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Management of type 2 diabetes after metabolic bariatric surgery

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Abstract

Metabolic and bariatric surgery has been proven to be effective in the glycemic and metabolic control of type 2 diabetes (T2D) and obesity. While most patients experience remission of T2D after surgery, some individuals remain with suboptimal glycemic control. In addition, a significant subset of patients experience relapse of diabetes in the long term after attaining diabetes remission. As a heterogenous disease, the underlying etiology of T2D and response to treatment can be variable in different individuals. The mechanism of diabetes relapse is not completely understood as is the optimal medical management of T2D after metabolic and bariatric surgery. Nonetheless, person-centred collaborative and supportive care beyond the monitoring of parameters forms the cornerstone in formulating care for people with diabetes. This paper reviews the clinical management of T2D after bariatric surgery, including persistent T2D or diabetes relapse after initial remission.

Keywords: Metabolic bariatric surgery, remission and relapse, pharmacotherapy, outcomes

INTRODUCTION

With the advent of bariatric surgery, the armamentarium for the treatment of obesity and obesity-related complications such as type 2 diabetes (T2D) has broadened significantly[1]. Commonly regarded as metabolic-bariatric surgery (MBS) due to its positive impact on obesity-related metabolic diseases, this modality has now been positioned as an efficacious treatment adjunct in management algorithms adopted

worldwide, in particular for T2D[2-5].

The gastrointestinal (GI) tract plays a key role in metabolic regulation, and interventions to manipulate the GI tract have resulted in significant metabolic and glycemic benefits in patients with T2D. A meta-analysis of randomized controlled trials (RCTs) comparing MBS with non-surgical management of T2D showed that MBS was associated with greater weight loss, improved glycemic control and higher rates of T2D remission[6]. After MBS, HbA_{1c} reductions of 2%-3.5% from baseline were observed compared to 1%-1.5% with medical therapy[7]. Diabetes remission has also been reported in 29%-95% of patients with T2D within 1-2 years of MBS[8-11]. Long-term follow-up points towards durability of metabolic effect, although relapse of T2D after initial remission is frequently observed (33%-67%) 5 years on after MBS[11-14]. Furthermore, most studies were conducted before the era of more potent and novel anti-diabetes and anti-obesity treatments which are currently widely in use.

The trajectory and natural course of T2D after MBS remains unclear, in particular of sustained metabolic outcomes and the long-term outcomes of diabetes-related complications[1,15]. Rapid changes in metabolic parameters from enforced dietary changes and weight loss after MBS also necessitate adjustments in medications for control of blood pressure, glucose and lipids. With a significant percentage of patients either remaining with T2D or experiencing relapse of T2D in the long-term, ongoing management of T2D after MBS remains crucial to reduce the morbidity and mortality of people with T2D. However, the optimal management of T2D after MBS is not well-studied. We aim to discuss and explore current evidence surrounding the clinical management of T2D after MBS.

T2D - A CHRONIC, PROGRESSIVE YET HETEROGENOUS DISEASE

A chronic, progressive metabolic disorder characterized by hyperglycemia and lipid dysmetabolism, T2D is complex with a multi-faceted pathophysiology. Insulin resistance coupled with impaired (defective) insulin secretion from β-cell dysfunction form the two main distinct pathophysiologic drivers of T2D[16]. Obesity serves as a major etiologic factor of insulin resistance. Ectopic deposition of intraorgan fat within the liver and muscle results in insulin resistance with cascading sequalae which can ultimately impair β-cell function while that in the pancreas disrupts normal glucose and lipid metabolism, leading to impaired insulin secretion[17]. In addition, concomitant pathophysiologic defects such as reduced incretin effect, increased renal glucose reabsorption, elevated fasting glucagon levels leading to increase hepatic gluconeogenesis can further exacerbate hyperglycemia[16,18].

