Gastrointestinal Surgery as a Treatment for Diabetes

David E. Cummings, MD
David R. Flum, MD, MPH

Approximately one-third of adults in the United States are obese,[1] and largely because of this, at least as many have diabetes or prediabetes.[2] With these escalating twin epidemics, the health care community has been challenged to develop novel treatment strategies.

In this issue of *JAMA*, Dixon and colleagues[3] report a 2-year study in which patients with recently diagnosed type 2 diabetes and a body mass index (BMI) of 30 to 40 were randomly assigned to receive conventional medical/behavioral therapy (medical therapy and a focus on weight loss through lifestyle modification) or laparoscopic adjustable gastric banding (LAGB) plus conventional medical/behavioral therapy. The results were clear and striking. Complete remission of diabetes at 2 years was achieved in 73% of the patients in the LAGB group vs only 13% of those in the medical/behavioral therapy group, and the former experienced larger reductions in blood glucose levels, glycated hemoglobin levels, estimated insulin resistance, use of diabetes medication, and several features of the metabolic syndrome. No serious surgical complications were reported, and minor surgical mishaps seemed no worse than the adverse reactions to diabetes-related pharmacotherapy.

As expected, the surgical group lost more weight than the medical/behavioral group (20.7% vs 1.7%), and the amount of weight lost was the dominant predictor of diabetes remission. The percentage weight loss generally required for diabetes resolution was 10%, which was achieved in 86% of surgical patients but in only 1 patient in the medical group. Of the 34 patients who lost less than 10% of body weight, only 4 experienced diabetes remission, and these individuals had particularly mild baseline disease. Conversely, of the 26 patients who lost more than 10% of body weight, diabetes remitted in all but 4. In short, diabetes remission after LAGB appeared attributable to weight loss, with no evidence of additional antidiabetes mechanisms; but by promoting greater weight loss, LAGB was far more effective than medical/behavioral therapy at improving diabetes.

For a study in which surgery outperformed nonsurgical interventions, a natural question is whether the medical/behavioral program was as good as it could be. Pharmacotherapy was determined individually by an experienced diabetologist, using all diabetes medications available at the time. In addition, lifestyle optimization was stressed, including reduced intake of fats, saturated fats, foods with high glycemic index, and overall calories, together with a physical activity program of more than 10 000 steps per day and 200 minutes per week of moderate-intensity exercise. Whether this program constitutes the optimal medical/behavioral intervention can be debated. However, participants visited a physician, nurse, dietician, and/or diabetes educator at least once every 6 weeks for 2 years—an intensity of follow-up unlikely to be exceeded in common practice. Moreover, because both study groups had access to the same nonsurgical interventions, the greater improvement in diabetes following surgery is attributable to the benefits of LAGB in this randomized trial.

The general applicability of these findings remains to be determined. The authors' bariatric surgical team in Melbourne, Australia, is among the most experienced groups in the world using LAGB, and their excellent results may not be readily reproducible elsewhere. Their reported post-LAGB weight loss[4] often exceeds that observed by other investigators.[5-9] The discrepancy likely results from the Melbourne group's acclaimed long-term, multidisciplinary post-LAGB follow-up program. The widespread feasibility and cost of such postoperative coaching are unclear, and results in the community at large are unknown. Moreover, participants in this study had relatively mild diabetes, as characterized by less than 2 years' duration, no retinopathy or nephropathy, a mean baseline glycated hemoglobin value of 7.7%, and only 1 patient taking insulin. It is unclear whether secondary effects from weight loss alone after LAGB, without apparent direct antidiabetes surgical mechanisms,

See also p 316.

Author Affiliations: Division of Metabolism, Endocrinology and Nutrition, Department of Medicine (Dr Cummings) and Department of Surgery (Dr Flum), University of Washington, Seattle; and VA Puget Sound Health Care System, Seattle (Dr Cummings). Dr Flum is Contributing Editor, *JAMA*.
Corresponding Author: David E. Cummings, MD, Department of Medicine, University of Washington, VA Puget Sound Health Care System, 1660 S Columbian Way, S-111-Endo, Seattle, WA 98108 (davidec@u.washington.edu).

would suffice to reverse more severe, longstanding disease with greater β-cell deterioration.

