



Does
Metabolic
Surgery

“Cure” Diabetes?

The combination of type 2 diabetes and being significantly overweight is a huge burden.

Doctors tell you to lose weight, in essence, to save your life. Weight loss, in addition to diabetes medications, they say, will manage the major symptom of your diabetes: high blood glucose. If not controlled, experts warn, the excess glucose will lead to circulatory problems, high blood pressure, heart and kidney disease, blindness, limb amputations, and the many other complications of diabetes. Also, an obese person, or someone with a body mass index – BMI – over 30, has an increased risk of heart disease, cancer, arthritis, and sleep apnea.

The solution: two simple words, lose weight. The reality: not that simple. Losing so much weight by diet alone and keeping the weight off are extremely difficult for someone with a BMI over 30. Exercise also is likely to be difficult for someone with a high BMI.

Various types of weight loss surgery help people who have type 2 diabetes and BMIs over 35 lose weight, sometimes as much as 50 percent or more of their origi-

By Robin Eisner

Experts disagree about how surgery treats diabetes but agree more research needs to be done

nal weight, depending on the surgery. Besides allowing these patients to lose and keep off excess weight, surgery helps most patients manage their diabetes and blood glucose levels, with some people needing fewer medications and others stopping drugs completely.

The debate about the surgery and diabetes

Although weight loss surgery helps patients with diabetes and BMIs over 35 (the minimum BMI for surgery) lose weight, it remains unclear how it helps treat diabetes. Because most patients have substantially improved glucose control soon after surgery and before losing significant weight, some clinicians argue that the surgery alters the gastrointestinal system's anatomy and hormonal milieu to cause the remission of symptoms. The new hormone balance, they say, influences insulin and glucose levels, appetite, and overall metabolism. As a result, they call these procedures metabolic instead of bariatric, the traditional term for weight loss surgery.

Other physicians, however, say it is more likely the reduction in the amounts of food patients eat before and soon after surgery, not altered hormones, that leads to the metabolic changes and rapid glucose control after surgery. Calorie restriction can directly lower glucose levels. It is not hormonal changes contributing to the diminution of diabetes symptoms, they say, but reduced calories and, ultimately, weight loss.

Still others say hormonal changes and weight loss may act together.

Does it matter why patients are being helped? Surgeons say no other treatment is better for helping many patients with diabetes and BMIs over 35 lose weight and manage their diabetes. Endocrinologists agree

How do hormones work to help diabetes after surgery, and how long do improvements last?
Which patients are the best surgery candidates?
When should surgery be offered? Will surgery also help diabetes patients with lower BMIs?

but want to see if the hormonal effects from the surgery, independent of reduced calories and weight loss, may point the way to development of better drugs or other interventions that work on these biochemical pathways, a less extreme alternative to surgery. Not all morbidly obese patients are candidates for surgery, which has risks and causes life-long medical issues, such as vitamin and mineral absorption problems that must be treated with supplements.

Many questions about surgery inform the debate: How might gut hormones work to help diabetes after surgery? How long do the improvements last after surgery? Which patients are the best surgery candidates? When should surgery be offered: at first diagnosis of diabetes or perhaps even before full-fledged diabetes occurs? Will surgery also help diabetes patients with lower BMIs?

Columbia scientists and others worldwide are engaged in basic and clinical research to answer these questions. The need is evident in the statistics: The federal government estimates that more than 24 million

Americans have type 2 diabetes, and about half of them are obese with a BMI over 30. Some estimates suggest one in every five U.S. health care dollars goes for medications, hospitalization, or emergency room visits to treat diabetes, which costs 2.3 times more than any other chronic condition, according to Kaiser Health News. Approximately \$83 billion is spent annually just in hospital fees for diabetes, almost a quarter of all hospital spending, with Medicare paying 60 percent of those hospitalizations due to the complications of diabetes. The economic burden of diabetes alone makes all the more urgent the hopes suggested by metabolic surgery or novel interventions derived from surgery's effectiveness.

