Diabetes Surgery: A New Approach to an Old Disease

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Since its earliest description several thousand years ago, diabetes has remained a chronic progressive disease (1). The disease now affects ~200 million people worldwide, and diabetes-related death is expected to increase by >50% in the next 10 years (2). The situation is only getting worse. The prevalence of diabetes among the elderly has increased 63% in the 10 years 1994–2004 (3). This increasing prevalence is a testament to improvement in managing diabetes-related complications, as well as our global “modernization” and the accompanying metabolic derangements. Diabetes is now ranked as the sixth leading cause of death by disease in the U.S. (4). In many places, it ranks far higher. The economic burden in 2007 alone exceeded $174 billion (5).

Diet modification and oral hypoglycemic medications have proven inadequate, whereas insulin therapy only solves the problem temporarily. In the U.K. Prospective Diabetes Study, diabetic patients were treated with diet modification, metformin, sulfonylurea, or insulin. Consistent with the progressive nature of diabetes, monotherapy was abandoned in 75% of the patients studied in a follow-up of 9 years (6). Even with the newest pharmacotherapies, patients continue to develop macro- and microvascular complications. Diabetes is associated with increased cardiac- and stroke-related deaths, kidney failure, blindness, and 60% of nontrauma lower-limb amputations (4). In cardiac surgery, diabetes as a preoperative risk factor confers greater morbidity than a previous myocardial infarction (7,8).

While these numbers show that diabetes will be the global health crisis of the next generation, its true pathophysiology has yet to be delineated. Alternative treatments targeting different models of this disease require careful and responsible examination. A large body of evidence now demonstrates surgery for type 2 diabetes can achieve up to complete disease remission, a goal almost unheard of in current diabetes care. Evidence collected over decades of bariatric surgery demonstrates the effectiveness and durability of diabetes control gained after gastrointestinal bypass surgeries (9–13). “Metabolic surgery” is now emerging as an area dedicated to the establishment of surgical procedures specifically aimed at treating diabetes. This article will focus on the rationale for surgery as a new therapy for type 2 diabetes and explore the various surgical options currently available and those under investigation.

EVIDENCE — In the early 1980s, surgeons realized that many patients with type 2 diabetes who had undergone gastric bypass for the treatment of morbid obesity experienced a complete diabetes remission. This remission proved durable (11,14,15). Since then, there have been many studies confirming the efficacy of bariatric procedures in treating type 2 diabetes. In the meta-analysis of 22,094 patients, Buchwald et al. (11) found diabetes resolution in 98.9% of patients undergoing biliopancreatic diversion or duodenal switch, 83.7% resolution after gastric bypass, and 47.9% after laparoscopic gastric banding. In the Swedish Obesity Study, a prospective case-matched investigation compared obese patients undergoing gastric banding, vertical banded gastroplasty, or gastric bypass with obese control subjects maintained with conventional treatment. The data were collected for 4,047 patients who were followed for over 2 years, with 1,703 followed over 10 years. The incidence of diabetes at 2 and 10 years was significantly lower in the surgery group, 1 and 7%, respectively, compared with the control subjects, 8 and 24% (P < 0.001). Diabetes remission rates at 2 and 10 years were 72 and 37% after surgery and 21 and 13% with medical therapy (12). Many have commented that the 10-year remission rate of the Swedish Obesity Study is lower than expected because of the high percentage of purely restrictive procedures performed on that population (vertical banded gastroplasty and gastric banding), operations less effective for diabetes resolution.

Diabetes control and remission seems to be best obtained with procedures that include an intestinal bypass, as in gastric bypass or biliopancreatic diversion. With a 14-year follow-up, Pories et al. (14) found an 83% resolution of type 2 diabetes in 608 patients after gastric bypass. These data were confirmed by Schauer et al. (10) with the same 83% resolution rate in 240 obese patients undergoing laparoscopic gastric bypass. Scopinaro et al. (16) reported a 97% diabetes remission rate in 312 patients maintained at 10 years postoperative follow-up. Purely restrictive procedures also significantly improve diabetes, although seemingly less effectively than bypass operations. Their efficacy relies more on decreased calorie intake and weight loss to ameliorate the diabetes. Remission is typically not seen until several months postoperatively, only once weight loss has occurred (17).

