Should We "Bypass" Meds In Favor of Surgery? Bariatric Surgery for the Moderately Obese Diabetic Patient

Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA 2013;309:2240–9.

Study Overview

Objective. To determine whether gastric bypass surgery is superior to lifestyle and medical management for improvement of diabetes, dyslipidemia and hypertension in patients with BMI of 30.0–39.9 kg/m^2.

Study design. Randomized controlled trial (RCT).

Setting and participants. The Diabetes Surgery Study was a 2008–2011 multicenter trial of Roux-en-Y gastric bypass (RYGBP) plus lifestyle change and medication versus intensive lifestyle and medical therapy for obese diabetic patients. Three of the 4 trial centers were in the United States; the fourth was in Taiwan. In order to participate in the trial, patients had to be 30 to 67 years of age, have a BMI of 30.0–39.9 kg/m^2, have suboptimally controlled type 2 diabetes (HbA1c > 8.0%) of at least 6 months' duration, be free from comorbidities such as known cardiovascular, psychological, or malignant disease, and have no prior history of gastrointestinal surgery.

120 patients were enrolled. 60 were randomized to the lifestyle and medical management arm and 60 to gastric bypass (in addition to the lifestyle intervention). Because of the multisite nature of the trial, block randomization was used to ensure roughly equal numbers in both arms at each site.

Intervention. All participants received an intensive and evidence-based lifestyle modification intervention. This consisted of counseling sessions with a trained interventionist for a total of 24 weekly meetings over 6 months, followed by every other week meetings during months 7–9, then monthly meetings for the rest of the year (months 10–12). Goals were for participants to reach 325 min of physical activity per week and decrease their daily caloric intake to produce weight loss of 1–2 lb per week (recommended calorie limits varied according to starting body weight and treatment arm). Participants in the medical management group were also treated with the weight loss medications orlistat or sibutramine when the pace of their weight loss was deemed inadequate.

All participants were treated with the same medication regimen protocols for diabetes, LDL lowering, and hypertension. Medications were titrated toward the following goals: HbA1c < 7%, LDL < 100 mg/dL, and systolic blood pressure (SBP) < 130 mm Hg.

Participants randomized to the surgical arm underwent RYGBP at baseline, with discontinuation of

their glycemic, lipid-lowering, and BP medications in the immediate postoperative period. Medications were restarted as needed to meet or maintain the aforementioned goals for HbA1c, LDL, and SBP. As much as possible, the surgical procedures were standardized and performed by the same surgeon in each site.

Participants were followed from baseline forward with monthly medical visits for 6 months, then quarterly visits until the 12-month mark.

Main outcome measures. The primary outcome of interest was a triple composite endpoint of HbA1c < 7%, LDL < 100 mg/dL, and SBP < 130 mm Hg at the end of the 1-year follow-up period. Secondary outcomes included weight loss, adverse events, additional serum measures (triglycerides [TG], HDL), medication use, and waist circumference.

Logistic regression was used to determine whether the odds of achieving the primary outcome differed according to treatment arm. Linear regression was used to model continuous outcomes. Analysis was intention-to-treat, and there was some missingness at the 12-month visit, so multiple imputation techniques were used to project the composite outcome for participants who did not complete 12-month follow-up. A sensitivity analysis was also performed where missing surgical participants were all presumed to have failed to achieve the composite outcome, while missing medical participants were all presumed to have achieved the composite outcome—the primary findings of the analyses did not change under these assumptions.