The more relevant lessons about bariatric surgery and diabetes may come from an operation more common in the United States, the Roux-en-Y gastric bypass (RYGB). This procedure and biliopancreatic diversion—bariatric operations that rearrange gastrointestinal tract anatomy—appear to engage antidiabetes mechanisms beyond those related to weight loss. Evidence supporting this is mounting on several fronts.[10] For example, diabetes typically resolves within a few days to weeks following these operations, long before substantial weight loss has occurred. Among the approximately 84% of patients with diabetes whose disease remits entirely after RYGB,[11-13] one-third have blood glucose levels within reference range without use of antidiabetes medications before discharge from their surgical hospitalization, at an average of less than 3 postoperative days.[13] Most of the remainder discontinue antidiabetes medications within 1 month. In sharp contrast, none of the patients undergoing LAGB surgery in the study by Dixon et al had experienced diabetes remission by 6 months after surgery.[3] When evaluated at an equivalent percentage weight loss, patients who have undergone RYGB surgery display greater improvements in glucose tolerance than those who have undergone LAGB surgery. The RYGB procedure increases insulin sensitivity but also might directly improve β-cell function, as suggested by increasing, although still uncommon, reports of patients who had undergone RYGB surgery and who develop late-onset, severe hyperinsulinemic hypoglycemia (sometimes necessitating pancreatectomy), implying a β-cell-stimulatory effect of RYGB.[14-17] Antidiabetes mechanisms of bariatric operations with intestinal bypass probably include enhanced nutrient-stimulated secretion of glucagon-like peptide 1 from the distal intestine, compromised ghrelin production, and intriguing but poorly characterized consequences of excluding the proximal intestine from digestive continuity.[10,18,19]

For policy makers, professional societies, clinicians, and patients, studies like the one by Dixon et al have important implications; consequently, interest in this topic is increasing. The first International Diabetes Surgery Summit was recently convened in Rome, Italy, to comprehensively evaluate surgical options for diabetes treatment. Summit delegates called for increased basic and clinical or translational research to elucidate the mechanisms that mediate effects of gastrointestinal tract surgery on diabetes. They noted that despite hundreds of observational studies demonstrating benefits of surgical weight loss on diabetes, the American Diabetes Association and similar international and pediatric societies have yet to highlight surgery as an important treatment option. Although National Institutes of Health consensus guidelines from 1991 indicate that patients with diabetes and BMI greater than 35 can be considered for bariatric surgery, more than 90% of such individuals do not undergo these procedures, and most are probably not referred for surgical evaluation or even informed of surgical vs nonsurgical options. Commonly used decision trees for diabetes treatment currently do not mention surgery at all, even for severely obese patients.[20]

There has been concern over inadequate safety and effectiveness studies, but researchers are rectifying this. For example, the Longitudinal Assessment of Bariatric Surgery, a multicenter study funded by the National Institutes of Health, is evaluating safety, efficacy, and mechanisms of bariatric operations.[21] The recently reported results from more than 10 years of the Swedish Obese Subjects (SOS) study[22] assessing more than 4000 matched obese patients receiving nonsurgical care vs various bariatric procedures demonstrated that the prevention of new diabetes as well as resolution of existing diabetes were substantially improved in patients undergoing surgery. Bariatric surgery also decreases overall long-term mortality, including a remarkable 92% reduction in diabetes-related deaths following RYGB.[9,23]

With class 1 evidence such as that from the study by Dixon et al,[3] with large observational studies such as the Swedish Study,[22] and with increasing recognition that nonsurgical interventions rarely lead to major, long-term weight loss, professional societies and clinicians should reconsider the role of surgery to treat diabetes. For example, Dixon et al demonstrated that LAGB was superior to conventional diabetes therapy, including among patients with BMI less than 35. Comparable randomized controlled trials might be expected to be even more compelling for RYGB and biliopancreatic diversion, which activate direct glucose-lowering mechanisms additional to those resulting from weight loss. Although these operations are even more effective than LAGB surgery at reversing obesity and diabetes, they also confer greater surgical risks, so long-term comparative trials of these procedures are warranted.

Given the relative effects of surgical vs conventional approaches, it may be time to view bariatric operations not as treatments for patients with BMI greater than a certain level, but rather as interventions about which all obese patients with diabetes should be informed and given access. Within the past year alone, bariatric surgery societies in the United States, South America, and Europe have changed their names to highlight this concept of "metabolic surgery."