In a recent clinical study, resolution of diabetes after gastric banding was strongly correlated with amount of weight lost, and none of the patients in this study experienced remission before 6 months (18).

The mechanism of diabetes resolution after gastrointestinal bypass remains unclear but is apparently not related to weight loss alone. In most cases, remission is observed in the days to weeks after surgery before any substantial weight loss.
has occurred (10,15,19). Furthermore, emerging evidence now shows that these effects may be achievable in the nonobese population as well. Several human studies have shown dramatic diabetes control in patients with BMI <35 kg/m² (20,21). Lee et al. (22) showed that 89.5% of diabetic patients with BMI <35 kg/m² had returned to euglycemia at 1 year after gastric bypass. The mean A1C level was reduced from 7.3% preoperatively to 5.6% at 1 year after surgery.

These clinical data corroborate earlier animal findings showing that surgical control of diabetes can be obtained in both obese and nonobese rodents (23). Clinical studies also show that the effect on diabetes after gastric bypass procedures does not depend only on the amount of weight loss (24,25). The antidiabetic mechanism of the surgery may be from a combination of hormonal changes seen after exclusion of the proximal intestine and increasing nutrient delivery to the distal small bowel. Both mechanisms are currently being investigated (26,27).

Given the success of bariatric surgeries in treating diabetes, should we now move toward the establishment of specific surgical interventions to treat diabetes? As with all other surgical procedures, the benefits of surgery must be weighed against the potential risks. In other words, one must consider the possible complications and mortality of surgery versus the probable remission of diabetes and decrease in lifelong diabetes-related morbidity and mortality. Contrary to commonly held misperceptions, bariatric surgery has a strikingly safe operative profile and associated low mortality. In the Buchwald meta-analysis of 361 studies encompassing 85,048 patients, early (<30 days) or late (30 days to 2 years) mortality was 0.28% (95% CI 0.22–0.34) and 0.35% (0.12–0.58) (28). This is in line with more recent studies that report bariatric surgery mortality rates ranging from 0.25 to 0.5% (28–31). These good numbers likely reflect a move by most centers toward a predominantly laparoscopic technique, the implemented system of wide controls, and incorporation of a multidisciplinary approach (32,33). These mortality rates are comparable to those of patients undergoing laparoscopic cholecystectomy (0.26–0.6%), a commonly performed elective procedure (34).

In the medical community, as well as in the general public, cholecystectomy is generally considered a safe and routine procedure, whereas bariatric surgery is often seen as extreme and dangerous. While obesity has only recently become accepted as a genuine disease, bariatric surgery continues to be considered as too drastic a measure as elective treatment, although data show it is as safe or even safer compared with most other surgical interventions. The mortality rates of coronary artery bypass graft for the treatment of coronary artery disease are reported to be on average 3.5% (30). If the risk associated with surgical treatment of coronary artery disease (a chronic progressive disease with no known cure) is acceptable, then the 0.5% risk of gastrointestinal bypass surgery should not be seen as a drastic measure to treat patients with diabetes. Mortality in a vacuum should not be a deterrent to surgery, but rather should be weighed against the potential long-term benefits conferred and the low procedure-related complication rates (32).

The benefits of diabetes resolution accomplished by surgery are significant. Diabetes-related mortality after Roux-en-Y gastric bypass has been followed over a period of 7 years and decreased 92% compared with controls (35). In a retrospective review of 23,803 morbidly obese patients, 5,347 of whom had diabetes, survival rates were increased, and the presence of comorbidities decreased in surgical patients compared with the nonsurgical group (P < 0.001). This survival benefit occurred as early as 6 months for patients under 65 years and at 11 months for patients older than 65 years (36). Another benefit of the surgery is the general improvement in metabolic syndrome, which contributes to a decrease in cardiovascular risk factors. Studies have shown a significant improvement in all components of the metabolic syndrome (type 2 diabetes, hypertension, increased fasting glucose and triglycerides, decreased HDL, and abdominal obesity) and an overall resolution of 95.6% at 1 year (37–40). Despite the compelling outcome data, the decision to operate should be made based on a risk factor assessment for each patient.