Results. There were no significant differences reported between the 2 groups with regard to baseline characteristics. The mean (SD) age of participants was 49 years (8 for surgical, 9 for medical), just over half were women, and half were non-Hispanic white (27%–28% were East Asian). Mean (SD) BMI was 34.6 (3.1) kg/m^2. Mean (SD) baseline SBP was 132 (14) mm Hg in the lifestyle group and 127 (15) mm Hg in the surgical group. Diabetes was fairly long-standing in both groups (9.1 years in lifestyle group and 8.9 years in surgical group), with both groups having a mean (SD) baseline HbA1c of 9.6 (1.2)%. Mean (SD) baseline LDL was 105 (43) mg/dL in the lifestyle group and 103 (36) mg/dL in the surgical group. More of the surgical participants (62%) were on insulin at baseline than the lifestyle participants (43%), but baseline medication use for dyslipidemia and hypertension were similar. Overall, participants in the lifestyle group were using a combined mean (SD) of 4.4 (1.5) medications to control glycemia, lipids, and blood pressure, versus 4.1 (1.9) medications in the surgical group. At 12 months, only 6 participants were lost to follow-up (3 in each arm), and 3 crossed over (1 lifestyle participant got gastric bypass outside the trial, 2 surgical participants declined surgery).

Among medical management participants, 19% achieved the triple composite endpoint compared with 49% in the surgical group (odds ratio [OR] 4.8, 95% confidence interval [CI] 1.9 to 11.7). When the composite endpoint was broken down into three parts, however, the "HbA1c < 7%" component appeared to be driving this difference—it was the only significant treatment effect of the 3 (OR 6.0, 95% CI 2.6 to 13.9). There was no significant difference between groups for odds of achieving LDL < 100 (OR 1.6, 95% CI 0.7 to 3.8), or SBP < 130 mm Hg (OR 1.7, 95% CI 0.6 to 4.6).

Surgical participants did lose significantly more weight than lifestyle participants at 1 year post-randomization (–17.5% difference, 95% CI –20.7% to –14.2%) and ended up on significantly fewer medications in order to control glycemia, dyslipidemia, and blood pressure (3.0 fewer, 95% CI –3.6 to –2.3). A sensitivity analysis to determine whether clinic location had a significant treatment effect was negative (P value 0.7 for test of homogeneity across clinics).

The authors do report a number of adverse events that occurred during the trial, some of which were clearly related to surgery (eg, anastamotic leak), and others (eg, bronchitis, pregnancy, motor vehicle crash) that would less clearly have been related to the individual having participated in the trial. Overall, they report 15 such adverse events for the medical management arm and 22 for the surgical arm. Nutritional deficiencies known to be associated with gastric bypass (eg, iron deficiency, vitamin B deficiency) were more also common in the surgical group than in the medical management group. There were no deaths reported during the trial period.

Conclusion. In obese diabetic patients who are not successful at lifestyle and medical management alone, gastric bypass can improve the chances of significant weight loss and diabetes remission, but these benefits must be weighed against potential risks of the procedure.

Commentary

Obesity and type 2 diabetes account for a growing percentage of morbidity and mortality from chronic illness

in the United States, and, increasingly, in other countries across the globe. Unfortunately, despite medical advances in glycemic agents, lipid-lowering medications, and antihypertensives, many patients struggle to obtain and maintain control of diabetes, dyslipidemia and high blood pressure [1–3]. As a result, as many as 15.7% of adult deaths annually in North America may be attributable to diabetes and its micro- and macrovascular complications [4].

Several recent trials, such as the Look AHEAD study [5], have attempted, with mixed success, to use intensive lifestyle interventions based on the Diabetes Prevention Program (DPP) [6] to reverse the course of disease for existing type 2 diabetics, operating under the assumption that even a moderate amount of weight loss might lead to remission. Meanwhile, a parallel movement in the surgical realm has been gaining momentum over the past 5 to 10 years to use bariatric surgery as a treatment not just for obesity, but for diabetes [7]. In addition to numerous observational studies, there have now been several small randomized trials of surgical techniques, such as laparoscopic adjustable gastric banding (LAGB), compared with medical management of diabetes in which the surgical procedures have produced superior results [8]. These trials, although small, have impressed policy makers enough that the FDA in 2011 changed eligibility criteria for the LAGB procedure to include patients with lower BMI, opening the door to potentially large increases in uptake of these procedures [9]. As the authors of this current study point out, however, many previous trials of bariatric surgery versus medical management did not use intensive medical and lifestyle interventions as a comparison group, thus potentially underestimating the impact of this line of treatment compared with surgery.

