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Review Article

Metabolic bariatric surgery and type 2 diabetes mellitus: an endocrinologist's perspective

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Abstract

Traditional treatment of T2DM consisting of modification of diet, an exercise regimen, and pharmacotherapy has problems of poor lifestyle modifications and fail tend of treatment over time, now bariatric surgery is recommended for treatment of obese patients with T2DM because its great improvements on weight loss and metabolic. In this article, effects of bariatric surgery on diabetes and diabetes–related complications are reviewed.

Keywords: type 2 diabetes mellitus, metabolic bariatric surgery, diabetes remission

Introduction

Obesity is a worldwide epidemic which contributes to numerous medical complications including type 2 diabetes mellitus (T2DM). T2DM is a progressive disorder resulting in micro- and macro-vascular disease which confer significant morbidity and mortality. Thus, treatment of a T2DM patient aims to reduce these associated complications. Traditional treatment of T2DM consists of modification of diet, an exercise regimen, and pharmacotherapy. However, overall patient compliance with lifestyle modifications is often poor and treatment with pharmacotherapy tends to fail over time[1]. In addition, many medications are associated with hypoglycaemia and weight gain, especially during intensification of treatment. The resultant hypoglycaemia is associated with a higher incidence of cardiovascular deaths in intensive treatment and the weight gain may lead to further deterioration in glycemic control[1,2].

In recent years, bariatric surgery has emerged as a potential treatment for obese patients suffering from T2DM. Both the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) now recommend bariatric surgery in their treatment guidelines for obese patients with T2DM[3,4]. Improvement in glycemic control following gastrointestinal surgery was first noted in the first half of the 20th century. Patients undergoing gastric resection for peptic ulcer disease or gastric cancer were found to have improvement in diabetes control[5]. Early observational studies noted the benefit bariatric surgery had on glycemic control[6]. In more recent years, several randomized controlled trials (RCTs) have compared medical management of T2DM with surgical management of T2DM. These studies confirm that bariatric surgery is indeed more effective than medical management of T2DM[7–9].

We hereby discuss in detail the effects of bariatric surgery on diabetes and diabetes-related complications.

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Table 1 **Summary of the various criteria for diabetes mellitus remission used in trials.**

Study	Fasting glucose (mg/dL)	HbA1C (%)	Medication usage
Dixon et al.[7]	< 126	< 6.2%	No
Mingrone et al.[8]	< 100	< 6.5%	No
Schauer et al.[9,10]	–	≤ 6.0%	Yes/No
Ikramuddin et al.[13]	–	< 7%	Yes/No

The role of the endocrinologist in the short- and long-term management of the diabetic patient undergoing bariatric surgery is also discussed.

T2DM remission

Apart from substantial weight loss, the positive impact on T2DM control is the greatest metabolic improvement after bariatric surgery. Diabetes remission, defined as normoglycemia without the use of any hypoglycaemic medications or therapeutic procedures, is achieved in a substantial number of patients with T2DM following bariatric surgery.

However, reports of DM remission are highly variable, ranging anywhere from 24% to 95%[7–10]. The reason for this wide variation is mostly due to use of different definitions of DM remission, different kinds of procedures studied and variable duration of post-operative follow-up, with most studies reporting outcomes within 2 years. In addition, most studies were retrospective, observational or prospective observations with high drop-out rates.

In Buchwald's 2004 meta-analysis, the overall rate of complete DM remission for all procedures was 76.8%[11]. The remission rates for gastric banding, gastroplasty, gastric bypass (GB), and biliopancreatic diversion (BPD) or duodenal switch (DS) procedures were 48%, 72%, 84% and 99%, respectively. The magnitude of the DM remission correlated to the amount of weight loss after surgery. The definition of resolution of T2DM in this meta-analysis was "the ability to stop all diabetes-related medications and maintain blood glucose levels within the normal range."[11]

In an effort to standardize the definition of diabetes remission, a consensus by a group of specialists (Buse et al.) defined complete resolution of T2DM as a totally normal glycemic state (HbA1C < 5.7% with fasting plasma glucose < 5.6 mmol/L) and partial remission as glucose control in the non-diabetic range (HbA1C < 6.4% with fasting plasma glucose < 6.0 mmol/L) without the need for DM medications for at least 1 year[12].

