

## TOPIC COLLECTION: BENEFITS OF METABOLIC SURGERY

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### Letter from the Editor

A plethora of studies comparing the metabolic benefits of bariatric surgery with usual medical management of obese patients has increased the focus on surgical management — either Roux-en-Y gastric bypass or, increasingly often, sleeve gastrectomy. These studies initially focused on enhanced insulin sensitivity, improved glucose regulation, and a higher likelihood of reversing prediabetes and diabetes. This last benefit was presumed to be the result of the superior effects of surgical over medical management on caloric restriction and weight loss.

These studies were extended to show benefit in reducing the risk for other consequences of metabolic dysregulation. One NEJM summary in this collection discusses Cohen and colleagues' comparison of surgical management versus medical therapy for remission of microalbuminuria. Another looks at Aminian and colleagues' examination of the effects of surgery on adverse cardiovascular events in diabetic patients. Other researchers have compared the two approaches for reducing hypertension (*Ann Intern Med* 2020 Aug 18; <https://doi.org/10.7326/M19-3781>).

Over time, investigators suggested that other, unexplained mechanisms of metabolic regulation caused at least some of these benefits to accrue to patients shortly after surgery, long before any weight loss occurred (*Diabetes Care* 2017; 40:7). Such studies led to a reframing of these procedures as “metabolic” rather than “bariatric” surgery, suggesting that metabolic benefits were unrelated to caloric restriction and resultant weight loss. Inge and colleagues studied the benefits of surgical management of obese adolescents. Other researchers have considered the body mass index (BMI) threshold at which benefits outweighed risks. These studies led many primary care physicians and surgeons to favor surgical rather than medical management of obese patients.

In the *New England Journal of Medicine* article, the authors refute the claims of improved metabolic regulation separate from caloric restriction and weight loss through a robust comparison of the metabolic function of a small group of patients managed either surgically or medically. A wide range of metabolic measures were shown to be entirely correlated with corresponding weight loss. This study appears to put to rest for now the notion that metabolic benefits accrue independently of weight loss. Pound for pound, weight loss by either medical or surgical means is equally beneficial. However, clinicians must still sort out the benefits of lowering the BMI threshold and/or the age at which obese patients should be managed surgically. In addition, there are likely regional variations that influence care, as well as widely varying levels of insurance coverage for metabolic surgery that influence decision making.

Thomas L. Schwenk, MD

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## ORIGINAL ARTICLE

# Effects of Diet versus Gastric Bypass on Metabolic Function in Diabetes

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## ABSTRACT

**BACKGROUND**

Some studies have suggested that in people with type 2 diabetes, Roux-en-Y gastric bypass has therapeutic effects on metabolic function that are independent of weight loss.

**METHODS**

We evaluated metabolic regulators of glucose homeostasis before and after matched (approximately 18%) weight loss induced by gastric bypass (surgery group) or diet alone (diet group) in 22 patients with obesity and diabetes. The primary outcome was the change in hepatic insulin sensitivity, assessed by infusion of insulin at low rates (stages 1 and 2 of a 3-stage hyperinsulinemic euglycemic pancreatic clamp). Secondary outcomes were changes in muscle insulin sensitivity, beta-cell function, and 24-hour plasma glucose and insulin profiles.

**RESULTS**

Weight loss was associated with increases in mean suppression of glucose production from baseline, by 7.04  $\mu\text{mol}$  per kilogram of fat-free mass per minute (95% confidence interval [CI], 4.74 to 9.33) in the diet group and by 7.02  $\mu\text{mol}$  per kilogram of fat-free mass per minute (95% CI, 3.21 to 10.84) in the surgery group during clamp stage 1, and by 5.39 (95% CI, 2.44 to 8.34) and 5.37 (95% CI, 2.41 to 8.33)  $\mu\text{mol}$  per kilogram of fat-free mass per minute in the two groups, respectively, during clamp stage 2; there were no significant differences between the groups. Weight loss was associated with increased insulin-stimulated glucose disposal, from 30.5 $\pm$ 15.9 to 61.6 $\pm$ 13.0  $\mu\text{mol}$  per kilogram of fat-free mass per minute in the diet group and from 29.4 $\pm$ 12.6 to 54.5 $\pm$ 10.4  $\mu\text{mol}$  per kilogram of fat-free mass per minute in the surgery group; there was no significant difference between the groups. Weight loss increased beta-cell function (insulin secretion relative to insulin sensitivity) by 1.83 units (95% CI, 1.22 to 2.44) in the diet group and by 1.11 units (95% CI, 0.08 to 2.15) in the surgery group, with no significant difference between the groups, and it decreased the areas under the curve for 24-hour plasma glucose and insulin levels in both groups, with no significant difference between the groups. No major complications occurred in either group.

**CONCLUSIONS**

In this study involving patients with obesity and type 2 diabetes, the metabolic benefits of gastric bypass surgery and diet were similar and were apparently related to weight loss itself, with no evident clinically important effects independent of weight loss. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT02207777.)