There is, however, inter-individual variability in the relative contribution of each factor to the etiology of disease, rendering T2D a heterogenous disease. Contributing to the heterogeneity of clinical phenotypes, onset and course of T2D, and to the response to treatment, are factors like the presence of autoimmunity, genes, epigenetics, ethnicity and "fat mass setpoint"[17,18]. The set-point theory posits that the human body has a predetermined fat mass set-point range and compensatory physiological mechanisms maintain that set point and resist deviation from it. The set-point can vary widely across individuals. It has been also postulated that there is interindividual variation in the susceptibility of the metabolic organs (e.g., liver, pancreas) to visceral adiposity (liposusceptibility) and this contributes to the manifestation of insulin resistance and adverse effect of excess fat at variable body mass index (BMI), and in different ethnic groups[17]. For example, Asians are particularly susceptible to visceral adiposity and its deleterious metabolic sequelae. Even among Asians, heterogeneity in clinical phenotypes is observed with South Asians more "liposusceptible" than East Asians and T2D manifesting at seemingly normal BMI and waist circumference ranges[19,20]. East Asians, on the other hand, display a lower insulin-secreting capacity compared to their Caucasian counterparts, manifesting at the pre-diabetes or early T2D stages[21].

Regardless, β-cell failure is the hallmark of the development of overt hyperglycemia in diabetes[22]. By the time fasting hyperglycemia manifests, it is postulated that 50% of β-cell function is lost[23]. With time, there is an inevitable progressive decline in β-cell function despite anti-diabetic treatment, with the requirement of additional glucose-lowering agents including insulin therapy in many individuals 6 years after diagnosis[24]. The rate of β-cell decline is variable, with factors like hyperglycemia, lipotoxicity, obesity and increasing age accelerating the process, and others such as intentional weight loss and early intervention of T2D, retarding it[17,18,25].

TARGET UNDERLYING PATHOPHYSIOLOGY IN T2D TREATMENT

Regardless of the modality used, optimal and effective treatment of T2D aims at targeting the multiple underlying pathophysiologic defects. Recent attempts by Wesolowska-Andersen *et al.* to map clinical heterogeneity in T2D to individual etiologic processes using soft clustering of 32 anthropometric, clinical, and biochemical phenotypes in early T2D identified 4 archetypes based on obesity, insulin resistance, dyslipidemia, and β-cell glucose sensitivity[26]. Disease progression and risk of diabetes complications can be predicted and treatment strategies deployed based on the predominant archetype[26]. Such an approach can potentially lead to individualized treatment strategies targeting the predominant pathophysiology of T2D to improve clinical outcomes. These strategies can include increased vigilance in monitoring and the early use of anti-diabetic, reno- and cardio-protective medications to retard the progression of T2D and delay the development of diabetes complications.

Any reversal of the defects to attain diabetes remission hinges upon the intrinsic insulin-secreting capacity of the β-cells[27,28]. Sustainability of remission would, therefore, depend on having a critical mass and function of residual β-cells. With increasing duration of T2D typically beyond 10 years, the possibility of restoring β-cell function diminishes drastically[23,27]. On a background of variable contribution of each pathophysiologic defect in every individual, e.g., severity of insulin deficiency, insulin resistance or incretin defect, the response to each treatment modality of T2D, including MBS, can be heterogenous. Patient factors such as duration of T2D, age, pre-operative use of insulin and C-peptide levels, can serve as surrogates of residual β-cell function and double up as predictors of diabetes remission induction and maintenance while the surrogates of insulin resistance such as pre-operative BMI, waist-hip ratio may predict better response with weight loss[29,30].