In recent years, there have been at least 5 RCTs comparing conventional or intensive medical therapy with bariatric surgery on the effect of glycemic control in T2DM patients. Results continue to vary due to different methodologies employed in the studies. Several variables including type of procedure, presurgical duration of DM, severity of DM, study endpoints of DM remission and duration of follow-up exist amongst these studies.

It is important to note that the higher remission rates occurred in the patients with the shortest duration of diabetes. Remission rates decreased in the studies which included patients with longer duration of diabetes. Additionally, the majority of reported DM remission rates are based on 1-2 year postoperative outcomes. Due to the relatively short duration of follow-up in these newer RCTs, the concerning issues of long-term remission (lasting > 5 years) and the recurrence of type 2 diabetes are not yet fully addressed.

Durability of DM remission and relapse of DM

On medium term follow-up of patients post-bariatric surgery (over 3–5 years), a substantial percentage of patients (60%–91%) can achieve DM remission[14–17]. Jimenez et al. observed that 66% of their patients were in remission throughout the entire follow-up period (mean 35 months) after RYGB with a handful (17%) achieving remission only after 12 months postoperatively[15].

In prospective follow-up studies of medium-term follow-up, relapse into the diabetic state can occur in 12%–25% of the patients who have attained remission 1 year postoperatively[15,18]. The only RCT with medium-term follow-up is the STAMPEDE trial in which patients with T2DM were followed up for up to 3 years after randomization[10]. A significantly greater proportion of patients who underwent SG (29%) or GB (46%) were still able to achieve any DM remission (HbA1c < 6.5% without medications) compared to those in the intensive medical treatment arm (0%). In addition, the mean HbA1c attained in the surgical group was significantly lower than that in the intensive medical arm. However, after 3 years, 25% in the GB group and 50% in the SG group who attained DM remission at 1 year had relapsed into the diabetic state[10].

Table 2 **Summary of remission rates amongst the various studies.**

Study	Procedure	Remission rates	Followup period	Duration of diabetes
Dixon et al.[7]	LAGB	73%	2 years	< 2 years
Mingrone et al.[8]	GB	75%	2 years	5 years
	BPD	95%		
Schauer et al.[9]	GB	42%	1 year	8 years
	SG	37%		
Schauer et al.[10]	GB	38%	3 years	8 years
	SG	24%		
Ikramuddin et al.[13]	GB	75%	1 year	⩾6 months

LAGB: laprascopic adjustable gastric band; GB: gastric bypass; BPD: biliopancreatic diversion; SG: sleeve gastrectomy.

In long-term studies of 5 years and beyond, reported rates of complete DM remission range from 24% to 88%, with higher rates reported in studies using a higher HbA1c cut-off and for bypass type procedures[19]. The Swedish Obese Subjects (SOS) study, a prospective case-matched study of various bariatric surgery procedures, reported that 36% of patients had recovered from their DM 10 years after surgery, indicating that 50% of patients who had initial DM remission suffered a recurrence of diabetes[20].

In a follow-up of 217 patients over 6 years, Brethauer et al.[19] reported that 24% of all patients achieved long-term complete remission with an additional 26% with partial remission (i.e. 50% of all patients can achieve long-term DM remission) with better glycemic outcomes noted after RYGB compared to SG or LAGB, and 27% of those in complete remission maintained this throughout the 6 years. However, 19% of those who achieved an initial complete remission suffered a relapse of DM over this period.

Patients who tended to experience relapse had a longer duration of DM (> 5 years), had regained weight, were of older age, and required insulin before surgery. Nonetheless, even with recurrence of DM, fewer patients required insulin associated with a significant reduction in the number of glucose-lowering medications. They were also able to attain a lower HbA1c, blood pressure and lipid targets better than compared to baseline[16,19].

DM remission after bariatric surgery can be durable beyond 5 years after surgery. However, it is prudent to continue follow-up especially in patients who are at risk for DM recurrence. We now await further long-term results from the recent RCTs.

What predicts DM remission?

There are several variables to consider in determining what helps predict diabetes remission. As mentioned earlier, it does appear that duration of diabetes plays a pivotal role. A 2012 retrospective study of 88 Asian patients found that shorter duration of diabetes was indeed a predictor of DM remission post surgery[21]. In the STAMPEDE trial and in long-term follow-up studies in Asian and Caucasian populations, patients with the shortest duration of diabetes were those most likely to achieve complete resolution of their diabetes after surgery[9,14,19,22].

