

Editorial

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Metabolic and bariatric surgery: diabetes - a decade of discovery

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How to cite this article: Veilleux E, Lutfi R. Metabolic and bariatric surgery: diabetes - a decade of discovery. *Mini-invasive Surg* 2020;4:4. <http://dx.doi.org/10.20517/2574-1225.2020.01>

Received: 1 Jan 2020 **Accepted:** 13 Jan 2020 **Published:** 20 Jan 2020

Science Editor: Daniel B. Jones **Copy Editor:** Jing-Wen Zhang **Production Editor:** Jing Yu

INTRODUCTION

Diabetes is a progressive and chronic condition that affects a growing percentage of the population each year. Obesity is considered to be the central risk factor in the development of type 2 diabetes mellitus (T2DM) in adults. In 2019, the top three countries for diabetes prevalence were found to be China, India, and the United States, affecting 116, 77, and 31 million adults, respectively^[1,2]. More than 420 million adults are affected worldwide, representing a significant burden to healthcare systems as well as the wellbeing of the global population^[3].

Metabolic and Bariatric surgery for the treatment of T2DM has been of significant interest in recent years. At the start of the decade (2011), the International Diabetes Federation wrote a consensus statement promoting the use of bariatric surgery in obese patients with poorly controlled diabetes^[4]. However, as the number of adults with T2DM worldwide grows exponentially each year, metabolic and bariatric surgery for treatment remains a topic of substantial interest. In 2019, the American Society for Metabolic and Bariatric Surgery (ASMBS) held its annual Obesity Week Conference, electing diabetes as the central topic. The presidential address (Eric J. DeMaria, MD Fellow of the American Society of Metabolic and Bariatric Surgery) at this meeting highlighted a growing effort to raise awareness on the beneficial effects of surgery for glycemic control. Dr. DeMaria suggested increasingly referring to metabolic surgery with patients as “diabetes surgery” in order to promote the concept in the general population. As we continue to raise awareness of the benefits of metabolic and bariatric surgery to those in the healthcare field as well as the general population, it is important to evaluate what we have learned and what has yet to be discovered.



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A DECADE OF DISCOVERY

Historically, the primary treatment for diabetes was through behavioral modification and pharmacologic treatment. Frequently, combination therapy would be necessary, increasing the number of medications prescribed to patients^[5]. Although glucose control was improved, management often became more challenging for clinicians, and many patients were burdened with increased costs, intolerable side effects, and poor compliance. The overall goal was always to improve glycemic control; however, remission or cure of the disease was often thought to be unattainable. Even with maximal drug therapy, some patients still struggled with achieving desired HbA1C levels. Given these difficulties in management, the beneficial effects of surgery on glycemic control garnered immediate attention.

While observational studies were abundant, the emergence of several randomized controlled trials (with long-term follow up) helped to raise awareness in both the medical and surgical communities regarding the significant diabetic improvement seen after metabolic and bariatric surgery. Not only was surgery found to be effective, but it showed superiority to medical therapy in glycemic control, medication reduction, and weight loss^[6,7]. In 134 patients at five-year follow up, the randomized STAMPEDE trial (Surgical Treatment and Medications Potentially Eradicate Diabetes Effectively) demonstrated sustained remission of diabetes (HbA1C < 6.0% without glucose lowering medications) in 22% of the gastric bypass group, 15% of the sleeve gastrectomy group, and 0% of the medical therapy group. Similarly, comparing medical treatment to surgery, Mingrone *et al.*^[7] found in 53 patients at five years that 42% of gastric bypass and 68% of biliopancreatic diversion patients were able to achieve remission of their diabetes (HbA1C < 6.5% without glucose lowering medications) while none of those in the medical treatment group had.

The outcomes from these as well as many other studies helped to broaden the awareness of surgery as a tool for the treatment of diabetes and extend this knowledge outside the surgical community. Given the overwhelming evidence, at the 2nd Diabetes Surgery Summit, a consensus was reached among international diabetes organizations to promote the use of bariatric surgery for type 2 diabetes^[8,9]. The endorsement was approved by many medical and surgical societies including the American Diabetes Association, the International Diabetes Federation, ASMBS, Diabetes UK, and The American College of Surgeons^[9]. The consensus stated that “metabolic surgery should be recommended to treat T2DM in patients with class III obesity [body mass index (BMI) ≥ 40 kg/m²] and in those with class II obesity (BMI 35.0-39.9 kg/m²) when hyperglycemia is inadequately controlled by lifestyle and optimal medical therapy. Surgery should also be considered for patients with T2DM and BMI 30.0-34.9 kg/m² if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications”^[8,9]. Despite many publications, it is a continued effort for surgeons to spread this knowledge to other physicians (primary care, endocrinology) as well as to insurance companies. The goal is to reach and obtain coverage for a greater number of patients who would benefit from bariatric and metabolic surgery.

