five-year preoperative duration of T2DM.

Pories *et al*. investigated the resolution of diabetes in their patients who underwent gastric bypass. Only 9% (27) of the patients continued to have diabetes after their operation. Analysis of these patients revealed that 10 of them had breakdown of their gastric staple line leading to lack of diabetes remission. In contrast, the 17 patients with intact operations but continued diabetes were older and had a longer history of diabetes compared to their counterparts who had remission of their diabetes.[11] Along these lines, Dixon and O'Brien found that there was decreased beta-cell function with increasing duration of diabetes.[13]

Conclusion

Obesity and T2DM are increasing in incidence. Having one treatment that can alleviate both diseases is ideal. Although these diseases have traditionally been thought of as medical, there is validity in altering the treatment paradigm to include surgical treatment. Currently only 1% of those who qualify to have weight loss surgery actually undergo the operation. When laparoscopic bariatric surgery first started to become widespread in the late 1990s, there was an enormous increase in the number of bariatric surgeons and the number of RYGBs performed.[52] However, at that time, some surgeons lacked the experience or training to perform complex laparoscopic surgery, such as bariatric surgery, which resulted in an increase in the morbidity and mortality associated with these operations. This, in-turn, led to insurance companies not reimbursing for this operation or malpractice carriers not insuring bariatric surgeons.[52,53] The need for quality improvement was recognized and many papers were published showing the safety of bariatric surgery when performed by experienced surgeons at high-volume centers. This, in addition to the fact that bariatric surgery has been shown to be cost effective, turned the tide so that the stigma of bariatric surgery no longer exists.[52,54] Today, bariatric surgery is typically done by well-trained and well-qualified surgeons in specialized bariatric centers. The mortality and morbidity have significantly decreased, while the patients' lives have improved drastically.

The exact nature of the diabetic remission through surgery is controversial. It is likely that a combination of a calorie-restricted diet, gastrointestinal hormonal changes, and weight loss result in an early and long-lasting remission for T2DM. Clinically, the profound effect that an operation can have on improving T2DM is important. Operatively treating T2DM patients who qualify could lead to decreased morbidity and mortality from diabetes over a lifetime. It would be important, though, for the patient to undergo the operation while still in the early stages of T2DM to increase the chances of complete remission. This treatment, which is now supported by nearly 30 years' of long-term data, along with other existing treatments, could have a significant impact not only on the quality of an individual patient's life, but also on society as a whole.

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