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Recurrent Diabetes Following Bariatric Surgery: Incidence and Management

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Abstract
Purpose While bariatric surgery has been shown to be the most effective treatment for type-2 diabetes (T2D), recurrence following an initial period of remission is a known phenomenon. The purpose of this review is to better characterize the incidence and management of recurrent diabetes following bariatric surgery.
Recent Findings The durability of T2D remission is heavily influenced on the severity of baseline disease, adherence to prescribed life-style modifications, and to a lesser extent, procedure type.
Summary Recurrent diabetes following bariatric surgery is significant and challenging to manage. Therapeutic options range from medical management to revisional surgery. Treatment algorithms should follow a tiered approach, starting with the least invasive modality. Thus, a multidisciplinary approach is essential.

Keywords Obesity · Bariatric surgery · Type 2 diabetes · Metabolic syndrome · Diabetes remission · Diabetes treatment · Diabetes recurrence

Introduction

The prevalence of obesity and obesity-related comorbidities (ORC) continues to increase in every region of the world with current data suggesting that an estimated 50 million girls, 74 million boys, 390 million women, and 281 million men worldwide have obesity [1]. In the United States, obesity has increased from 30.5% in 2000 to 42.4% in 2018, with severe obesity climbing to 9.2% from 4.7% [2]. Unsurprisingly, elevated body mass index (BMI) significantly increases one's risk for the development of diabetes such that the prevalence of type-2 diabetes (T2D) has risen in lockstep with obesity [3]. Currently, the worldwide prevalence of T2D is estimated to be 9.3% (463 million people), climbing to 10.9% (700 million) by 2045 [4, 5]. Thirty-one million people are presently living with T2D in the United States [5]. The magnitude of these figures is of global pandemic status and the economic consequences and impact on personal health cannot be overstated. T2D is among the top 10 causes of death in adults with a global health expenditure estimated to be USD 727 billion [6].

Compared to medical management, bariatric surgery is more effective in treating T2D in patients with severe obesity and, in fact, it has been proposed as a potential option even for moderately obese individuals patients with mild obesity and poorly controlled T2D [7–13]. That said, there are a myriad of factors that influence outcomes, and response to bariatric surgery spans the continuum from attenuation to remission of T2D.

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Defining Remission

Given that T2D is a chronic disease, the term 'remission' rather than 'cure' is more appropriate when describing the maximum attainable effect of any given intervention. While there is considerable heterogeneity in defining diabetes remission in the literature, the most commonly used definition for remission comes from a 2009 consensus statement by a panel of endocrinologists including experts in pediatric/adult endocrinology, diabetes education, transplantation, metabolism, bariatric/metabolic surgery, and hematology/oncology. Per the consensus statement, *partial remission* is defined as hyperglycemia below diagnostic thresholds for diabetes, at least 1 year's duration, and no active pharmacologic therapy or ongoing procedures; *complete remission* is defined as normal glycemic measures, at least 1 year's duration, and no active pharmacologic therapy or ongoing procedures; and *prolonged remission* is *complete remission* of at least 5 years' duration [14].

Predicting Remission of T2D Following Metabolic Surgery

As previously mentioned, metabolic surgery has been shown to be the most effective and durable treatment for T2D. Nevertheless, not all patients with diabetes achieve remission after metabolic surgery. Acknowledgment that responder rates vary and procedure type may influence remission rates has spurred extensive research into the matter.

One of the most comprehensive and long-term studies providing information on the effects of bariatric surgery is the Swedish Obese Subject (SOS) study. The study prospectively followed 2010 obese subjects who underwent bariatric surgery and 2037 matched controls [15]. Patients were followed for 12–25 years starting from 1987. At 2 years, remission of diabetes was found in 72% in the surgery group versus 16.4% in controls and decreased to 30.4% and 6.5% at 15 years, respectively [15, 16]. However, the majority of patients in the SOS study underwent procedures that are no longer offered or rarely performed (i.e., vertical banded gastroplasty, non-adjustable gastric banding) [16]. The Seven-Year Weight Trajectories and Health Outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study followed 2348 participants for 7 years. Of the participants, 1738 (74%) underwent laparoscopic Roux-en-Y gastric bypass (RYGB) and 610 (26%) underwent laparoscopic adjustable gastric banding (AGB). Remission rates of diabetes for RYGB at 1, 5, and 7 years were 71.2%, 64.6%, and 60.2%, and for AGB, 30.7%, 29.2%, and 20.3%, respectively [17]. Currently however, AGB accounts for only 1.1% of all metabolic surgery types and the most common procedures performed are the laparoscopic sleeve gastrectomy (SG) and the RYGB at 61.4% and 17%, respectively. [18].