**DIABETES SURGERY: A NEW DISCIPLINE?** — While conventional bariatric surgery seems to treat diabetes, many are evaluating procedures specifically geared to treat diabetes on its own. Conventional operations already in practice addressing obesity include laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass, biliopancreatic diversion with duodenal switch, and sleeve gastrectomy. Laparoscopic adjustable gastric banding is strictly restrictive, with the band wrapping the proximal stomach, just below the gastro-esophageal junction. The patient loses weight because he or she feels full early with distension of the banded stomach after a few bites of food. The amount of gastric restriction can be adjusted based on injection or withdrawal of saline from within the inflatable plastic core. Roux-en-Y gastric bypass provides restriction via a small vertically oriented gastric pouch along the lesser curvature of the stomach. The jejunum is divided and rerouted to reestablish gastrointestinal continuity and allow nutrients to bypass the duodenum and proximal small bowel. The biliopancreatic diversion in its “duodenal switch” variant consists of a vertical gastrectomy (“sleeve gastrectomy”) and an extensive bypass of the bowel, with a duodeno-ileoectomy leaving only a short segment for absorption. The sleeve gastrectomy component of the biliopancreatic diversion with duodenal switch has been recently found to be effective as a stand-alone procedure in many overweight individuals (41). Because a malabsorptive component is missing, attention is paid to making a narrow sleeve and resecting the ghrelin-producing fundus to limit stomach dilation and weight regain. Novel operations are geared toward the treatment of diabetes and not necessarily to induce weight loss. Among the most prominent of these operations are the duodenal-jejunal bypass and ileal transposition. Duodenal-jejunal bypass is a stomach sparing bypass of a short segment of the proximal intestine, a gastric bypass without the stomach stapling. Duodenal-jejunal bypass has been shown to improve diabetes in both lean and obese animal models (23). It is currently being investigated in select early human trials. Published data on a sampling of cases shows that normal-weight type 2 diabetic patients undergoing duodenal-jejunal bypass had normalized fasting blood glucose levels <100 mg/dl. A1C dropped to <6%, from a preoperative level of 8–9% (20). It is expected that this procedure might duplicate the well-described safety profile of the Roux-en-Y gastric bypass.

Ileal interposition, previously called “transposition,” is another procedure being investigated to treat type 2 diabetes. Ileal transposition involves the removal of a small segment of the ileum with its vas-
cular and nervous supply and inserting it into the proximal small intestine. Animal studies of ileal transposition show exaggerated release of the gastrointestinal hormone glucagon like peptide-1. Glucagon like peptide-1 is a potent insulinotropic hormone that improves glucose tolerance, this action being used in drug therapy for diabetes (42,43). Early human studies with ileal transposition show promise, and the procedure is often combined with a sleeve gastrectomy when weight loss is desired. In a study of 60 patients with diabetes and BMI ranging from 23.6 to 34.4 kg/m², 86.7% achieved glycemic control at a mean follow-up of 7.4 months (44). The exact mechanism at work in this surgery is unclear, and diabetes improvement may be due to weight loss, the neurohormonal changes that accompany rearrangement of the intestine, or a combination of the two. Long-term outcomes of this operation regarding safety as well as metabolic complications have yet to be reported.

