

## **Leitthema**

# **TYPE 2 DIABETES IS NO LONGER A HOPELESS DISEASE: FULL AND DURABLE REMISSION WITH SURGERY OF THE FOREGUT**

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When Frederick Banting and Ian Macleod received the Nobel Prize for the discovery of insulin in 1923, the world rejoiced because diabetes had, at last, been conquered. Unfortunately, that hope was unfounded. Although the discovery of insulin was, indeed, a major advance, diabetes has not been defeated. In fact, in the USA, the prevalence of the disease has doubled in the last ten years. In 2007, 37.2 million Americans, 20 years or older, were estimated to have diagnosed or undiagnosed diabetes; 1,636,000 new cases are added each year.

Despite the release of multiple anti-diabetic drugs, billions of dollars in research and wide-spread educational programs emphasizing diets, exercise and behavioral modification, diabetes has become the USA's most expensive disease. Adults with diabetes have stroke and heart attack rates two to four times higher than aged matched comparison groups. It is the leading cause of blindness, accounting for 12,000 to 24,000 new cases each year. Diabetes is also the leading cause of kidney failure accounting for 44 percent of new cases in 2005, a total of 178,689 people. The disease also accounts for the majority of non-traumatic amputations with 71,000 performed in 2004. In 2007, the total annual economic cost of diabetes was estimated to be \$174 billion and the per capita annual costs of health care for people with diabetes was \$11,744 a year, of which \$6,649 (57%) was attributed to diabetes.

Nor is the USA alone. Germany is currently among the top ten countries worldwide in terms of absolute numbers of people with diabetes. Experts estimate that there will be at least 10 million people with diabetes in Germany by 2010, an increase of 50 percent over 2004. According to insurer the German carrier, AOK, the healthcare costs of the condition, due to its complications, amount to at least €23.5 billion<sup>1</sup>.

### **The first hope: a side effect of an operation to treat severe obesity**

The first hope that diabetes might be defeated came about by serendipity. In 1978, in pursuit of an operation to achieve weight loss in the severely obese, we developed the Greenville version of the gastric bypass, an adaptation of the bariatric procedure developed by Mason in 1964<sup>2</sup>. The operation 1) limited intake with a 30 cc proximal gastric pouch and a 10 mm gastro-enterostomy and 2) interfered with digestion through the exclusion of the remaining stomach, duodenum and 60 cm beyond the Ligament of Treitz. The gastric bypass (Fig. 1) certainly proved to be an effective treatment for severe obesity. In our series of 608 patients with a 95% follow-up with a standardized operation for up to 16 years, durable mean weight loss was 106 lbs. (48.2 kg) (317 – 211 lb/ 144.1 – 95.9 kg)<sup>3</sup>, an outcome confirmed by Schauer in 2004 who found a mean weight loss of 104 lb (47.2 Kg) after five years of follow-up<sup>4</sup>.

### **The unexpected outcome: the full and durable remission of type 2 diabetes**

In the initial trials of the gastric bypass, we accepted only obese patients without type 2 diabetes. After the operations proved to be successful, however, we began to accept operative candidates whether or not they had normal glucose levels. However, instead of the expected elevations of glucose and increased demands for insulin due to the stress of surgery, these patients rapidly returned to euglycemia. Table 1 shows the rate of this dramatic resolution in our fifth case on 16 November 1980. L.T., a severely obese woman presented on the morning of surgery with a plasma glucose level of 495 g/dl and required 90 units, her daily maintenance dose before we were able to begin anesthesia and carry out the gastric bypass. Her insulin requirements fell to 8 units the next day, according to a sliding scale regimen. On the 22 of November, her fifth

postoperative day, she received the last dose of insulin and required no additional diabetes medication over the next fourteen years of follow-up.

Our series eventually included 608 severely obese patients treated with a standardized gastric bypass with a 95% follow-up for up to 16 years. The cohort included 146 diabetic patients and 152 individuals with impaired glucose tolerance. Of these 121 (83%) and 150 (99%), respectively, developed and maintained full and durable remission of their T2DM with return to euglycemia, no dietary restrictions and cessation of anti-diabetic medication<sup>5</sup>. Schauer also reported an 83% rate of remission in his series<sup>6</sup>.