While SG has replaced the RYGB as the most commonly performed bariatric surgery, the latter is still considered the most effective for achieving T2D remission by many experts [19]. The evidence to support this, however, has been mixed. An early randomized controlled trial involving small numbers of patients showed remission rates of 93% in patients undergoing RYGB versus 47% in LSG at 1 year [20]. In a prospectively collected cohort (PCORnet Bariatric Study (PBS)) study, investigators followed 9710 patients of which 6233 (64.2%) underwent RYGB, and 3477 (35.8%) had SG. Diabetes remission occurred in 59.2% of patients who had RYGB vs 55.9% of those who had SG at 1 year, 84.3% vs 81.5% at 3 years, and 86.1% vs 83.5% at 5 years [21•]. In contrast, a non-randomized cohort study of 504 patients, of which 390 underwent RYGB and 134 SG, showed no significant effect of surgery type on T2D remission at 10 years [22]. Similarly, a recent meta-analysis of four randomized control trials (RCTs) compared diabetes remission in patients with mild obesity who underwent RGB or SG. There were 151 patients in the RYGB group and 145 in the SG group. Follow-up ranged from 24 to 60 months. T2D remission rates, partial and complete, were not statistically different between the two groups with 54.0% in the RYGB group and 56.7% in the SG group achieving remission [23].

As demonstrated by the above studies, variability in patient factors, remission parameters, and follow-up intervals contribute to the heterogeneity in outcomes after metabolic surgery and support the concept of a tailored approach to patient care rather than a 'one-size fits all' strategy. Recognition that patient factors (e.g., age, baseline BMI, severity of diabetes) significantly impact diabetes response following metabolic surgery has led to the development of several scoring systems aimed at optimizing patient selection.

Based on results of a large prospective study, the ABCD score is multidimensional grading system that calculates a score from 0 to 10 based on age, body mass index (BMI), C-peptide level, and duration of T2D. A 1-point increase in the ABCD score translates to an absolute 6.7% in the success rate of diabetes remission [24, 25]. The DiaRem (Diabetes Remission) score is an externally validated scoring model based on a retrospective study of 690 patients with diabetes that consider four preoperative clinical variables: insulin use, age, glycated hemoglobin (HbA1c), and type of antidiabetic drugs used. Scores range from 0 to 22 and are partitioned into five groups corresponding to five probability ranges for T2D remission: 0–2

(88–99%), 3–7 (64–88%), 8–12 (23–49%), 13–17 (11–33%), 18–22 (2–16%) [26, 27].

However, the predictive power of the DiaRem score is limited in patients with severe disease [28, 29]. The individualized metabolic surgery (IMS) score is a more recent prediction model based on the largest reported cohort (n = 900) with long-term (median = 7 years) postoperative glycemic follow-up. The score is based on four preoperative variables including duration of T2D, number of diabetes medications, insulin use, and glycemic control (HbA1c< 7%). The IMS score categorizes T2D into three severity stages for evidence-based procedure selection. Using this calculator, patients with milder disease severity have a similar high probability of long-term T2D remission after either procedure (RYGB or SG). In this group, the procedure choice does not need to hinge solely on the chances of T2D remission as both operations are powerful enough to achieve remission in the majority of these patients. Patients with long-standing T2D and other risk factors such as insulin use at the time of surgery and advanced age have significantly lower rates of long-term remission with either procedure. Since these patients are often higher risk surgical candidates, SG should strongly be considered since the additional risk of RYGB may not be justified based on T2D outcomes. In the moderate severity group, though, the rate long-term remission after RYGB is significantly higher than with SG and RYGB is the recommended procedure in terms of T2D outcomes. Of course, there are other patient factors that may impact the procedure choice and these must be considered alongside the benefits of T2D remission [30, 31••].

Incidence of Recurrent T2D Following Metabolic Surgery

The fact that some bariatric surgery patients will experience recurrence of T2D following an initial period of regression is a known phenomenon. Like obesity, T2D is a chronic, unremitting disease and even some patients who undergo a powerful intervention such as surgery will have recurrent disease [32]. Despite recurrence of T2D in some patients, though, there is metabolic benefit from a period of tight glycemic control. This "legacy" effect results in lower long-term risk of micro- and macro-vascular complications, even in patients who have recurrent disease [33, 34••].

However, attempts to capture the precise incidence of relapse are exceedingly difficult for various reasons. Many of the studies investigating the effects of bariatric surgery on T2D focus on remission of diabetes rather than relapse and those that have data regarding recurrence often report outcomes of the total cohort rather than describing only those patients who experience remission [8, 9, 11, 32, 35]. Furthermore, differences in follow-up intervals, procedure type, and definitions of recurrence make the precise incidence of relapse difficult to characterize.