It is time for a major shift in the way the health care community considers diabetes treatment goals. Currently, diabetes is viewed as a chronic disease, with glycemic control and minimization of end-organ dysfunction considered the principle management targets. Gastrointestinal tract surgery, whether through weight loss or yet-to-be-determined additional mechanisms, offers a novel end point: the notion of complete disease remission. Discussing remission as an option for patients necessitates rethinking the current

approach to counseling, disease management, and resource allocation.

Finally, there is much to learn about surgical treatments for diabetes. Researchers are striving to elucidate surgical mechanisms of diabetes improvement, hoping ultimately to harness the effects of "surgery in a pill"—ie, a formulation providing the desired effects without operative risks. Policy and health care leaders are grappling with the costs and risks of surgical interventions, which must be balanced against the costs and risks of not taking advantage of surgically induced diabetes remission, in the face of an expanding pandemic. Addressing these issues requires time and resources, but in this era of advanced diabetes research, the insights already beginning to be gained by studying surgical interventions for diabetes may be the most profound since the discovery of insulin. As a result, the future looks brighter for patients.

Financial Disclosures: Dr Cummings reported receiving support from National Institutes of Health (NIH) grants RO1 DK61516, PO1 DK68384, UO1 DK66568, and DERC DK17047. Dr Flum reported receiving support from NIH grants U01 DK066568-01 and R21 DK069677-01; and receiving a 2007 research grant from Tyco to develop an animal model to evaluate the use of gastrointestinal tract operations to treat type 2 diabetes. Drs Cummings and Flum reported receiving travel grants to attend the 2007 Diabetes Surgery Summit, sponsored by Johnson & Johnson, Autosuture, Allergan, Roche, Storz, GI Dynamics, Amylin, and Power Medical Interventions.

REFERENCES

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006; 295(13):1549-1555.
2. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care*. 2006;29(6):1263-1268.
3. 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(3):316-323.
4. O'Brien PE, Dixon JB, Brown W, et al. The laparoscopic adjustable gastric band (Lap-Band): a prospective study of medium-term effects on weight, health and quality of life. *Obes Surg*. 2002;12(5):652-660.
5. Favretti F, Segato G, Ashton D, et al. Laparoscopic adjustable gastric banding in 1,791 consecutive obese patients: 12-year results. *Obes Surg*. 2007;17(2): 168-175.
6. Angrisani L, Lorenzo M, Borrelli V. Laparoscopic adjustable gastric banding versus Roux-en-Y gastric bypass: 5-year results of a prospective randomized trial. *Surg Obes Relat Dis*. 2007;3(2):127-133.
7. Gustavsson S, Westling A. Laparoscopic adjustable gastric banding: complications and side effects responsible for the poor long-term outcome. *Semin Laparosc Surg*. 2002;9(2):115-124.
8. Himpens J, Dapri G, Cadiere GB. A prospective randomized study between laparoscopic gastric banding and laparoscopic isolated sleeve gastrectomy: results after 1 and 3 years. *Obes Surg*. 2006;16(11):1450-1456.
9. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357(8):741-752.
10. Cummings DE, Overduin J, Shannon MH, Foster-Schubert KE. Hormonal mechanisms of weight loss and diabetes resolution after bariatric surgery. *Surg Obes Relat Dis*. 2005;1(3):358-368.
11. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292(14):1724-1737.
12. 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(3):339-352.
13. 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(4):467-485.
14. Service GJ, Thompson GB, Service FJ, Andrews JC, Callazo-Clavell ML, Lloyd R. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric bypass surgery. *N Engl J Med*. 2005;353(3):249-254.
15. Patti ME, McMahon G, Mun EC, et al. Severe hypoglycemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. *Diabetologia*. 2005;48(11):2236-2240.
16. Bantle JP, Ikramuddin S, Kellogg TA, Buchwald H. Hyperinsulinemic hypoglycemia developing late after gastric bypass. *Obes Surg*. 2007;17(5):592-594.
17. Cummings DE. Gastric bypass and nesidioblastosis—too much of a good thing for islets? *N Engl J Med*. 2005;353(3):300-302.
18. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med*. 2002;346(21):1623-1630.
19. Rubino F, Forgione A, Cummings DE, et al. 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(5):741-749.
20. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2006;49(8):1711-1721.
21. Belle SH, Berk PD, Courcoulas AP, et al. Safety and efficacy of bariatric surgery: Longitudinal Assessment of Bariatric Surgery. *Surg Obes Relat Dis*. 2007; 3(2):116-126.
22. Sjöström L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004;351 (26):2683-2693.
23. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007;357(8):753-761.