### **The gastric bypass also lowers mortality and morbidity from T2DM**

This improvement was not merely a matter of a normalization of glucose values. The gastric bypass also restored quality of life and actually prolonged long-term survival. During the years that the 154 diabetic patients received the gastric bypass, another 78 patients were scheduled for surgery but did not undergo operation primarily due to failure to obtain insurance coverage or, much less commonly, because they had changed their minds. Comparison of these two groups, similar but not randomized, revealed a striking difference in mortality with 9/154 deaths over nine years in the surgical group (1%/year) vs. 22/78 deaths in 6.2 years (4.5 %/year) ( $p < 0.003$ )<sup>6</sup>. Adams<sup>7</sup> and Sjostrom<sup>8</sup> have reported similar reductions in mortality of the severely obese following bariatric surgery, although those series were not limited solely to diabetic patients.

### **Exploring the mechanism: Is the remission of T2DM due to reduced intake and weight loss?**

We initially ascribed the remission of diabetes to weight loss due to food restriction<sup>9</sup>, It made sense. After all, dietary restriction is one of the fundamental concepts of the medical management of T2DM.

Food intake is certainly restricted following the gastric bypass. Immediately following the surgery, patients are allowed only doses of 30 cc of a high protein supplement every four hours, supplemented by water during the next two weeks after

surgery. Even months later, they are still limited by their small gastric pouches and a limited outflow through the 1 cm. gastro-jejunostomies.

Further, the patients also experienced and maintained significant weight loss. The 608 patients in our series maintained a mean weight loss of 48.2 kg ( 144 – 95.9 kg) over the 16 years of follow-up.

### **Weight loss cannot be the whole story...**

Four observations, however, raised doubts about the explanation that the reversal of diabetes was merely due to weight loss. The first was the rapid and total return to euglycemia even in severely diabetic individuals before there was significant weight loss. While it is true that diabetic patients return to euglycemia with sharply reduced dietary intake, it is also true that their hyperglycemia returns with normal feeding.

Second, diabetic patients who undergo surgery will generally return to their previous levels of anti-diabetic therapy when they resume their usual diets. In contrast, patients who undergo the gastric bypass remain euglycemic, even when they become weight stable and are no longer in caloric imbalance.

Third, the remission of the diabetes is durable even when the patients had resumed regular, unrestricted diets

Fourth, and least obvious, contrary to popular belief, patients with gastric bypasses eat more than their normal weight counterparts. To maintain a mean weight of 95.9 kg, the mean weight of our group fourteen years after gastric bypass, these individuals start to eat more than lean normal persons weighing 70 kg. In spite of this excessive intake, their T2DM remained in remission.

### **The tenuous relationship between obesity and diabetes**

One of the tenets of diabetology is that weight and T2DM are closely related: T2DM responds well to weight loss programs with improvement of hyperglycemia, insulin resistance and hyperinsulinemia. In addition, the epidemic spread of obesity is directly associated with the increased prevalence of T2DM around the world.

However, the association should not be immediately interpreted as cause and effect. If that relationship is true, how do we explain the ten percent of T2DM patients who are lean and not obese? Also, how do we explain the observation that only one third of the severely obese population is diabetic?

Hormonal studies raise additional questions. In the study by Laferrere and colleagues of obese women with T2DM studied before and 1 month after the gastric bypass (n=9) or after a diet-induced equivalent weight loss in a matched group (n=10), total GLP-1 levels after oral glucose increased six times and the incretin effect, i.e. the difference in insulin levels in response to oral and to an isoglycemic iv. glucose load, increased five times. The authors concluded, "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."<sup>10</sup>

### **If the remission of T2DM is not due solely to weight loss, could the surgery of the gut play a role?**

In 1998, based on our observations, we suggested that the remission of the diabetes was not due to weight loss alone but was also due to the bypass of the gut<sup>11</sup>.

Since then several observations in animals and man have supported this hypothesis: Rubino and his colleagues conducted three elegant studies in the Goto-Kakizaki (GK) rat, a lean diabetic animal model, that underscored the role of the proximal foregut (Figure 2)<sup>12</sup>: 1) a stomach sparing bypass of the duodenum and upper jejunum that allows normal intake, normal growth and prevents weight loss restores these genetic diabetic rats to euglycemia.

2) A gastro-enterostomy that allows food to flow in two directions, i.e. to the duodenum or the proximal jejunum, has little or no effect on the diabetes in these animals.

However, division of the pylorus, preventing food from entering the duodenum, also restores euglycemia and 3) lining the duodenum and upper jejunum of these rats with Silastic sleeves that prevent contact of food with the mucosa also restores euglycemia. When the sleeves are perforated to allow contact of food with the foregut mucosa, T2DM returns.