Types of surgery

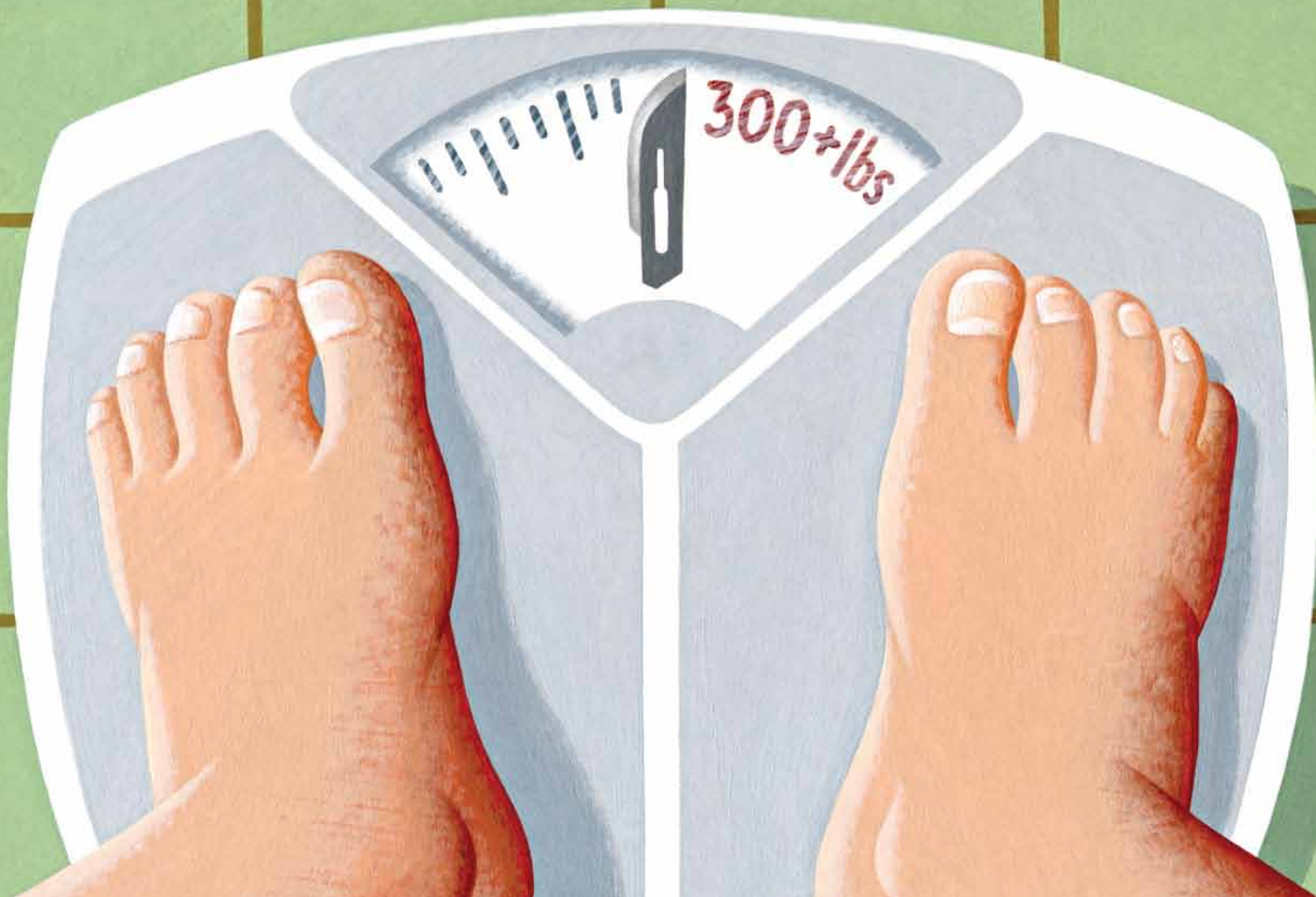
All the surgeries, including Roux-en-Y (gastric bypass), sleeve gastrectomy, and gastric band, reduce the stomach's size, make the person feel fuller after eating less, and lead to weight loss. Gastric bypass decreases the stomach's size to that of an egg and redesigns gastrointestinal anatomy. The smaller stomach is connected to the small intestine's jejunum, avoiding the duodenum, normally the first region of the small intestine where stomach contents empty. Gastric bypass surgery has been the most successful in ameliorating diabetes symptoms and is believed to contribute to the hormonal changes by rearranging the intestine's structure. Sleeve gastrectomy eliminates about 80 percent of the stomach, creating a tube where a bulging pouch had been. Gastric band surgery, best known by the brand name LAP-BAND, employs a band around the top portion of the stomach to limit the food volume that enters. All the surgeries are performed laparoscopically.

Studies show 90 percent to 95 percent of patients with BMIs over 35, who have had type 2 diabetes for less than 10 years, and were taking oral medications – but not insulin – before surgery resolve or significantly improve their diabetes after gastric bypass, says Marc Bessler, M.D., professor of clinical surgery and director of the Center for Metabolic and Weight Loss Surgery at Columbia. Eighty percent to 85 percent of patients with diabetes for more than 10 years who were taking insulin before surgery see resolution or significant improvement of their diabetes after gastric bypass. Sleeve gastrectomy and band surgery have lower success rates in reducing the symptoms for people with diabetes and BMIs over 35.