The delineation of pathophysiologic defects impacting an individual allows us to harness the mechanisms of MBS to target these defects in the individual and guide the choice of procedure. When faced with a reduced probability of robust β-cell function as encountered in diabetes of long duration, if significant weight loss and maintenance can be achieved, insulin sensitivity can be restored and the strain upon an already compromised β-cell can be lifted. It has been shown that despite maintaining clinical remission, there is limited recovery of β-cell function 3 years after gastric bypass. However, normoglycemia can be attained through augmented incretin effect which enhances insulin secretion after gastric bypass[31]. Weight loss improves insulin sensitivity and can augment incretin effect which, in turn, improves insulin secretion and reduces β-cell apoptosis. There is emerging evidence of re-differentiation of β-cells after weight loss which can improve insulin secretion[27,28]. In addition, the magnitude of weight loss has been shown to correlate with diabetes remission after MBS, with weight loss being the biggest predictor of diabetes remission and its sustenance after MBS[25,29,31]. Several studies have observed that weight loss and diabetes remission in the long-term is greater in bypass procedures compared with other types of procedures[7,32] possibly related to the above mechanisms. Unfortunately, when β-cell deterioration is severe as it is in long-standing diabetes, it can be challenging to attain remission even with the large degree of weight loss associated with MBS[18]. The use of clinical surrogates to stratify the likelihood of insulin deficiency pre-operatively - and hence the

likelihood of diabetes remission - has been proposed to guide choice of procedures, with a careful balance of risk from surgical complications[33].

COURSE OF DIABETES AFTER METABOLIC SURGERY: MECHANISMS AND PREDICTORS OF DIABETES REMISSION AND RELAPSE AFTER MBS

During the immediate pre- and post-MBS periods, patients generally consume a very low-calorie diet. Such acute caloric restriction has been shown to rapidly reverse β-cell dysfunction and restore insulin secretion in those with a shorter duration of T2D[25,31,34], with hepatic insulin sensitivity and fasting plasma glucoses normalizing as early as 1 week even in the absence of significant weight loss[34]. Augmented incretin effect and insulin secretion is observed within the first week, with normalization of insulin secretion about 1 month post-gastric bypass. The 5- to 7-fold increase in post-meal glucagon-like peptide-1 (GLP-1) levels from baseline is maintained even years after surgery. However, in the long-term, intrinsic β-cell function shows minimal improvement despite clinical diabetes remission post-MBS, with progressive diminished function over time[31]. Other mechanisms of improvement in diabetes control after MBS include increase in gut glucose utilization and intestinal gluconeogenesis, reduced gut glucose absorption, changes in adipose tissue, circulating bile acids and gut microbiota, among others[35]. Hence, rapid improvement and even normalization of blood glucoses can be observed immediately after MBS, with diabetes remission occurring as early as 3-6 months after surgery.

In a Consensus Report jointly published in 2021 by the American Diabetes Association and other major scientific societies, diabetes remission is used to describe a "sustained metabolic improvement in T2D to nearly normal levels". Its definition was largely simplified and re-determined as "a return of HbA_{1c} to < 6.5% (< 48 mmol/mol) that occurs spontaneously or following an intervention and that persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy"[15]. Hence, the earliest determination of diabetes remission after MBS is at least 3 months after the procedure and 3 months after the cessation of any glucose-lowering medication. Due to changes in caloric and nutrient intake, and ongoing weight loss, blood glucose changes can be rapid especially in the first 6 to 12 months after MBS, necessitating regular monitoring. To determine ongoing and long-term maintenance of remission, testing of glycemic control, preferably with HbA_{1c}, should be done at least once a year. Periodic screening of diabetes complications and monitoring of cardiovascular risk factors per recommended guidelines should continue regardless of glycemic status.

The incidence of diabetes remission after sleeve gastrectomy (SG) and gastric bypass (GB) can range from 23% to 75% depending on the definitions used for diabetes remission, the type of surgical procedure, age and severity of T2D, amongst other factors[29,35]. Prediction models have been proposed to assess the likelihood of diabetes remission after bariatric surgery. These models generally include factors such as age, BMI, duration of diabetes, HbA_{1c} level and insulin use[33,35]. In terms of procedure type, GB is more effective than SG in inducing diabetes remission, likely related to its more pronounced neurohormonal effects[33]. Studies have shown that post-operative weight loss is the strongest predictor for "restoration" of β-cell function along with baseline (pre-operative) β-cell function and post-operative GLP-1 response[36]. However, pre-operative pancreatic β-cell reserve remains the most important predictor of diabetes remission. In advanced diabetes and β-cell exhaustion, it is unlikely that diabetes remission can be achieved post-operatively despite significant weight loss.