Other variables to consider are preoperative body mass index (BMI), type of procedure, amount of weight loss, and preoperative glycemic control. Buchwald et al. reported more frequent diabetes remission with the procedures that have a malabsorptive component versus those that are solely restrictive[11]. Dixon et al. found that the degree of weight loss had major impact on glycemic improvement, not the type of procedure[7]. However, it is important to note that the procedure used in the Dixon study was a purely restrictive one–LAGB. Mingrone et al. compared 2 procedures with malabsorptive component (GB and BPD) and found no relationship between improved glycemic control and weight loss or preoperative BMI[8].

Kashyap et al. demonstrated that 2 years post-SG and RYGB, there were substantially more patients in the GB group than the SG group being able to attain HbA1c < 6%. In addition, there was a more durable effect on DM remission after GB compared to SG with an overall reduction in medication use[23]. In the long-term, there is a tendency for a lower rate of relapse into the glycemic state from DM remission after GB compared to SG[19]. This was despite a similar weight loss between the 2 groups. This implies that malabsorptive procedures may improve diabetes control independent of weight loss.

Preoperative predictors of remission reflect surrogate factors predicting ''healthier'' pancreatic beta-cells, a better residual pancreatic beta-cell function preoperatively and a greater degree of insulin resistance. These included younger age, higher preoperative BMI, greater levels of fasting C-peptide levels,

a higher homeostatic model assessment of beta-cell function (HOMA %B) and a shorter duration of diabetes[23–25].

Therefore, selection of appropriate patients based on these predictors, coupled with selecting the most appropriate procedure will help patients get the maximal benefit of metabolic bariatric surgery.

Mechanism of DM remission-weight loss effect versus bypass/hormonal changes effect or both?

Several acute and chronic physiological changes occur as a result of bariatric surgery, which contribute to improved glycemic control or remission of type 2 diabetes. The most potent mechanism of DM remission is no doubt weight loss, in particular loss of truncal fat[23]. Weight loss causes decreased peripheral insulin resistance, thereby improving glycemic control.

However, very often-especially in the case of post-GB, glycemic control improves quite acutely, before weight loss has even occurred. The underlying mechanisms for this are manifold. First, acute caloric restriction contributes to improved glycemic control through rapid improvement in insulin sensitivity with reduction in hepatic insulin resistance. Even in the absence of surgery, improved beta cell function with increased post-prandial insulin release, can be seen as early as 1 week after acute caloric restriction[26–28].

Many studies have also demonstrated that after GB, there is an earlier and enhanced glucagon-like peptide 1 (GLP-1) secretion in response to nutrients[23–26]. This can occur as early as a few days after GB and persist beyond 2–3 years after surgery. However, this may not be an important mechanism in glucose control in the immediate postoperative period[26,29].

Kashyap et al. demonstrated that 2 years post SG and RYGB, the GB group had greater relative reduction in truncal than subcutaneous fat, greater improvement in insulin sensitivity and pancreatic beta-cell function compared to SG group[23]. There is also a tendency for a lower rate of relapse into the glycemic state from DM remission after GB compared to SG[19].

Several studies have reported that an enhanced GLP-1 secretion during oral glucose tolerance test confers benefits of DM remission and is durable up to 3 years after surgery (SG or RYGB)[15,24,28,30]. All these imply that after metabolic surgery, in addition to weight loss, factors related to intestinal bypass and involving incretin changes play a major role in DM remission and improvement of the metabolic state. Salehi et al. demonstrated that enteral factors account for 80% of insulin secretion in response to a meal after RYGB as opposed to 53% in non-surgical obese controls[29]. However, there is growing evidence that a concomitant improvement in beta-cell function after surgery plays a key role in DM remission, especially in the long term[23,25,29,30].

Lastly, bile acids have been noted to be elevated after RYGB and SG. Bile acids are known to reduce food intake, gluconeogenesis, and insulin resistance. They are also known to increase gut hormone production and increase energy expenditure[28].

Coupled with clinical observations of DM remission outcomes, there are clearly multiple mechanisms of DM remission after bariatric surgery – acute caloric restriction, intestinal bypass or rapid transit after SG causing enhanced GLP-1 secretion in response to food, bile acid effect amongst others. These ultimately exert their impact on glycemic control via reduction in insulin resistance and increase in insulin secretion in response to nutrients – basic pathophysiologic defects of in T2DM development. Perhaps in different patients, the predominant factor inducing remission or the lack thereof may be different. Regardless of which mechanism is the predominant factor, it is imperative that a certain level of pancreatic beta-cell function exist presurgically, with subsequent postoperative improvement in its function, for any meaningful clinical improvements in glycemia, especially DM remission, to occur after surgery.