RISK FACTORS FOR REMISSION

As we discovered the potential for the surgical improvement of diabetes, risk factors for failure of remission (or likelihood of relapse) also became evident. Increased age, longer duration of diabetes (> 8 years), preoperative insulin usage, number of oral antidiabetic medications at time of surgery, and poor preop glycemic control were found to adversely affect outcomes^[6,10-12]. It is theorized that these risk factors represent the pathologic concept of diminished β -cell reserve in the pancreas, and its ability to improve in response to metabolic surgery. These observations underscore the importance of intervening early with surgery in the progressive course of diabetes^[6,10].

Initial investigation into remission rates after sleeve gastrectomy by Schauer *et al.*^[6] found 14.9% of patients remained in remission at 5 years. However, much of the cohort in the Cleveland study was known to

have comparatively advanced diabetes, with mean preoperative HbA1C at 9.2 ± 1.5 , duration of disease of 8.5 ± 5.2 years, and 44% on insulin therapy preoperatively. In a study from Argentina, Viscido *et al.*^[13] found much higher rates of remission at five years post sleeve gastrectomy (71%) in their cohort of patients, of whom only 13% were on insulin preoperatively, and mean HbA1C was 7.15. As we might expect, of their patients who were taking insulin preoperatively, the remission rate at five years was much lower at 37.5%. Sánchez-Pernaute *et al.*^[14] further supported this finding in a study of 97 patients undergoing single anastomosis duodenal ileal bypass (SADI-S). Duodenal switch and SADI are regarded by many as the most efficacious surgeries for diabetes. However, in their study, we still observe a large disparity in remission rates in patients taking preoperative oral antidiabetics *vs.* insulin. Absolute remission rate in these two groups was 92.5% *vs.* 47% at one year, and 75% *vs.* 38.4% at five years^[14].

Indeed, we see large variability in the remission rates between studies, as a strong determining factor is the patient selection and the severity of preoperative diabetes. This is acknowledged by the authors of multiple studies when comparing their higher remission rates to that of the STAMPEDE trial, typically quoting lower HbA1C, shorter duration of disease, and lower use of insulin in their patient populations^[13]. The discerning reader must also be aware of the differing values that denote “remission” amongst the various studies, which can yield results that appear inflated when cutoffs are less stringent. Further multi-institutional studies inclusive of a broader, more generalizable range of patients with subgroup analysis will help to elucidate accurate remission rates.

CHOICE OF PROCEDURE

Sleeve gastrectomy is currently the most common procedure performed for weight loss. When evaluating the effectiveness of metabolic procedures on long-term diabetic improvement, current studies suggest anastomotic procedures to be more efficacious over restrictive procedures, with duodenal switch outperforming gastric bypass^[6,7]. However, many of the randomized controlled trials from which we abstract these data were not powered to detect significant differences between procedures. Considering this, Aminian *et al.*^[10] evaluated the pooled data from four randomized controlled trials^[6,15-17] of T2DM remission for sleeve and bypass (each providing at least five-year follow up data). Interestingly, they found that there was no significant difference between procedures, or, at most, if we assume a difference exists that the pooled power was insufficient to show, a 15% advantage in remission rate of bypass over sleeve would exist^[10].

In a larger, single center, triple blind, randomized controlled study from Norway, Hofsø *et al.*^[18] sought to compare the effects of bypass *vs.* sleeve on remission of T2DM in obese individuals while also looking at the improvement in β -cell function. With 107 patients at one-year follow up, they found a 75% remission rate for gastric bypass and 48% remission rate for sleeve gastrectomy. Interestingly, despite a higher rate of resolution with the bypass, the authors did not find a significant difference between procedures when they assessed improvement in β -cell function. This was tested by the validated method of intravenous glucose tolerance test.

Despite these results from randomized trials which tend to favor duodenal switch or gastric bypass, the most efficacious procedure does not always equate to be the best choice for all patients. It can be easy to lose sight of other mitigating variables when intending to follow the published evidence. At our practice, we agree it is essential to consider a variety of factors when discussing procedure choice with our patients. Clearly, there are several technical, nutritional, pathologic, pharmacologic, and behavioral factors that may dictate the appropriateness of one procedure over another. However, in terms of guiding the choice as it relates to metabolic improvement, it is important to consider the severity of the disease and ability of the pancreas' β -cell reserve to respond to the gastrointestinal modulatory effects of surgery.

While duodenal switch and bypass may trend toward the most optimal outcomes^[7,14], for a patient with advanced diabetes of long duration, the β -cell reserve of the pancreas is likely minimal and incapable of improving significantly regardless of the chosen operation. To further evaluate this, Aminian *et al.*^[19] examined a large cohort ($n = 900$) of patients in order to create the individualized metabolic surgery score. This score, which uses previously discussed preoperative risk factors for resolution of diabetes (duration, HbA1C, number of oral medications, and insulin use), categorizes T2DM into three stages of severity. What this score highlights is that in patients with severe T2DM (Diabetes > 10 years, multiple oral antidiabetic drugs + insulin, and HbA1C of 8%), both sleeve and bypass have similarly poor efficacy in diabetes improvement (12% long-term remission for both)^[10,19]. Thus, there is little evidence that choosing bypass over sleeve in this group of patients will lead to improved glycemic outcomes, and the most clinically safe procedure is likely the best choice. Similarly, yet at the other end of the spectrum, for patients with diabetes of minor severity, the cohort was observed to have high rates of diabetes remission at long-term follow up with both sleeve (74%) and bypass (92%)^[19]. Thus, while bypass had slightly higher rates of remission, the patient should be counseled that sleeve is also a very efficacious option. It is in the intermediate patients with moderate severity diabetes where bypass was observed to have significantly improved outcomes compared to sleeve. This difference is much more likely to be of clinical importance when choosing procedure. In the intermediate group, 60% of patients who underwent gastric bypass showed long-term diabetes remission compared to 35% of those who had sleeve gastrectomy^[19].

