Diabetes Surgery: A New Approach to an Old Disease

FRANCESCO RUBINO, MD
TRACY-ANN MOO, MD
DANIEL J. ROSEN, MD
GREG F. DAKIN, MD
ALFONS POMP, MD

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 pharmaco-therapies, 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

From the Department of Surgery, Sanford I. Weill Medical College of Cornell University, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, New York.
Corresponding author: Francesco Rubino, frr2007@med.cornell.edu.
The publication of this supplement was made possible in part by unrestricted educational grants from Eli Lilly, Ethicon Endo-Surgery, Generex Biotechnology, Hoffmann-La Roche, Johnson & Johnson, LifeScan, Medtronic, MSD, Novo Nordisk, Pfizer, sanofi-aventis, and WorldWIDE.
DOI: 10.2337/dc09-S341

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/m^2 (20,21). Lee et al. (22) showed that 89.5% of diabetic patients with BMI <35 kg/m^2 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 "duodena switch" variant consists of a vertical gastrectomy ("sleeve gastrectomy") and an extensive bypass of the bowel, with a duodeno-ileostomy 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 vascular 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/m^2, 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 duodenal-jejunal 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/m^2. 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 cursed 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.

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. Montenero P. *La Storia del Diabete*. Rome, Italy. Luigi vittorio de Stefano, 2000
2. World Health Organization. World Health Organization fact sheet number 312, September 2006
3. Sloan F, Bethel M, Ruiz DJ, Shea AH, Feinglos MN. The growing burden of diabetes mellitus in the US elderly population. Arch Intern Med 2008;168:192–199
4. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2003, Centers for Disease Control and Prevention, Ed. Atlanta, GA, U.S. Department of Health and

Human Services, Centers for Disease Control and Prevention, 2004
5. Dall T, Edge Mann S, Zhang Y, Martin J, Chen Y, Hogan P. Economic costs of diabetes in the U.S. in 2007. Diabetes Care 2007;31:596–615
6. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49): UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281:2005–2012
7. Fox C, Coady S, Sorlie P, D'Agostino RB, Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115:1544–1550
8. Haffner S, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
9. Pories W, MacDonald KJ, Morgan E, Sinha MK, Dohm GL, Swanson MS, Barakat HA, Khazanie PG, Leggett-Frazier N, Long SD, O'Brien KF, Caro JF. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. Am J Clin Nutr 1992;55 (Suppl. 2):582S–585S
10. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash D, Hamad G, Eid GM, Mattar S, Ramanathan R, Barinas-Mitchel E, Rao RH, Kuller L, Kelley D. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg 2003; 238:467–485
11. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004;292: 1724–1737
12. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H. Swedish Obese Subjects Study Scientific Group: Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–2693
13. Wittgrove AC, Clark GW. Laparoscopic gastric bypass, Roux-en-Y: 500 patients: technique and results, with 3–60 month follow-up. Obes Surg 2000;10:233–239
14. Pories W, Swanson M, MacDonald K, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM, Dohm L. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995;222:339–352
15. Pories WJ. Diabetes: the evolution of a new paradigm. Ann Surg 2004;239:12–13
16. Scopinaro N, Marinari G, Camerini G, Papadia FS, Adami GF. Specific effects of biliopancreatic diversion on the major components of metabolic syndrome: a long-term follow-up study. Diabetes Care 2005;28:2406–2411
17. Cummings D, Flum D. Gastrointestinal surgery as a treatment for diabetes. JAMA 2008;299:341–343
18. Dixon J, O'Brien P, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA 2008;299:316–323
19. Briatore L, Salani B, Andraghetti G, Danovaro C, Sferrazzo E, Scopinaro N, Adami GF, Maggi D, Cordera R. Restoration of acute insulin response in T2DM subjects 1 month after biliopancreatic diversion. Obesity (Silver Spring) 2008;16:77–81
20. Cohen RV, Schiavon CA, Pinheiro JS, Luiz Correa J, Rubino F. 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
21. Scopinaro N, Papadia F, Marinari G, Camarini G, Adami G. Long-term control of type 2 diabetes mellitus and the other major components of the metabolic syndrome after biliopancreatic diversion in patients with BMI $<$ 35 kg/m2. Obes Surg 2007;17:185–192
22. Lee W, Wang W, Lee Y, Huang MT, Ser KH, Chen JC. Effect of laparoscopic minigastric bypass for type 2 diabetes mellitus: comparison of BMI $>$35 and $<$35 kg/m(2). J Gastrointest Surg 2008;12:945–952
23. 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
24. Depaula A, Macedo A, Rassi N, Vencio S, Machado CA, Mota BR, Silva LO, Halpern A, Schraubman V. Laparoscopic treatment of metabolic syndrome in patients with type 2 diabetes mellitus. Surg Endosc 2008;22:2670–2678
25. Cummings D, Overduin J, Shannon M, Foster-Schubert K. Hormonal mechanisms of weight loss and diabetes resolution after bariatric surgery. Surg Obes Relat Dis 2005;1:358–368
26. Rubino F, Forgione A, Cummings DE, Vix M, Gnuli Donatella, Mingrone G, Castagneto M, Marescaux J. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg 2006;244:741–749
27. le Roux CW, Aylwin SJ, Batterham RL, Borg CM, Coyle F, Prasad V, Shurey S, Ghatei MA, Patel AG, Bloom SR. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg 2006;243:108–114
28. Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. Surgery 2007;142:621–632 (discussion 632–635)
29. Flum DR, Salem L, Elrod JA, Dellinger EP, Cheadle A, Chan L. Early mortality among Medicare beneficiaries undergoing bariatric surgical procedures. JAMA 2005;294:1903–1908
30. Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality: the problem with small sample size. JAMA 2004;292:847–851
31. Morino M, Toppino M, Forestieri P, Angrisani L, Allaix M, Scopinaro N. Mortality after bariatric surgery: analysis of 13,871 morbidly obese patients from a national registry. Ann Surg 2007;246: 1002–1009
32. Nguyen NT, Hinojosa M, Fayad C, Varela E, Wilson SE. Use and outcomes of laparoscopic versus open gastric bypass at academic medical centers. J Am Coll Surg 2007;205:248–255
33. Han SH, Gracia C, Mehran A, Basa N, Hines J, Suleman L, Darshni V, Dutson E. Improved outcomes using a systematic and evidence-based approach to the laparoscopic Roux-en-Y gastric bypass in a single academic institution. Am Surg 2007;73:955–958
34. Khuri S, Najjar S, Daley J, Krasnicka B, Hossain M, Henerson WG, Aust JB, Bass B, Bishop MJ, Demakis J, DePalma R, Fabri PJ, Fink A, Gibbs J, Grover F, Hammermeister K, McDonald G, Neumayer L, Roswell RH, Spencer J, Turnage RH. VA National Surgical Quality Improvement Program: Comparison of surgical outcomes between teaching and nonteaching hospitals in the Department of Veterans Affairs. Ann Surg 2001;234:370–382 (discussion 382–383)
35. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, LaMonte MJ, Stroup AM, Hunt SC. Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753–761
36. Perry CD, Hutter MM, Smith DB, Newhouse JP, McNeil BJ. Survival and changes in comorbidities after bariatric surgery. Ann Surg 2008;247:21–27
37. Rossi M, Barretto Ferreira da Silva R, Chaves Alcântara G Jr, Regina PF, Martin Bianco Rossi FM, Serpa Neto A, Zimberg Chehter E. Remission of metabolic syndrome: a study of 140 patients six months after Roux-en-Y gastric bypass. Obes Surg 2008;18:601–606
38. Nguyen N, Varela E, Sabio A, Tran C, Stamos M, Wilson S. Resolution of hyperlipidemia after laparoscopic Roux-en-Y gastric bypass. J Am Coll Surg 2006;203:24–29
39. Nugent C, Bai C, Elariny H, Gopalakrishnan P, Quigley C, Garone M Jr, Afendy M,