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## Gastric Bypass Surgery in Patients with Diabetes and Microalbuminuria

*Microalbuminuria remitted more commonly with surgery than with medical management.*

Bariatric surgery is superior to intensive medical therapy for weight loss and improved metabolic function in appropriately selected patients. In this trial, researchers looked specifically at the effect of bariatric surgery on proteinuria in 100 obese patients with type 2 diabetes and microalbuminuria (median urinary albumin-creatinine ratio [uACR], 73 mg/g). At baseline, mean age was 51, mean body-mass index was 33 kg/m<sup>2</sup>, and median serum creatinine was 0.8 mg/dL. Patients were randomized to receive either laparoscopic roux-en-Y gastric bypass or best medical therapy.

At 24 months, microalbuminuria had resolved (uACR levels, <30 mg/g) in 84% of the gastric bypass group versus 56% of the medical therapy group. Mean weight loss among patients in the gastric bypass group was 25.4% compared with 4.5% in the medical therapy group. Incidence of serious adverse events was similar in both groups.

### COMMENT

This study shows that gastric bypass surgery can improve microalbuminuria in type 2 diabetes patients with otherwise preserved renal function. Given that follow-up was only 2 years, it remains unclear whether this outcome will translate into long-term improvement in clinically meaningful renal outcomes.

— **Thomas L. Schwenk, MD**

*Cohen RV et al. Effect of gastric bypass vs best medical treatment on early-stage chronic kidney disease in patients with type 2 diabetes and obesity: A randomized clinical trial. JAMA Surg 2020 Jun 3; [e-pub]. (https://doi.org/10.1001/jamasurg.2020.0420)*

## Metabolic Surgery Is Associated with Fewer Adverse Cardiovascular Events in Diabetic Patients

*In a retrospective case-control study, surgical patients also had lower all-cause mortality at 8 years.*

Metabolic surgery (surgery that induces weight loss and alters gastrointestinal and glucose physiology) improves diabetes control, but data on changes in risk for adverse cardiovascular events are sparse. Cleveland Clinic researchers identified 2287 patients with type 2 diabetes who underwent metabolic surgery (nearly all Roux-en-Y gastric bypasses or sleeve gastrectomies) and matched these patients on 37 variables to 11,435 patients who did not undergo metabolic surgery. Two thirds of patients were women; median age was 54, and median body-mass index was ≈44 kg/m<sup>2</sup>.

Median follow-up was 4 years, but the researchers calculated 8-year estimated outcomes. The 8-year cumulative incidence of major adverse events (i.e., all-cause mortality, coronary artery events, cerebrovascular events, heart failure, nephropathy, or atrial fibrillation) was significantly lower in the surgical group than in the nonsurgical group (31% vs. 48%). Analyses of various secondary endpoints, including all-cause mortality alone, showed similar differences. Roughly 7% of surgical patients experienced 90-day postoperative complications, including transfusion and

pulmonary events, and 25% required various postoperative endoscopy and imaging procedures.

### COMMENT

Retrospective cohort studies are fraught with potential bias, but this large, well-matched study with good statistical adjustment shows a clear benefit for metabolic surgery with regard to lower risk for major adverse cardiovascular events and all-cause mortality. A trade-off is the nontrivial incidence of early- and intermediate-term complications of surgery. — **Thomas L. Schwenk, MD**

*Aminian A et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA 2019 Sep 2; [e-pub]. (https://doi.org/10.1001/jama.2019.14231)*

## Five-Year Bariatric Outcomes: Adolescents vs. Adults

*After gastric bypass surgery, type 2 diabetes and hypertension improved more frequently in adolescents than adults.*

Bariatric surgery has the potential for weight loss and improvement of obesity-related health conditions in both adolescents and adults. However, whether outcomes differ by age at surgery has been questioned.

Researchers examined 5-year outcomes in 161 adolescents (aged 13–19 years) and 396 adults (aged 25–50) with obesity since adolescence who underwent Roux-en-Y gastric bypass. The two groups had similar and significant weight loss. Adolescents were significantly more likely to have remission of diabetes and hypertension. Among adolescents, the prevalence of diabetes dropped from 14% at baseline to 2% at 5 years; among adults, prevalence dropped from 31% to 12%. No adolescent had to take diabetes-related medication, at 5 years, compared with 26% of adults. Among patients who were hypertensive at baseline, 68% of adolescents versus 41% of adults were in remission at 5 years. Death rates were similar, but significantly more adolescents than adults had abdominal reoperations (19 vs. 10 per 500 person-years) and low ferritin levels (48% vs. 29%).

### COMMENT

Sustained obesity into adulthood may carry cumulative adverse health effects. If shown to be effective and safe, bariatric surgery during adolescence could yield improved health outcomes during adulthood. While this study adds important information about the reversal of obesity-related outcomes, the lifetime risk of this surgery remains unknown. The more-frequent reoperation and higher prevalence of nutritional deficiencies in adolescents merits attention. In discussing the pros and cons of this procedure with teens, pediatricians should be transparent about the lack of information on adult outcomes. We should consider lifestyle and pharmacologic interventions first. However, this study provides reassurance that surgery may be a reasonable consideration for adolescents who do not respond to less-invasive approaches.

— **Catherine M. Gordon, MD, MSc**

*Inge TH et al. Five-year outcomes of gastric bypass in adolescents as compared with adults (TEEN-LABS). N Engl J Med 2019 May 30; 380:2136. (https://doi.org/10.1056/NEJMoa1813909)*

*Adams TD. In teens with severe obesity, can bariatric surgery wait until adulthood? N Engl J Med 2019 May 30; 380:2175. (https://doi.org/10.1056/NEJMe1905778)*