## **Human studies confirm the remission of T2DM is primarily due to the changes in the gut, not weight loss.**

Efforts to compare the effects of weight loss and exclusion of parts of the foregut suggest that both play a role. The salutary effect of weight loss is evident to anyone caring for T2DM patients. The reduction of weight by modest means, even as low as 10%, may induce remission or marked improvement. The best data, however, came from Dixon, who, in a prospective randomized study, documented that “participants randomized to adjustable gastric banding,” an operation that simulated dieting through the control of intake, “were more likely to achieve remission of T2DM through greater weight loss”<sup>13</sup>. Unfortunately, dietary management produces only limited effects in practice because patients have difficulty complying with weight loss programs.

The best evidence that the remission of T2DM is primarily due to the exclusion of foregut from the alimentary stream comes from three small and short-term studies by Ramos<sup>14</sup>, Cohen<sup>15</sup> and Lakdawala<sup>16</sup> in which non-obese, diabetic patients have undergone duodeno-jejunal bypasses that preserved stomach volume and the ability to consume normal diets<sup>17</sup>. In Lakdawala’s series, the operation lowered Hb1Ac from 9,10.4 and 9.5 to 5.1,6.3 and 6.0 in three non-obese patients with BMI’s of 27.5, 28, and 29.5 without significant weight.

## **The working hypotheses**

Usually in medicine, discoveries progress from observations in the laboratory through animal studies, and human trials before implementation in clinical practice. In bariatric surgery, the process has been sharply reversed. The discovery that T2DM can be reversed totally and for decades with sharp reductions in morbidity and mortality is already amply confirmed. The explanation for the remission is now the object of vigorous research with the hope that understanding the mechanism might lead to molecular therapies that could replace surgical intervention.

One explanation of the remission is based on the hypothesis that T2DM is due to inappropriate incretin secretion from the gut in response to food that stimulates the islets to produce excess insulin with secondary insulin resistance. With that view,

partial exclusion of the foregut reduces the levels of incretin with correction of the hyperinsulinemia and insulin resistance.

That explanation, however, is very much still the minority opinion. Most diabetologists ascribe T2DM to peripheral insulin resistance, primarily in muscle in part caused by obesity and a lack of exercise. With that view, the effects of bariatric surgery might be due to the secretion of “anti-incretins” that lead to insulin resistance in muscle and liver.

In fact, both views may be correct. It is not impossible for one gut signal to over stimulate the beta cells, in the pancreas, to cause insulin resistance at the mitochondrial level in muscle and, simultaneously to induce excessive gluconeogenesis in the liver. It is also not impossible that all of these effects are produced by several signals simultaneously or in tandem. There are many other examples of hormones, such as adrenaline and dopamine, with multiple actions of different organ systems.

For further reading about this exciting area of research, please see the writings of Cummings<sup>18, 19</sup>, Kaplan<sup>20</sup> and Dohm<sup>21</sup>.

## **Current practice**

Bariatric surgery is now widely accepted in the US. In 2007, about 200,000 bariatric operations were performed. The 2008 data are not yet available but are expected to indicate significant growth.

Medicare and the major insurance carriers generally reimburse for bariatric surgery for 1) patients with a Body Mass Index ( $BMI = \text{Kg}/\text{M}^2$ )  $\geq 35$  and significant co-morbidities such as diabetes, asthma or heart failure or for 2) those with a BMI  $\geq 40$ . Most carriers require documentation of 1) failure of a six month supervised diet, 2) control of emotional disorders or substance abuse, 3) capability to understand the operation and its long-term effects 4) a contract indication agreement to long-term follow-up as well as 5) evaluation by a nutritionist, dietician and psychologist or psychiatrist.

Currently, almost all carriers will reimburse for the gastric bypass operation and adjustable gastric banding. A few also approve the bilio-pancreatic bypass with duodenal switch and the gastric sleeve. Other operations including the loop mini gastric

bypass, gastric stimulation, the Scopinaro biliopancreatic bypass with gastric resection and ileal transposition are considered investigational procedures by almost all insurers.

Short term complications are similar to those of other abdominal procedures. They include anastomotic leak, hemorrhage, intestinal obstruction, internal hernia, pulmonary emboli, and sepsis. These are managed in the same manner as those following other operations in the gut, but, in general, severely obese patients require more prompt intervention than lean individuals because they tend to deteriorate rapidly. Long term complications include the same list as other abdominal operations with two major additions: internal hernias and malnutrition. Due to the complexity of gastric bypass complications and the need to respond promptly, physicians treating these individuals should seek consultation with bariatric surgeons promptly.

In terms of value, bariatric surgery can provide a reduction in mortality and full remission or significant improvement not only of diabetes but also asthma, cardiopulmonary failure, stress incontinence, pseudotumor cerebri, polycystic ovary disease and sharply improve arthritis of weight bearing joints. In fiscal terms, the cost of the operations is amortized within two to three years, primarily due to savings in medication and health care costs.