Patients who initially attained diabetes remission after MBS may subsequently experience recurrence of T2D, a phenomenon known as diabetes relapse, occurring most frequently within the first 5 years after MBS. Data from a large Swedish registry showed that of the 2,090 subjects who achieved complete diabetes

remission, 20.1% had diabetes relapse[37]. Pre-operative predictors of diabetes relapse include longer duration of diabetes, higher pre-operative HbA_{1c}, number of diabetes medications pre-operatively, pre-operative insulin use, female gender and type of surgery (relapse 2.2 times more likely with SG *vs.* GB)[37-39]. A more recent Japanese study has also shown similar findings, with the identification of preoperative HbA_{1c}, poor weight loss, and excess weight regain after SG as risk factors for diabetes relapse[36]. Age is another factor that can predict long-term diabetes remission after MBS. A recent study showed that despite similar baseline insulin use and percentage total weight loss at 5 years, adolescents who underwent MBS were more likely to achieve durable diabetes remission at 5 years compared with adults (86% *vs.* 53%, $P < 0.05$)[40]. Most studies also show an independent association between poor weight loss outcomes after MBS (either insufficient weight loss or significant late weight regain) and diabetes relapse[30,36-39]. Hence, maximizing weight loss outcomes after MBS and prevention of weight regain is of paramount importance to reduce the risk of diabetes relapse.

Although diabetes relapse after initial diabetes remission is common (33%-67%), most patients can achieve significantly better glycemic control and improvement in cardiovascular risk factors compared to their pre-operative state. In a large cohort study, a third of patients who had diabetes remission had subsequent diabetes relapse[38]. However, even in patients who had relapse, 77% of them maintained adequate glycemic control ($HbA_{1c} < 7\%$). Diabetes medication requirements also decreased, with average number of diabetes medications reducing from two before surgery to one long-term, and insulin use decreasing from 29% before surgery to 12% long-term. Other metabolic parameters such as blood pressure and lipid levels have also improved compared to pre-surgery. Data from a Singapore centre showed similar results, and ethnicity did not influence glycemic outcomes or diabetes remission in the multi-ethnic Asian cohort[41].

The specific mechanisms that underpin the long-term diabetes remission, or that influence diabetes relapse remains unclear. The role of gut hormones, insulin, glucagon, and adipokines need to be investigated to gain better understanding of these mechanisms[42]. Nevertheless, the treatment of diabetes relapse should be multi-pronged and targeted towards the two main causes of relapse: those who are surgical non-responders with inadequate weight loss or weight regain after surgery, and those with poorer baseline β-cell reserve and develop progressive β-cell exhaustion over time.

MANAGEMENT OF T2D: A GENERAL AND COMPREHENSIVE APPROACH

The fundamental principles of management of a person with T2D remain unchanged regardless of type of therapy, with lifestyle management and psychosocial care forming the cornerstones of diabetes management[43]. The ultimate goals of treatment for diabetes are to prevent or delay complications and optimize quality of life in those living with diabetes and go beyond focusing on parameters. However, these goals should always be person-centric and individualized, considering multiple factors including ability for self-management, social situation, age, cognitive ability, educational level, health literacy, financial concerns, personal preferences for care and support systems, and the presence or risk of renal and cardiovascular disease. Patients should be empowered for problem-solving self-management as much as possible, supported by a multi-disciplinary team. Treatment plans collaboratively developed with people with diabetes, their families and the healthcare team can significantly improve well-being and disease outcomes[44].