Consideration in special populations with DM: the lower BMI patient and Asian population

In Asia, the burden of T2DM is rapidly increasing. It is predicted that China, India, Pakistan, Indonesia and Bangladesh are among the top 10 countries predicted to have the highest number of DM by 2030[31]. Distinctively in Asia, T2DM develops at least a decade earlier and at a lower BMI than in white populations. Asians are more insulin resistant than people of many other races; they are metabolically obese, displaying signs of insulin resistance even in the absence of obesity[31,32]. This is related to a greater degree of adiposity, especially visceral adiposity, characteristically seen in Asians even for the same waist circumference and BMI. Hence, for any given BMI level and waist circumference measurement, the risk for T2DM development is higher in Asians than people of Europid origin, especially Asian Indians[33,34]. Lower BMI cut-offs compared to Europid populations for any clinical intervention including bariatric surgery is taken in this context. The IDF recommends that MBS be considered in Asian patients with DM and BMI 27–30 kg/m^2 if

HbA1c remains suboptimal despite maximal medical therapy[4].

Bariatric surgery in Asian patients with lower BMI (classically defined as < 35 kg/m^2) has seen lower rates of metabolic improvements compared to those with BMI > 35 kg/m^2[35]. One would wonder then that if Asians experience a larger burden of disease and insulin resistance at a lower BMI, would bariatric surgery benefit diabetes and related metabolic disorders when intervened at a lower BMI?

Dixon et al. studied a group of 103 Chinese and Korean patients with T2DM and BMI < 30 kg/m^2 (mean 26.0; range 18.9–30.0 kg/m^2) after GB. DM remission (HbA1c $\leq$6%) at 1 year post-surgery occurred in 30% of patients[36]. In a prospective study of 29 non-obese Chinese patients with T2DM and BMI of 20.9–26.9 kg/m^2 who had undergone RYGB, Malapan et al. reported that 38% of patients attained DM remission (HbA1c $< 6.5\%$ without any glucose-lowering medications) at 1 year[37]. These remission rates are clearly below previously reported rates of up to 93% in Asians after RYGB[38].

Predictors of DM remission at 1 year postoperatively in Asian patients are no different from other populations. A shorter presurgical duration of DM, higher baseline C-peptide levels (surrogate of inter-play of presurgical pancreatic beta-cell function and insulin resistance), higher preoperative BMI (which influences insulin resistance), a younger age and greater postoperative weight loss are strong predictors of DM remission 1 year after RYGB[22,38].

While metabolic improvements after bariatric surgery are seen in lower BMI patients, these outcomes are not as favourable as those with higher BMI. Perhaps the selection of T2DM Asian patients for metabolic surgery should take into consideration assessment and measurement of visceral obesity appropriate for ethnicity, insulin resistance and baseline pancreatic beta-cell function apart from BMI alone, for maximal benefits and long-term risk reduction from metabolic surgery. However, more long-term studies in this group of patients are needed before a general recommendation can be made in T2DM patients with lower BMI for consideration of metabolic surgery.

Reducing outcomes of DM

Clearly, there is copious data for the beneficial effect bariatric surgery has on glycemic control. However, diabetes patients often suffer additional comorbidities such as hypertension and dyslipidemia which collectively confer significant risk for microvascular and macrovascular complications such as renal failure, retinopathy, stroke and coronary artery disease[40]. Multi-factorial intervention targeting euglycemia, blood pressure and optimal lipid levels have been proven to reduce the risk of cardiovascular disease and various microvascular complications[41]. However, there remains a paucity of data on micro- and macrovascular disease outcomes following bariatric surgery.

The Swedish Obese Subjects (SOS) study reported reduced rates of myocardial infarction in obese type 2 diabetes patients who underwent bariatric surgery. This occurred despite a 50% recurrence rate of diabetes in these patients. An extended follow-up of 16 years revealed decreased overall mortality in obese patients with type 2 diabetes who had undergone bariatric surgery[42,43].

In the 3 year follow-up of the STAMPEDE trial, there were no significant differences in blood pressure and LDL levels among the 3 study groups. However the number of medications needed to treat hyperlipidemia and hypertension was significantly reduced in the surgical groups[10].