Bariatric surgery is remarkably safe when the care is provided at Centers of Excellence. In the 364 hospitals certified by the American Society for Metabolic and Obesity Surgery (ASMBS), hospital mortality has been reduced to 0.14% and 90 day mortality to 0.35%, about the same level as elective cholecystectomy, in spite of the fact that severely obese patients present with serious surgical risks<sup>22</sup>.

## **Conclusion**

Bariatric surgery offers safe and effective therapy of type 2 diabetes for severely obese individuals with full and durable remission of the disease as well as a sharp reduction in mortality. Recent data now suggest that the surgery should also be extended to overweight and even lean patients.

Bariatric surgery also provides invaluable new tools for the study of T2DM. The demonstration that the gut plays a major role in the pathogenesis of the disease opens promising pathways for better treatment of this calamitous disease.



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Figure 1

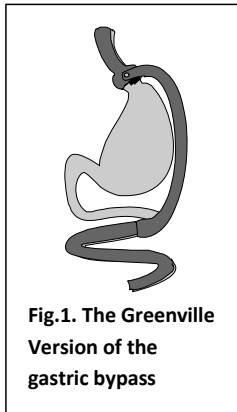
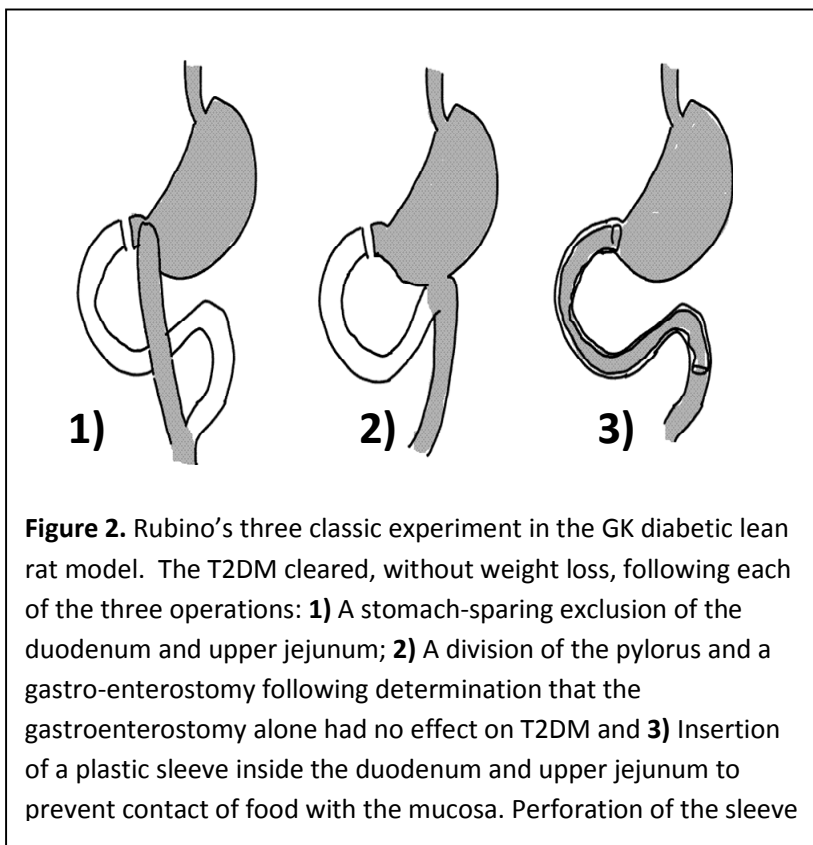


Figure 2



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Table 1

<b>Table 1. Remission Of T2DM After Gastric Bypass (Pt. L.T.)</b>		
<b>Date</b>	<b>Glucose (g/dl)</b>	<b>Insulin (units) Given per sliding scale</b>
<b>16 Nov '80 Operation</b>	<b>495</b>	<b>90</b>
<b>17 Nov</b>	<b>281\</b>	<b>8</b>
<b>18 Nov</b>	<b>308</b>	<b>16</b>
<b>19 Nov</b>	<b>240</b>	<b>8</b>
<b>20 Nov</b>	<b>210</b>	<b>4</b>
<b>21 Nov</b>	<b>230</b>	<b>8</b>
<b>22 Nov</b>	<b>216</b>	<b>4</b>
<b>28 Nov</b>	<b>193</b>	<b>0</b>
<b>30 Nov</b>	<b>153</b>	<b>0</b>
<b>14 Dec</b>	<b>155</b>	<b>0</b>