Holistic care of the patient with T2D should include counseling for smoking cessation, weight, stress and sleep management, and ensuring up-to-date vaccinations[43]. Simultaneous control of multiple metabolic targets (glycemia, blood pressure and lipids) compared to that of individual metabolic parameters have been shown to have greater impact in reducing diabetes micro- and macro-vascular complications and mortality

and with legacy effect[45,46]. Each metabolic target should be individualized according to the presence of pre-existing diabetes complications and hypoglycemia risk[47]. Vigilant regular monitoring for diabetes complications with at least an annual cardiovascular risk assessment and screening for retinopathy, nephropathy, neuropathy and diabetic foot ulcers should be performed as early detection and intervention of complications can delay progression of these complications[48].

Follow-up visits should be scheduled at least every 3-6 months initially and once stabilized, can be individualized accordingly but at least annually. Treatment plans and goals of therapy should be reviewed and agreed upon with the patient at every visit and adjusted according to the patient's needs rather than implementing a one-size-fits-all treatment plan[43,47]. Even in diabetes remission, holistic care of the patient with T2D should remain unchanged. Table 1 provides a summary on the goals of therapy and the recommended monitoring of all patients with T2D even in the presence of diabetes remission.

Factors predicting diabetes remission or relapse should be considered in pre-operative counseling and post-operative monitoring. The risk of diabetes relapse and the need for long-term monitoring of metabolic parameters and diabetes complications even in the advent of diabetes remission should always be made clear to patient.

MANAGEMENT OF RESIDUAL DIABETES AND DIABETES RELAPSE: CHOICE OF PHARMACOTHERAPY

Management of diabetes in the peri-operative and early post-operative phase

Good glycemic control during the pre-operative and early post-operative period is important to reduce the risk of peri-operative complications, and perhaps even improve the chances of remission after MBS[49,50]. Anaesthesia and surgical stress, abrupt cessation of insulin during the perioperative period, postoperative infection, prolonged poor oral intake, and severe dehydration can precipitate diabetic ketoacidosis, which is a diabetic emergency[51].

While patients are on a very-low calorie diet in preparation for MBS, insulin doses should reduced by at least 50% due to the rapid insulin sensitizing effect of an acute caloric restriction and adjusted based on frequent self-monitoring of blood glucoses during this period[34]. For those with good glycemic control (i.e., HbA_{1c} < 7%) and relatively lower doses of insulin (e.g., < 30 units/day), cessation of insulin may be possible with frequent blood glucose monitoring. Similarly, for those on oral glucose-lowering medications, sulphonylureas are generally either halved or stopped while agents with a low risk for hypoglycemia (e.g., metformin and incretin-based therapies) may be continued[52].

During the peri-operative period, metformin should be stopped on the day of surgery, but may be restarted on the 3rd day after surgery if needed, provided that the renal function remains stable[53]. Metformin doses should be reduced after gastric bypass surgery as bioavailability of metformin increases by 50% after Roux-en-Y gastric bypass (RYGB)[54]. Due to its glycosuric effects and risk of dehydration and diabetic ketoacidosis, of sodium-glucose transporter-2 inhibitors (SGLT2i) should also be withheld prior to bariatric surgery, and only restarted after surgery when adequate hydration is established. Similar to routine treatment for hospitalised patients, a glucose target of 7.8-10.0 mmol/L may be adopted and insulin doses titrated to maintain glucose levels within this range[54].

Immediately after MBS, sulphonylureas and prandial insulins are generally avoided due to the risk of hypoglycemia. An approach the authors adopt is to stop all anti-diabetic medications immediately post-op except for oral metformin and dipeptidyl peptidase-4 (DPP-4) inhibitors (if prescribed pre-operatively) and

Table 1. Goals of therapy and recommended monitoring for a patient with T2D after MBS[47]

Parameter	Target	Caveats	Minimal frequency of monitoring (more frequent if not at target or with complications)
HbA_{1c}	< 7%	Tailored individually based on the risk of hypoglycemia and long-term outcomes	Six months
Blood pressure	< 130/80 mmHg	Preferential use of ACEi or ARB in those with CKD/DKD	Six months
LDL-cholesterol	< 1.7 mmol/L	< 1.5 mmol/dL in those with established CVD, CKD, or PVD	Annual
DR	Early detection of DR with diabetic retinal photography to allow for early intervention		Annual
DKD	Early detection and intervention of DKD with the use of serum creatinine and urine albumin:creatinine ratios		Annual
Diabetic neuropathy and foot screening	Early detection of those at risk for diabetes foot disease with routine screening for neuropathy and peripheral artery disease of the lower extremities		Annual
Immunisation	Vaccinated against pneumococcal and influenza per local guidelines		