The current literature shows that the durability of T2D remission following bariatric surgery is highly variable [36]. In a study of 178 patients undergoing RYGB followed for at least 10 years, 15.4% of patients were found to have recurrence [37]. A study of 1111 Danish patients with T2D treated with RYGB reported 27% recurrence at 5 years [38]. Aminian et al. reviewed outcomes in 134 patients who underwent SG followed for a median of 6 years. Relapse of T2DM after initial remission occurred in 44% [39]. A multi-institutional review of 4434 patients with uncontrolled or medication-controlled T2D who had gastric bypass reported a 35.1% rate of recurrence within 5 years [40]. In a small retrospective study, DiGiorgi et al. found that 26% of the RYGB patients who achieved remission relapsed within a mean of 6.1 years [41]. In a single-institution study of 177 patients, 89% initially achieved T2D remission after RYGB and 43% of these patients had recurrent disease at a mean of 8.6-year follow-up [42]. In a much larger retrospective review of 736 patients with T2D who underwent RYGB or SG, investigators reported a relapse rate of 32% with a median follow-up of 8 years [32].

Overall, the above studies show significant variability in the rate of T2D recurrence following bariatric surgery. Of those studies that investigated risk factors for recurrence however, predictors of relapse appear to be more consistent. In general, preoperative disease characteristics that indicate a greater severity of T2D (i.e., duration of T2D, number of diabetes medications, insulin use, higher HbA1c) portend a greater risk for recurrence over time [32, 36, 42–44]. A natural corollary to this observation is that patients with less severe diabetes are more likely to realize more durable remission following surgery. Furthermore, some studies indicate an association between recurrence of T2D and suboptimal weight loss and/or weight regain after surgery [41, 42, 45].

Management of Recurrent T2D Following Metabolic Surgery

While the definition varies, recurrence of T2D, most often defined as HbA1c $\geq$ 6.5% or need for antidiabetic medication after any period of remission, represents a therapeutic challenge [32, 46]. As is often the case in medicine, 'prevention is the best cure' and identifying at-risk patients for relapse is the first step in management. The aim of such a strategy is to delay diabetes relapse by attenuating risk factors. These patients, as discussed above, are likely those

with more advanced diabetes and/or those that experience less than expected weight loss or even weight gain in the postoperative period. In addition to an annual HbA1c level, continued regular self-monitoring of fasting blood glucose levels should be encouraged. Moreover, strict adherence to a low-carbohydrate, low-fat, and high-fiber diet with structured exercise training is indispensable for staving off weight gain and optimizing serum glucose levels [47, 48]. As bariatric surgery patients experience significant changes in digestive physiology, appropriate screening and supplementation must be practiced to avoid micronutrient deficiencies, particularly those associated with glucose metabolism or beta-cell function such as vitamin D and chromium [49, 50].

For those patients that do recur, antidiabetic medications should ideally support weight neutrality or weight loss and avoid hypoglycemia. In this context, Metformin would be the first-line medication [51]. Glucagon-like peptide 1 (GLP-1) agonists and the newer class of sodium-glucose co-transporter 2 (SGLT2) inhibitors are also associated with weight loss, but have not been studied in post bariatric surgery patients [52, 53].

Finally, if all non-surgical attempts have been exhausted, revisional bariatric surgery for recurrent T2D should be considered in select patients. Depending on the primary procedure, revisional surgery or conversion to a bypass procedure can be as effective as primary surgery [54, 55]. Specifically, conversion of gastric operations like AGB or SG to RYGB yields improvement in diabetes in 62–79% and remission in 23–40% of patients depending on the original surgery; and revision of pouch/stoma after RYGB yields improvement of T2D in 50–79% and remission in 23% of patients [55, 56].

Conclusion

Bariatric surgery has consistently been shown to be more effective that medical management alone in the treatment of type-2 diabetes. Effectiveness of surgery, however, varies with procedure type and baseline disease severity. While remission of diabetes has been described with all bariatric procedures, the RYGB remains the gold standard. Still, recurrence rates are significant and management starts with prevention. This strategy entails identifying patients that are high risk for relapse, vigilant surveillance of serum glucose levels and weight fluctuations, adherence to lifestyle modifications such as diet and exercise and avoidance of nutritional deficiencies, particularly those associated with glucose metabolism.

For those patients that relapse and require pharmacotherapy, antidiabetic medications should be geared towards weight neutrality or better yet, weight loss. Medication choice, dosage, and management should be conducted by an expert. When all non-surgical strategies have been exhausted, patients should be carefully considered for revisional surgery. Specifically, those patients whose indexed procedure was restrictive (e.g., vertical banded gastroplasty, adjustable gastric band, sleeve gastrectomy) can be converted to RYGB and those patients with RYGB should be considered for stoma or pouch revision if appropriate.

In short, recurrent diabetes after initial remission following bariatric surgery is challenging. More studies are needed to identify the optimal surgical and non-surgical treatment modalities.

Compliance with Ethics Guidelines

Conflict of interest SB reports personal fees from Speaker honoraria Medtronic, personal fees from Consultant GI Windows, outside the submitted work. JC declares no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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