Another novel procedure is the endoluminal duodenaljejunal bypass sleeve. This procedure entails the endoscopic delivery and anchoring of a plastic-coated sleeve implant that extends into the jejunum and effectively excludes the duodenum. The device theoretically mimics the duodenal-jejunal bypass, in that nutrients pass throughout the duodenum without contact with its mucosa, while the distal small bowel receives less processed foodstuffs. The endoluminal duodenal-jejunal bypass sleeve is able to do this without disrupting bowel continuity or creating new anastomosis. This method has been shown to improve diabetes in lean rodents (F.R., personal communication). Tarnoff et al. (45–47) tested the feasibility of the endoluminal duodenal-jejunal bypass sleeve in a porcine animal model, and results from the first human experiments were recently published. Twelve morbidly obese patients, four with diabetes, underwent endoscopic placement of the duodenal sleeve. The study duration was 12 weeks, with 17% requiring sleeve retrieval. All four diabetic patients were able to maintain normal fasting plasma glucose without medication for the 12 weeks of the study, and three patients had a 0.5% decrease in A1C by week 12 (47). The safety and efficacy of long-term device placement in humans has not been fully established, but in terms of effectiveness and applicability, these preliminary results are promising.

**SURGERY FOR DIABETES: OPPORTUNITIES, BARRIERS, AND LIMITATIONS** — The notion of surgery for diabetes brings with it certain understandings. First, surgery is by design an invasive treatment modality and carries risks related to both anesthesia and the procedure itself. Like with all other surgical treatments, patients will have to be carefully screened. For instance, not every patient with carotid stenosis merits or warrants an endarterectomy; likewise, a surgical treatment for diabetes is not for everyone. Furthermore, with our current limited knowledge, it is not yet possible to define exact indications and contraindications to surgery. With the need for guidelines and recommendations, the Diabetes Surgery Summit, a collaborative consensus conference including top international endocrinologists and surgeons, convened in Rome last year to address some of these issues. The position statement from the Diabetes Surgery Summit (submitted for publication at the time of this writing) promises to represent the foundation of a new discipline and provides a multidisciplinary scientifically solid grounded approach from the outset.

At this time, few people who want diabetes surgery have access to it, and the majority of those with access have not chosen it. The development of diabetes surgery will have to overcome several barriers, including the ingrained notion of diabetes as strictly a medical disease. Financial issues will also have to be addressed. Major insurance companies in the U.S. today will only cover surgical intervention for the treatment of diabetes for patients with a BMI >35 kg/m². However, even among patients who are already eligible under current National Institutes of Health criteria, barely 1% are usually referred for surgical treatment (48). This is due to several reasons including reluctance of major insurance plans to cover the procedures. For nearly all those without the appropriate level of health insurance coverage or those cured with only mild obesity, the surgical option for diabetes treatment is impossible. However, new studies reveal that surgery for diabetes and obesity is indeed cost-effective (49). Another barrier to overcome may be the lack of an adequate workforce of trained bariatric surgeons in advanced laparoscopy to perform metabolic surgery. However, general surgeons too may have the opportunity to learn the skills to safely and effectively provide so potentially valuable a tool in the treatment of such a prevalent disease.

Surgery seems to provide an additional weapon against diabetes. The use of metabolic surgery has caused a redefinition of diabetes treatment goals, from control to remission. The potential of surgery to delineate the complex physiology of the neurohormonal axes within the gastrointestinal tract may lead to an improved understanding of the same pathophysiology of diabetes. This can in turn lead to new targets for medical and interventional therapies. In the end, it may be a combination of surgical therapy and medical management that provides the best long-term outcomes in these patients. This is a road well tread in the treatment of cancer and cardiac diseases.

**CONCLUSIONS** — The economic, medical, and social burden of diabetes is immense. Given our current inability to achieve major remission and reduce death rates with medical management, metabolic surgery represents a new frontier in diabetic treatment. Over the past 20 years, bariatric surgery has proven successful in treating not just obesity but also type 2 diabetes. Surgery should now be looked at as a viable therapy for not only the morbidly obese, but also for diabetic patients who fall outside current BMI guidelines. The potential benefits of metabolic surgery are in fact enormous. However, its implementation requires a rethinking of diabetes treatments goals and strategies. In the meantime, investigation into the pathophysiological basis of diabetes continues, with the hope of discovering the optimal therapeutic targets and best-suited interventions.

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