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## Bariatric surgery for type 2 diabetes: getting closer to the long-term goal

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Bariatric surgery is more effective than intensive medical or lifestyle interventions for inducing weight loss and remission of type 2 diabetes (T2DM) as demonstrated in randomized clinical trials for obese patients - even for those with relatively lower body mass indices (BMI) ranging between 30.0 to 34.9 kg/m<sup>2</sup>.<sup>1</sup> Bariatric procedures may be associated with better survival and fewer cardiovascular events compared to non-surgical management of patients with diabetes as shown in long-term observational studies; but even the best observational studies may not be definitive because of concerns about unmeasured confounding variables and selection bias. Thus, longer-term RCTs are also needed to provide definitive evidence of the durability and superiority of bariatric procedures compared to the best available medical and lifestyle treatment of T2DM.

In a recent study published in *JAMA Surgery*, Courcoulas and colleagues randomized 61 adults with a BMI between 30 and 40 kg/m<sup>2</sup> and T2DM to receive Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), or an intensive lifestyle intervention for 1 year, followed by a low-level lifestyle intervention delivered to all three treatment groups in years 2 and 3.<sup>3</sup> The primary outcome, partial or complete diabetes remission – defined as a HbA1c <5.7% without taking any medications for T2DM – was achieved by 8 patients (40%) in the RYGB group, 6 (29%) in the LAGB group, and no patients in the intensive lifestyle group ( $P = 0.004$ ). Improvements in diabetes control were particularly impressive for RYGB given that this group had the highest baseline HbA1c (8.5% RYGB, 7.8% for LAGB, and 7.0% for lifestyle). At year 3, patients in the RYGB group also had greater weight loss, compared with the LAGB and lifestyle groups (–25% RYGB, –15% LAGB, and –5.7% for lifestyle;  $P < 0.01$ ). The higher HbA1c levels in the RYGB group at baseline almost certainly means that those patients had less endogenous insulin production than in the other two groups and were further along in the progressive beta-cell decline that accompanies T2DM, which likely explains the more rapid relapse of T2DM observed in the RYGB patients. Yet another important aspect of this study was that

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26 patients (43%) had a BMI <35 kg/m<sup>2</sup>, which further supports bariatric surgery as an effective treatment for T2DM in mild-to-moderately obese patients.

These findings are similar to the results of the STAMPEDE trial, in which 150 adults at a single medical center with a BMI between 27 and 43 kg/m<sup>2</sup> and uncontrolled T2DM were randomized to receive intensive medical therapy alone or to receive intensive medical therapy plus RYGB or sleeve gastrectomy (SG).<sup>2</sup> Patients randomized to undergo bariatric surgery had significantly greater improvements in weight, diabetes control, and quality of life at 3 years. Patients randomized to RYGB lost more weight and improved their diabetes more than those randomized to SG.

In addition to providing solid evidence on the efficacy of surgery relative to intensive lifestyle treatment, these studies and others indicate that RYGB is superior to both LAGB and SG in the initial control of T2DM.<sup>4</sup> In particular, the experience of Courcoulas et al with LAGB is likely to be the best-case scenario – their patients received intensive follow-up and lifestyle intervention in a clinical trial setting. Although LAGB is often characterized as less invasive and low risk, this characterization overlooks the longer-term risks of revisions and reoperations associated with the procedure. Two recently published studies of the 5- and 7-year experience of patients who had LAGB indicate that 15–16% will have their band removed or revised,<sup>5,6</sup> with 29% experiencing a complication during their reoperation (a 19-fold higher rate of complications than during the original procedure).<sup>6</sup> Perhaps LAGB still has a role for some patients who seek a reversible treatment for obesity and diabetes, but it is probably time to remove the ‘low-risk’ label for this procedure.

As observed in the reports by Courcoulas et al and Schauer et al, some weight regain is expected with all bariatric procedures, but it is still unclear how much and how soon, particularly among patients who undergo SG, for whom there is little to no long-term data available owing to its rapid introduction into mainstream bariatric practice. Furthermore, diabetes is also likely to worsen or recur in many patients who undergo bariatric procedures during long-term follow-up, and prior studies have shown that patients with less severe T2DM (i.e., those with recent onset, lower HbA1c, and no insulin use) at the time of surgery are more likely to achieve remission/control of T2DM and avoid relapse.<sup>7</sup> What is needed now is long-term evidence that surgery can durably improve glycemic control and reduce the risk of microvascular and macrovascular events. Towards that goal, four research groups (Cleveland Clinic, Joslin Diabetes Center Boston, the University of Pittsburgh, and the University of Washington) that have completed 1-to-3 year randomized trials of bariatric procedures compared to medical and lifestyle management of T2DM have now formed the Alliance of Randomized Trials of Medicine versus Metabolic Surgery in Type 2 Diabetes (ARMMS- T2D) Consortium (NIDDK U34DK107917) with planned follow-up of ~300 randomized participants through 7 years. In the next few years, large observational studies involving health care databases will shed further light on questions related to durability of weight loss and glycemic control and help identify the specific patient subgroups that are most likely to benefit – or be harmed – from bariatric procedures.

Finally, the report by Courcoulas *et al*, raise the issue of how to optimally manage patients with diabetes after bariatric surgery. As the authors report, 4 patients who had undergone

bariatric surgical procedures (11%) had relapse of T2DM by 3 years, and 5 surgical patients (14%) had a HbA1c  $\geq 6.5\%$  at year 3 but were not taking any T2DM medications. Many prior articles have focused on ‘cure’ or remission of diabetes after bariatric surgery, but given that one-third of patients will experience T2DM relapse by 5 years,<sup>7</sup> it is unclear whether physicians and patients should continue to focus on the discontinuation of all T2DM medications as a primary goal. Metformin should be stopped before surgery because of the risk of lactic acidosis, but because metformin is not associated with a risk for hypoglycemia or weight gain, this medication could be reintroduced in most patients with hyperglycemia following bariatric procedures, unless gastrointestinal adverse effects or contraindications such as renal failure are present.<sup>8</sup> Given what is currently known, the most important question isn’t whether bariatric surgery alone is superior to medical therapy alone. The question is: how can surgical and medical therapy be used together to keep this high-risk population of patients healthy longer?

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