Recommendations (apart from glycemic target) remain for those with remission of T2D. ACEi: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CKD: chronic kidney disease; CVD: cardiovascular disease; DKD: diabetic kidney disease; DR: diabetic retinopathy; LDL: low-density lipoprotein; MBS: metabolic bariatric surgery; PVD: peripheral vascular disease; T2D: type 2 diabetes.

use a supplemental rapid or short-acting insulin sliding scale. If the pre-meal capillary blood glucoses (CBG) levels are consistently > 12 mmol/L during the 48 h after surgery, basal insulin once daily at 20% of the patient's body weight is initiated until the next outpatient review 2-4 weeks after surgery. Basal insulin is stopped if pre-meal CBG levels are < 8 mmol/L. SGLT2i may be resumed at that point depending on CBG levels, hydration status or pre-existing history of heart failure and renal disease. Figure 1 provides a framework of managing diabetes in the peri-operative period.

Management of diabetes in the chronic post-operative phase and of diabetes relapse

Metformin has remained the backbone treatment for T2D due to its low cost, proven efficacy and safety profile and wide availability worldwide. Hence, metformin is the natural first choice of pharmacotherapy for patients with residual diabetes or diabetes relapse [Figure 1]. Meanwhile, the advent of new classes of glucose-lowering medications has dramatically altered the landscape of diabetes therapeutics. The choice of anti-diabetic medication after metformin is dependent on several factors such as the presence of atherosclerotic cardiovascular disease (ASCVD) or its risk, the presence of heart failure, history of stroke and/or chronic kidney disease. Agents which are weight neutral or result in weight loss should be considered first[47].

GLP-1 secretion is generally enhanced after RYGB and SG[55], leading to increased satiety, glucose-dependent insulin secretion. Patients with suboptimal weight loss[56] or non-remission of T2D[57] after RYGB had attenuated post-prandial GLP-1 response, which raised the possibility of using GLP-1 receptor agonists (GLP-1 RA) to treat residual diabetes or diabetes relapse.

In the GRAVITAS RCT, patients with residual or recurrent T2D after RYGB or SG who received liraglutide 1.8 mg daily had better glycemic control (HbA_{1c} -1.2%) and weight loss (4.2 kg) compared with placebo[58]. Interestingly, the effect of liraglutide on glucose and weight loss in this post-operative cohort is almost identical to the non-surgical T2D population[59]. It is hypothesized that GLP-1 release after MBS is triggered by food and fasting GLP-1 levels are similar to pre-surgery levels[60]. GLP-1RA augments fasting GLP-1 levels, providing complementary advantages on appetite suppression, weight loss and improvement in