In the Diabetes Surgery Study by Ikramuddin et al., the primary endpoint specifically looked at achieving the ABC targets (i.e. the American Diabetes Association recommended targets: A1c $< 7\%$, LDL $<$ 100 mg/dL, and SBP < 130 mmHg) in obese type 2 diabetes patients who were either treated medically or with RYGB surgery. At 12 months post intervention, 49% of RYGB patients achieved this composite endpoint, compared to only 19% of patients in the medically treated group[13].

In addition, improvements in renal function and microalbuminuria have been reported after bariatric surgery[19,44]. In the 3-year follow-up of the STAMPEDE trial, albuminuria improved in the surgical groups even with reduced usage of renin-angiotensin system blockers. This suggests that bariatric surgery can help delay the progression of kidney disease in T2DM[10].

Other studies have looked at outcomes other than micro- and macro-vascular endpoints. Neff et al. like others, reported that bariatric surgery can benefit metabolic and cardiovascular diseases but also found improvements in functional levels and socioeconomic factors. This was studied using the modified King's Obesity Staging System which takes into account physical, psychological, socioeconomic, and functional domains[45]. Hewitt et al. found that pulmonary function improved significantly 5 years after bariatric surgery. They also reported significant improvements in symptomatic asthma and obstructive sleep apnea[46].

Although there is some data to support the role of bariatric surgery in reducing micro- and macro-vascular outcomes in obese patients with T2DM, further

long-term studies are required. Earlier medical intervention studies demonstrated that even short periods of tight glycemic control translate into micro- and macro-vascular benefits later. This occurs despite loss of the initial tight glycemic control and has been referred to as the 'legacy effect'. It will be especially interesting to see the effect of bariatric surgery on end organ complications in those patients with recurrence of T2DM after remission.

Conclusions

Indeed, there is now a plethora of sound evidence for the use of metabolic surgery in the treatment of obese type 2 diabetes patients. Early glycemic improvements are often seen postoperatively with a durable effect of remission beyond 5 years. About 20–25% of these patients will relapse in the long term. Metabolic improvements with reduction in microvascular and macrovascular DM complications long term have also been reported after metabolic surgery.

T2DM is a chronic disorder characterized by progressive pancreatic beta-cell loss and dysfunction that can begin up to 5-10 years prior to its clinical manifestation and diagnosis. In follow-up of T2DM patients after bariatric surgery, the ''reversal'' of this pathophysiological state should be regarded in the same manner as its development. While there is a dramatic improvement of glycemic control involving even remission in the short and medium-term, outcomes of glycemic control after bariatric surgery should be viewed in the long-term, as with all chronic diseases. The potential for lack of remission and relapse after remission is a clear concern and all physicians involved in the management of the T2DM patient undergoing bariatric surgery should bear this in mind.

Hence, Buse et al. recommended that there be at least a 5-year continuous state of complete remission before a person with known T2DM can be considered potentially ''cured''[12]. Therefore, patients with DM who have undergone bariatric surgery should be treated holistically like any other T2DM patient prior to that. They should be followed up regularly for at least 5 years after DM remission. Appropriate hypoglycaemic agents should be instituted (or reinstituted) if there is residual diabetes or any sign of relapse into the diabetic range even though the optimal hypoglycaemic agent in this group of patients has not been well studied. In addition, blood pressure and lipid-lowering medications to achieve the appropriate targets for T2DM patients should be well managed. Regular screening for micro- and macro-vascular DM complications should continue and appropriate preventive and treatment measures taken[12]. Hence, the multi-disciplinary team involved in the care of the patient undergoing metabolic surgery should consist of a physician experienced in the management of T2DM patients.

As physicians looking after patients with diabetes, we must focus on glycemic control. However, it would be remiss to not address all of the medical problems that often accompany T2DM. More randomized controlled studies are needed to examine the long-term effects of bariatric surgery on all the comorbidities that patients with T2DM suffer, especially hypertension and hyperlipidemia. In addition, the long-term outcomes in these patients in terms of macrovascular and microvascular disease need to be studied, as the ultimate goal of treatment is to reduce the burden of morbidities associated with T2DM. Long-term quality of life and socio-economic benefits along with healthcare utilization and costs for various healthcare systems involved should also be carefully studied. Only then will we be able to know the true long-term benefits of metabolic surgery.

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