EDITORIAL

Bariatric Surgery: An Attractive Therapeutic Modality for Type 2 Diabetes Mellitus

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TYPE 2 DIABETES MELLITUS (T2DM) and obesity are closely related and together constitute two of the most common chronic health conditions affecting individuals in the Western world with significant epidemic growth over the past several decades. The number of adults in the United States diagnosed with T2DM has more than tripled between 1980 and 2011, including 1.9 million newly diagnosed patients in 2010.¹ There was a parallel increase in obesity rates in the United States from 1990 through 2010, with 34.9% of adults being obese during 2011–2012.² The consequences of T2DM and obesity, including cardiovascular disease and certain types of cancer, are among the leading causes of death in the United States and have dramatic societal and financial burdens. Together, these disorders have been described as the “twin epidemics.”³

The American Diabetes Association recommends moderate weight loss and pharmacotherapy for managing obese patients with T2DM. However, maintaining this weight loss through the traditional lifestyle changes of decreasing caloric intake and increasing physical activity can be quite challenging for patients. Over the past two decades, bariatric surgical procedures, which were initially intended for the management of morbid obesity, have emerged as favorable treatment options for T2DM even in the setting of those without severe morbid obesity.⁴

The spectrum of bariatric surgery includes operations such as Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), biliopancreatic diversion (BPD), and laparoscopic adjustable gastric banding (LAGB). The current standard of care for these options includes a minimally invasive approach. These operations are divided into restrictive versus restrictive/malabsorptive based on the main mechanism of weight loss. Restrictive procedures include SG and LAGB and result in weight loss by limiting the capacity of the stomach. Malabsorptive surgeries are designed to mainly reduce the intestinal absorption surface area (e.g., BPD) but can also have an additional restrictive component (e.g., RYGB). RYGB and BPD traditionally result in the most weight loss.⁵ Worldwide, RYGB is the most commonly per-

formed bariatric surgery (46.6%), followed by SG (27.8%), then LAGB (17.8%), and least commonly BPD (2.2%).⁶

When compared with nonsurgical modalities for managing T2DM, bariatric surgery has been shown to result in greater weight loss, higher rates of T2DM remission, and a better quality of life for patients.⁷ Indeed, bariatric surgery is currently the most effective and durable treatment option available for T2DM, achieving remission in up to 95% of patients. Variable remission rates (57–95%) of T2DM following bariatric surgery have been reported among different studies.⁸ This variability is related to the type of surgical procedure performed as well as differences in the definition of T2DM remission. Such definitions included withdrawal of antidiabetes medications and normalization of fasting plasma glucose levels (<100 to <126 mg/dL) and/or glycated hemoglobin (HbA1c) (<6% to <7%).⁹ The current criteria based on the National Institutes of Health guidelines to be eligible for bariatric surgery are largely driven by the body mass index (BMI): in general, a BMI >40 kg/m² or of >35 kg/m² if serious obesity-related comorbidities are present.¹⁰ A recent study showed that T2DM patients with a BMI of <35 kg/m² also experience overall improvement and remission rates as high as 95% and 55%, respectively, following an array of bariatric operations.¹¹ A very recent meta-analysis highlighted the safety of bariatric surgery, with an overall complication rate of 10–17%, a reoperation rate of about 7%, and a very low mortality rate of 0.08–0.35%.¹² Economically, the cost-effectiveness of bariatric surgery for treating T2DM tends to increase over time as the direct procedural costs dilute, while savings related to the decreased need for medications to treat diabetes and its associated complications accumulate.¹³

The mechanisms attributing to the improvement in glycemic control, and in many patients the remission of T2DM, following bariatric surgery have been an area of intensive research. The obvious weight loss and accompanying reduction in fat mass leading to enhanced insulin sensitivity have been postulated as potential mechanisms. Other mechanisms involved in the amelioration of T2DM include improved β -cell function and changes in gut microbiota, as well as

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alteration of bile acids and lipid metabolism. It is very interesting that the effect of RYGB on glycemic control occurs within days, far before any significant weight loss has occurred. Also, the glycemic control seems to be sustained despite the fact that these patients do not reach ideal body mass and may still be obese following surgery.⁴ Although the reduction in caloric intake is a plausible explanation, more complex theories involving gut hormones such as the incretin glucagon-like-peptide 1 (GLP-1), peptide YY, and preproglucagon have been proposed. GLP-1 promotes pancreatic insulin secretion and enhances glucose hemostasis. An increase in postprandial secretion of GLP-1 as high as 20-fold has been demonstrated following surgical procedures, such as RYGB, that enhance the delivery of undigested nutrients to the distal small intestines.¹⁴ Furthermore, this increased secretion is not the result of the weight reduction alone, as it is much more marked following surgery compared with similar weight loss from caloric restriction alone.¹⁵

Following numerous observational studies pointing to the role of bariatric surgery in hyperglycemia remission, several randomized clinical trials were conducted, and many others are underway, with the main aim of comparing the different bariatric operations with medical therapy for managing T2DM. Recently, 3-year follow-up results from the STAMPEDE clinical trial have been published. Primarily funded by Ethicon (Somerville, NJ) (EES IIS 19900), this study aimed to assess the improvement in glycemic control following the randomization of 150 obese patients with T2DM into three treatment groups: intensive medical therapy alone, intensive medical therapy and RYGB, or intensive medical therapy and SG.¹⁶ The target HbA1c level was 6.0% or less with or without the use of medications.

The results of the STAMPEDE trial are very impressive, with patients who underwent bariatric surgery achieving superior and sustained glycemic control and weight reduction compared with medical therapy alone. At the 3-year follow-up, 38% of patients who had an RYGB and 24% of those who had an SG were able to achieve the target HbA1c level versus only 5% of patients in the medical therapy group. It is important that 80% of patients who were treated medically and achieved the target HbA1c at 1 year did not maintain this target at 3 years, whereas patients who had bariatric surgery were much less likely to experience this glycemic relapse (only 24% of the RYGB group and 50% of the SG group). The use of glucose-lowering medications, including insulin, was significantly reduced in the surgical groups, with superior results in patients who had an RYGB. Also, the number of antihypertensive and antihyperlipidemic agents used in the surgical groups was decreased. Patients in the surgical groups, especially the RYGB group, demonstrated significant improvement in several mental and physical quality of life domains. In terms of safety, there was no excessive weight loss, life-threatening complications, or deaths in any of the groups.

In conclusion, bariatric surgery is being increasingly recognized as an attractive treatment option for T2DM in obese individuals. The rates of both improvement and remission of diabetes following surgery are both impressive and durable. Several factors were shown to predict higher diabetes remission rates, including younger age, less severe diabetes, and shorter duration of disease.¹⁷ Benefits of bariatric surgery on T2DM may even extend to include prevention of the

disease in obese patients who undergo these procedures.¹⁸ There are still several areas where randomized clinical trials are needed, as T2DM is a progressive disease, and long-term follow-up to identify sustainability of glycemic control and effect of surgery on disease outcomes is necessary. There is also a need for large randomized clinical trials to explore the role of bariatric surgery for T2DM in patients with a BMI of <35 kg/m². Bariatric surgery should also be viewed as an evolving target because clinical studies are typically a step behind the latest available surgical procedures. The low risk of surgery itself, along with the outstanding effects it has demonstrated in relation to T2DM remission, is promoting bariatric operations as an important therapeutic option for these patients, and discussion of surgery is being integrated in diabetes treatment guidelines.¹⁹

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