This novel multisite RCT by Ikramuddin and others has attempted to address several limitations of previous studies of surgery versus medical management. First, the randomized nature of the intervention protects against the self-selection bias that is so likely present in observational data—eg, are those who seek out and successfully obtain surgery more motivated or health-literate than those who don't? Second, although this study is not large, it is bigger than previous RCTs (total $n = 60$ in 2 recent trials) [8,10]. Also as noted by the authors of this study, it was important to have a trial that spanned multiple medical centers in order to assert that the treatment effects of surgery vs medical therapy persisted regardless of location.

Compared with previous trials of surgery versus lifestyle, this trial made a major effort to pick the best possible weight loss and diabetes treatments for both arms. They limited the surgical treatment arm to gastric bypass, a procedure that, although invasive, has the best track record for inducing diabetes remission compared with other common bariatric procedures (eg, LAGB, vertical sleeve gastrectomy). For lifestyle and medical management, they implemented not just routine care but an aggressive DPP- and Look AHEAD–like curriculum for lifestyle change, combined with weight loss medications and optimal medical management for comorbidities. Setting both arms up with the best possible scenarios was important for determining the efficacy of these different approaches (how does surgery compare to meds under optimal circumstances?) Another unique aspect of this trial is that it excluded patients with BMIs of 40 and higher, the group that has been the traditional focus of most bariatric surgical trials, in favor of studying those with more moderate degrees of obesity (BMI 30–39.9).

The authors justify their composite outcome by pointing out that it covers not just glycemic control but 2 other important predictors of micro- and macrovascular complications of type 2 diabetes. Interestingly, although their primary finding was that the composite endpoint was more likely to occur among surgical participants, this finding was driven solely by the effect of surgery on HbA1c. The apparent lack of difference between groups in LDL and SBP changes may be related to the population's starting points for these 2 outcome components. While mean HbA1c values (9.7%) indicated poor glycemic control at baseline, baseline LDL and SBP were already quite close to the dichotomized end goals of < 100 mg/dL and < 130 mm Hg. The trial had power to detect the kind of large difference seen for A1c (given the starting point), but for detecting a more subtle difference (odds of decreasing 3–5 points in LDL, or odds of achieving a very small change in SBP) its numbers may have been too few. Additionally, interpreting the composite outcome is somewhat complicated without also considering the number of medications required to achieve that outcome, which, while monitored separately, did not factor into the primary outcome. A metric that accounted for number of medications but also the doses of those medications would have been useful—being on 5 mg of lisinopril for renal protection is quite different from being on 40 mg of lisinopril for BP control, for example.

The follow-up period of 12 months used in this trial may result in an overestimate of the clinical impact of bariatric surgery; the first year after RYGBP is a known period of rapid weight loss and disease remission. Although long-term follow-up studies of bariatric patients are not numerous, those that exist suggest that a substantial fraction of surgical patients begin to regain weight and have relapse of comorbidities such as diabetes, perhaps within 5 years of surgery [11,12]. A longer-term follow-up study would be important for informing real-world clinical decisions about what patients can expect further out after surgery.

As with most RCTs, this trial has some shortcomings for generalizability. First, because such an idealized lifestyle and medical management intervention was used, the ability to orchestrate and pay for that intervention in clinical practice might be limited. Also, the number of patients who would have time and resources to comply with such an intense intervention may be limited in real clinical practice.

Applications for Clinical Practice

Gastric bypass surgery can offer weight loss and improved glycemic control for longstanding diabetics with moderate obesity, but the procedure does pose some significant and potentially long-lasting health risks, and little information can be given to this group of patients about long-term durability of initial procedure results. On the other hand, the long-term risks of living with poorly controlled diabetes are quite high and must enter the discussion as well. Interested and eligible patients should be told about possible short-term benefits, risks, and the uncertainty of long-term outcomes.

—Kristina Lewis, MD, MPH

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