Recognizing the above when planning with the patient will help to set appropriate expectations for disease response in the postoperative period. Additionally, given that many patients with severe diabetes may also be poor operative candidates, it is important to remember that their metabolic response from sleeve gastrectomy is likely to be the same as with an anastomotic procedure, potentially allowing for a quicker and thus safer surgery. To avoid choosing a more advanced procedure for a patient who may not benefit from improved outcomes, it is important to consider the degree of their β -cell reserve and thus potential for improvement.

REVISIONAL SURGERY

Although many studies focus their investigation on the sustained remission of diabetes, we should not consider relapse a failure of treatment. Many patients with relapse still experience the benefit of improved glycemic control/A1C while requiring fewer medications^[20]. However, similar to obesity, diabetes is a chronic illness that requires a long-term strategy for treatment. Mingrone *et al.*^[7] found that, at five years, hyperglycemia relapsed in 44% of the 34 surgical patients who had achieved two-year remission (however, they maintained a mean HbA1c of 6.7). As follow up time increases, the proportion of patients who maintain diabetes remission decreases^[6,21] and further options for treatment must be considered. Just as we are increasingly recognizing revisional surgery as a necessary approach for patients who obtain inadequate results in the treatment of their obesity, a similar approach will likely hold true for diabetes.

The current data however do not support adequate analysis of a revisional approach. Studies have typically evaluated whether patients remain in remission at a defined follow up period. This has mainly allowed for comparison on the efficacy between procedures at five years or more. However, if we consider total number of remission years obtained, we may find that a combination of procedures yields greater lifetime remission than any primary procedure alone. We have a paucity of evidence regarding the role of revisional surgery in the treatment of T2DM^[20,22]. In a review of multiple studies on revisional bariatric surgery, Yan *et al.*^[23] demonstrated that, in the majority of cases, reoperation has a positive effect on both improvement in diabetes and further weight reduction. Unfortunately, these observational studies were of rather low power, without investigation of diabetes being the primary end point^[23]. We have yet to evaluate with high-powered studies if the total years of diabetes improvement can be maximized with a stepwise approach.

Potentially, sleeve gastrectomy converted to an anastomotic procedure can be more efficacious than what is achieved with the primary anastomotic procedure alone. If some patients are destined for eventual relapse, even after anastomotic procedures, perhaps a stepwise approach would yield a greater number of total years in remission.

The ability of two procedures to surpass the diabetic results of the primary procedure may draw skepticism based off the results we have seen for revisional surgery and obesity. Revisional bariatric surgery has shown variable outcomes with weight loss when compared to the primary procedure. Indeed, in some observational studies, it has yielded lower total weight loss, with inferior durability^[24-26]. However, the same assumptions of inferiority should not be made for the effect of revisional surgery on diabetes. This has yet to be fully evaluated. We know there is not a direct correlation between a patient's weight loss and degree of diabetic improvement and that studies have shown multiple metabolic effects from surgery which are completely independent of weight loss^[7,20]. For example, improvement in glycemic control often occurs prior to any substantial weight loss and the degree of diabetic improvement does not parallel changes in BMI^[6,7,27]. Interestingly, in one sample of 105 gastric bypass patients who had inadequate weight loss (Excess Weight Loss < 15%), substantial glycemic improvement was still observed at one-year follow up (change in mean HbA1C from 7.3 ± 1.9 to 6.1 ± 1.0)^[20]. Additionally, newer studies have theorized several metabolic gastrointestinal modulations caused by surgery that act independent of weight loss. One such observation reveals that increased stimulation to the terminal ileum and large intestine by rapid nutrient delivery (increased gastric emptying or intestinal bypass) appears to have beneficial incretin (GLP-1) secretory effects^[20,27]. Although much research is still underway, it is clear that metabolic and bariatric procedures cause a complex change in gut physiology, with each procedure likely to have its own distinct response. Thus, an approach that combines multiple procedures to target separate pathways may one day be found to be the most efficacious for long-term diabetic improvement.

CONCLUSION

More than a decade of efforts to recognize the incredible glycemic improvement possible with surgery have now provided the foundation for further discoveries. Recently, the cardiovascular benefits from metabolic surgery in obese diabetics have shown dramatic risk reduction in complications such as heart failure, A-fib, stroke, myocardial infarction, and all-cause mortality^[28]. As we continue to recognize additional benefits, further study is needed to continue to guide appropriate procedure/patient selection and to formalize a surgical plan for the long-term care of diabetes.

DECLARATIONS

Authors' contributions

Both authors contributed equally to the entire editorial.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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