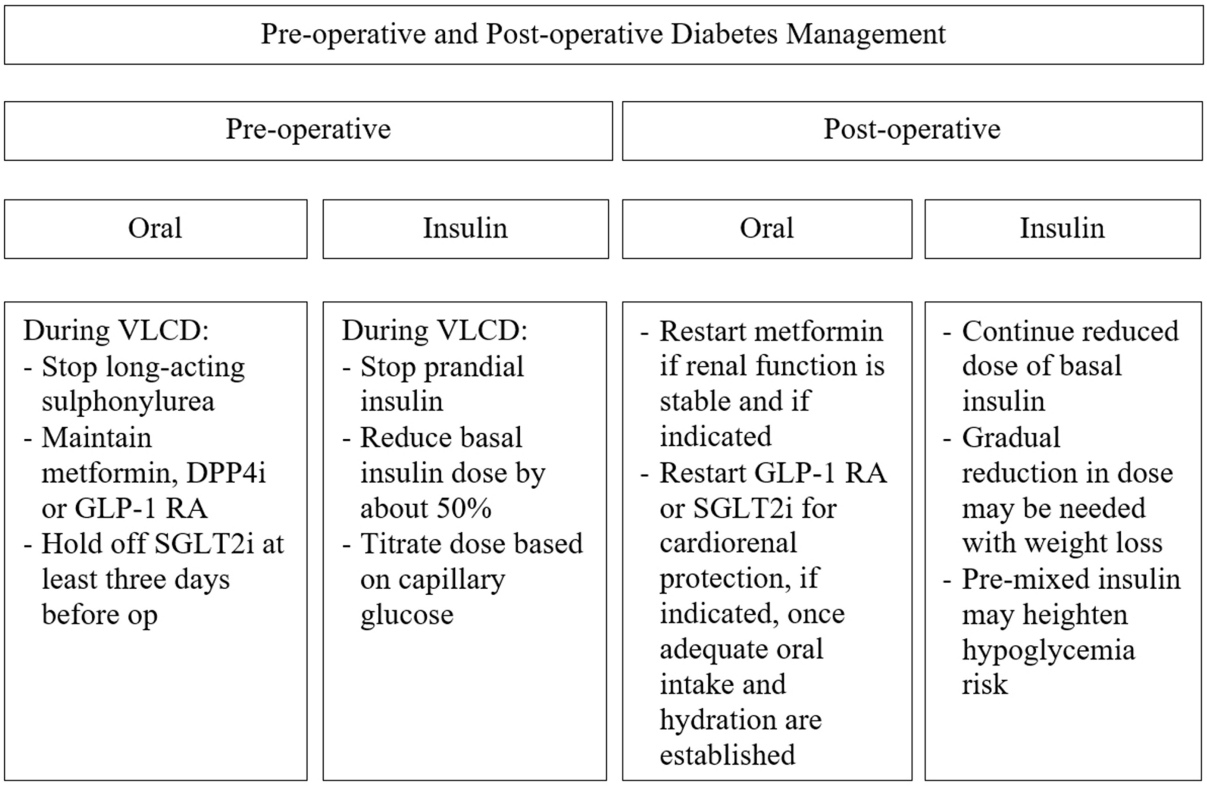

Figure 1. Medical management of diabetes in metabolic-bariatric surgery patients[52]. DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1: glucagon-like peptide-1; RA: receptor agonist; SGLT2i: sodium-glucose transporter-2 inhibitor; VLCD: very low-calorie diet.

insulin secretion and sensitivity[58].

Over the past few years, newer GLP-1 RA have been approved that allow for more convenient administration and greater weight loss. One example is semaglutide, a GLP-1 receptor agonist currently approved in countries such as the US and Singapore for treatment of T2D and obesity, which has been demonstrated to reduce CV events[61]. Placebo-subtracted weight loss of 12.4% was achieved with the higher dose of subcutaneous (SC) semaglutide 2.4 mg weekly used for obesity[62]. The STEP-2 RCT which examined the use of SC semaglutide 2.4 mg weekly in T2D and obesity demonstrated weight loss of 9.6%, with more than two-thirds of patients treated with semaglutide 2.4 mg achieved target HbA_{1c} of 6.5%[63]. Weight loss with weekly semaglutide 2.4 mg (15.8%) was more than double that of daily liraglutide 3.0 mg (6.4%)[64], which contributes to its popularity. Side effects are commonly gastrointestinal (nausea, diarrhoea, constipation) and typically mild and transient. There are no studies evaluating semaglutide specifically in the post-bariatric surgery population but the favourable risk-benefit profile of semaglutide makes it well-suited to treat post-bariatric surgery patients with residual diabetes or diabetes relapse. An RCT of semaglutide 2.4 mg in patients with inadequate weight loss following bariatric surgery is ongoing (BARI-STEP)[65], and the results should provide further insights on the use of semaglutide in this patient population. In its oral form at a maximum dose of 14 mg once daily, semaglutide is efficacious as an anti-diabetic treatment and spares the need for injections. The PIONEER PLUS study showed that higher doses of oral semaglutide (25 and 50 mg once daily) can lower HbA_{1c} by an additional 0.27%-0.53% (total HbA_{1c} drop of up to 2%) in T2D with 4% greater weight loss (50 mg once daily) compared to the currently approved 14 mg dosage[66]. For those without T2D, oral semaglutide 50 mg once daily in the OASIS 1 study resulted in a mean total weight loss of 15.1% at 68 weeks, with 85% of subjects losing ≥ 5% of body weight[67].