Chan O, Wheeler A, Afendy A, Younossi ZM. Metabolic syndrome after laparoscopic bariatric. Surgery Obes Surg 2008; 18:1278–1286
40. Lee WJ, Huang MT, Wang W, Lin CM, Chen TC, Lai IR. Effects of obesity surgery on the metabolic syndrome. Arch Surg 2004;139:1088–1092
41. Baltasar A, Serra C, Pérez N, Bou R, Bengochea M, Ferri L. Laparoscopic sleeve gastrectomy: a multi-purpose bariatric operation. Obes Surg 2005;15:1124–1128
42. Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab 2005;288:E447–E453
43. Patriti A, Facchiano E, Annetti C, Aisa MC, Galli F, Fanelli C, Donini A. Early improvement of glucose tolerance after ileal transposition in a non-obese type 2 diabetes rat model. Obes Surg 2005;15: 1258–1264
44. de Paula AL, Macedo AL, Prudente AS, Queiroz L, Schraibman V, Pinus J. Laparoscopic sleeve gastrectomy with ileal interposition ("neuroendocrine brake"): pilot study of a new operation. Surg Obes Relat Dis 2006;2:464–467
45. Tarnoff M, Shikora S, Lembo A. Acute technical feasibility of an endoscopic duodenal-jejunal bypass sleeve in a porcine model: a potentially novel treatment for obesity and type 2 diabetes. Surg Endosc 2008;22:772–776
46. Tarnoff M, Shikora S, Lembo A, Gersin K. Chronic in-vivo experience with an endoscopically delivered and retrieved duodenal-jejunal bypass sleeve in a porcine model. Surg Endosc 2008;22:1023–1028
47. Rodriguez-Grunert L, Galvao Neto M, Alamo M, Ramos AC, Baez PB, Tarnoff M. First human experience with endoscopically delivered and retrieved duodenal-jejunal bypass sleeve. Surg Obes Relat Dis 2008;4:55–59
48. Statistic available at the ASMBS website http://www.asbs.org
49. Crémieux PY, Buchwald H, Shikora SA, Ghosh A, Yang HE, Buessing M. A study on the economic impact of bariatric surgery. Am J Managed Care 2008;14:589–596