Today, private and government insurance companies reimburse for these procedures only in people who have BMIs over 35, have diabetes, and have been unsuccessful at losing weight after repeated attempts. "The insurers are not reimbursing to treat the diabetes, but for the weight loss," Dr. Bessler says. The surgery decreases mortality from obesity in these patients above and beyond the risk of the surgical procedure.

How does the gastrointestinal system work on metabolism?

That the gut plays an active role in weight loss and the regulation of eating behavior is a relatively new idea, explains Rudolph Leibel, M.D., the Christopher J. Murphy Professor of Diabetes Research, professor of pediatrics and medicine, co-director of the Naomi Berrie Diabetes Center, and co-director of the New York Obesity Research Center and the Columbia University Diabetes and Endocrinology Research Center.



“It used to be thought you ate, the gastrointestinal tract digested food and absorbed the calories,” says Dr. Leibel. “Now, we know there are important interactions of the gut with food and the gut plays a role in influencing behavior to start and stop eating and for food preference. It is not just a pipe.”

Gut hormones, such as the incretins GLP-1 and GIP, regulate insulin secretion, while others, such as PYY-1 and CCK, affect food intake. In fact, several new diabetes drugs, such as exenatide (Byetta) and liraglutide (Victoza), work as a GLP-1 receptor agonist to stimulate insulin release. Nerve signals from the gut can also stimulate the vagus nerve, a cranial nerve that extends from the brain stem to the viscera, with or without hormonal input.

“It is not surprising that manipulating the gut via surgery can affect glucose and insulin metabolism, leading to a reversal of symptoms and a decrease in the number of drugs needed to treat diabetes,” says Dr. Leibel. But the jury is still out as to whether calorie restriction or hormonal changes (or both) account for the improvements. “Patients are not in a neutral energy state before surgery. They eat less calories; negative energy balance can affect glucose metabolism.”

Doctors cannot force morbidly obese patients to lose, then maintain, the weight loss they need to effect metabolic changes. “It is hard for patients to reduce calories to lose weight and improve their metabolism but even harder to keep the weight off,” says endocrinologist Blandine Laferrère, M.D., associate professor of medicine and co-director of the hormonal core laboratory at the New York Obesity Nutrition Research Center, an NIH-funded collaboration of Columbia and St. Luke’s-Roos-

velt Hospital Center. Dr. Laferrère has researched the hormonal effects of bariatric surgery for the past 10 years.

Dr. Leibel acknowledges the surgery is vital for morbidly obese patients and thinks gut hormones may be playing a role in addition to weight loss. He also believes that research about the altered gut hormones’ mechanisms of action after the surgery may lead to new drugs and less invasive interventions.

Evidence for and against the metabolic argument

What evidence favors either calorie restriction/weight loss or hormonal changes?

Whether weight loss and calorie restriction play a more dominant role than hormonal changes after bariatric surgery is unclear. Gastric bypass seems to be working by both mechanisms. However, bypassing the duodenum may not be necessary. Animals with diabetes that have had sleeve gastrectomy lose weight, have an improvement in diabetes, and have an incretin-like response similar to what occurs in gastric bypass, points out Dr. Laferrère.

But Melissa Bagloo, M.D., assistant professor of clinical surgery in the Center for Metabolic and Weight Loss Surgery, thinks hormones are more at play. In a study in which type 2 diabetic rats underwent a duodenal-jejunal bypass, a gastrojejunal bypass, or a sham operation, the animals were fed the same type of diet. The animals that underwent the duodenal-jejunal bypass, which, similar to the Roux-en-Y, excludes the initial portion of the small intestine but does not alter the stomach, maintained significantly better glucose control, suggesting that the surgery’s hormonal effects – not fewer calories – were responsible, says Dr. Bagloo.

It would be unethical to allow morbidly obese human research subjects to eat whatever they want after a gastric bypass to see if glucose control improves even without calorie restriction, so researchers have inferred the effects of calorie restriction versus hormones in diabetes control.

In a 2007 study, Dr. Laferrère compared the hormonal profiles of patients with BMIs between 35 and 50 who had undergone surgery with people who had the same BMIs but ate very few calories. She measured the levels of incretins, such as GLP-1 that increase insulin secretion and glucose control, in both groups after they lost the same amount of weight. She found that incretin levels were much higher and the diabetes control better for patients who had the bypass surgery compared with patients who lost weight via calorie restriction.

"There is something special about surgery compared to weight loss alone," Dr. Laferrère says. "Both groups of patients lost the same amount of weight but there was a difference in hormone levels and diabetes improvement in the surgery group." She is now studying the mechanisms behind hormonal changes, such as food transit time and bile acid changes after bypass surgery. But the patients in her 2007 study had diabetes for less than five years, were not taking insulin, and may still have had residual insulin production. Patients who have had diabetes longer and who take insulin may have different hormonal results after surgery.

Ongoing research

To better understand the hormonal responses and glucose control in patients with BMIs over 35 who have had diabetes for any length of time and may or may not take insulin, Judith Korner, M.D., Ph.D., associate professor of medicine and director of the Weight Control Center

No drug currently available can help affected patients lose weight and manage their diabetes. Research should help determine ways to improve the surgery with the goal of increasing the number of patients who can benefit.

at Columbia, is directing an NIH-funded clinical trial comparing gastric bypass surgery with restricted diet alone in that population. The results of this study should shed light on whether it is caloric restriction or surgical manipulation of the gut that is responsible for early improvement in glucose control.

Encouraged by evidence that gastric bypass surgery has metabolic and hormonal effects beyond weight loss for type 2 diabetes patients with BMIs over 35, many clinicians at Columbia and elsewhere are investigating whether metabolic surgery can help type 2 diabetes patients with lower BMIs. Dr. Korner, in conjunction with Columbia surgeons Dr. Bessler and Leaque Ahmed, M.D., associate clinical professor of surgery at Harlem Hospital, are investigators in a five-location clinical trial of 120 patients who have BMIs between 30 to 39.9, have had type 2 diabetes for at least six months, and may or may not take insulin. Only individuals whose

diabetes is poorly controlled have been randomized. Sponsored by the surgical supply company Covidien, the study will compare gastric bypass with intensive medical management using diabetes drugs and lifestyle changes, focused on diet, exercise, and behavior. The sites are New York (Columbia), Minnesota (University of Minnesota and the Mayo Clinic), and two hospitals in Taiwan. "Because the race and ethnicities are different, with Caucasians, Hispanics, and African-Americans in New York, mostly Caucasians in Minnesota, and Asians in Taiwan, race and ethnicity may have an impact on the results," Dr. Korner says.

Asians can develop type 2 diabetes with much lower body weights and BMIs, such as 24, than Caucasians. A BMI of 24 for a Caucasian is considered normal weight. Research abroad has shown metabolic surgery in Asians with lower BMIs can help resolve their diabetes, Dr. Bessler says. "The results of this randomized study might help determine what type of patient is the best candidate for the surgery," Dr. Korner says. "By enrolling individuals with a BMI under 35, results from this study may be used to change current BMI criteria for metabolic surgery."

Dr. Bessler is directing a trial to compare LAP-BAND, gastric bypass, and sleeve gastrectomy to determine which surgery might be best for people with type 2 diabetes and BMIs between 30 and 34.9. Patients in the trial must pay for the treatment because insurance companies do not consider metabolic surgery in the lower BMI category standard of care.

The prevailing wisdom against surgery for the lower BMI patients with diabetes might be changing, says Dr. Bessler. In February 2011, the Food and Drug Administration extended the use of LAP-BAND for patients with BMIs of 30 who have another condition related to their obesity, such as diabetes. "This seems to be a first step in showing that these kinds of operations may be appropriate for the lower BMI population with diabetes," Dr. Bessler says. The FDA in 2001 had approved LAP-BAND for patients with a BMI of at least 40, patients who were at least 100 pounds overweight, and patients with a BMI of at least 35 who also had another severe condition due to their obesity, such as heart disease or diabetes.

On the basic research front, Domenico Accili, M.D., the Russell Berrie Foundation Professor of Diabetes (in Medicine) and co-director of the Columbia University Diabetes and Endocrinology Research Center, has a 10-year NIH grant to study how endocrine cells in the gut change after gastric bypass.

"Pharmaceutical and biotechnology companies are actively researching these gut hormones as potential new treatments," says Dr. Accili. "One of the great benefits of this attention to gut hormones and metabolic surgery is the effort to try to understand what is going on to help patients, perhaps, in new ways. The unresolved questions also remind us how complex diabetes is as a disease and what more needs to be learned."

Researchers outside of Columbia also are assessing how long the benefits of metabolic surgery last and the best timing of surgery following diagnosis. Also, cost benefit analyses are being used to compare the expense of the surgery with reduced costs in treating diabetes complications.

"For now, there is no drug that can help extremely obese patients with diabetes lose weight and help them manage their diabetes like the surgeries can," Dr. Bessler says. "All the research should help us determine how to improve the surgery and potentially increase the number of patients who can benefit." ♦