Tirzepatide is a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist given as a weekly subcutaneous injection, approved in the US for treatment of T2D in 2022 and for chronic obesity treatment in 2023. A 72-week RCT in participants with obesity and T2D showed a mean weight loss of 15.7% with 15 mg of tirzepatide *vs.* 3.3% with placebo[68]. (Another similar study in individuals with obesity but without T2D showed mean total weight loss of 16 to 22.5% after 72 weeks' of treatment with tirzepatide 5-15 mg weekly.) Adverse events observed are mostly mild to moderate, transient gastrointestinal symptoms[69]. Given the impressive amount of weight loss, coupled with low hypoglycemia risk, tirzepatide is potentially an ideal medication to treat residual diabetes or diabetes relapse after bariatric surgery especially with concurrent weight regain, but further studies are required to evaluate its use in the post-bariatric surgery setting. Recent phase 2 studies of CagriSema, a once-weekly combination of cagrilintide (an amylin analogue) and semaglutide, and triple-hormone (GLP1, GIP, glucagon) receptor agonist, retatrutide, demonstrated an average 2%-2.2% reduction in HbA_{1c} at 24 weeks and a mean 16%-17% reduction in body weight (with the highest doses) at 32-36 weeks in those with obesity and T2D[70,71]. In people with obesity without T2D, an average 24% drop in body weight after 48 weeks of treatment with the highest dose of retatrutide was observed[72]. Novel incretin- and gut-hormone based therapies are increasing the efficacy of pharmacological treatment options in T2D. Given that persistent diabetes and diabetes relapse are commonly associated with a lower degree of weight loss or weight regain, complementary use of these novel agents (if approved) after MBS can potentially result in greater weight loss while simultaneously serve to attain good glycemic control although studies are required to guide treatment strategies. As with the management of any other chronic disease, if these therapies are able to achieve good glycemic control and weight loss, they should be continued long-term as benefits can be attenuated or lost with discontinuation of the therapy.

DPP-4 inhibitors work by blocking the enzyme that inactivates GLP-1 and are generally well-tolerated and weight neutral, but with a modest glucose-lowering effect. A small study which investigated the use of sitagliptin over 4 weeks in persistent or recurrent diabetes after RYGB showed a mild decrease in post-prandial glucose excursion after mixed meal test[73]. In general, GLP-1RA provide superior weight loss and glucose-lowering efficacy and, hence, preferred over DPP-4 inhibitors in patients with persistent or recurrent diabetes after MBS.

Incretin-based therapy with DPP-4 inhibitors and GLP-1RA have been shown to be more effective in Asians[74,75] perhaps through increased incretin activity to overcome β cell dysfunction which East Asians are more susceptible to[21]. However, these have not specifically been studied in East Asians after MBS.

Apart from GLP-1RA, other medications used to treat T2D can also be used in the post-bariatric surgery setting. In a small RCT involving 16 patients post-MBS, a 6-month treatment with canagliflozin 300 mg once daily was able to create a 10 kg weight difference and a HbA_{1c} difference of -0.75% compared to placebo[76]. The cardiovascular and renal benefits SGLT2i have changed the treatment paradigm of T2D. SGLT2i decrease renal glucose reabsorption by acting on the renal proximal convoluted tubule, thus inducing glycosuria and lowers blood glucose independent of insulin sensitivity or insulin secretion[77]. Weight loss of 1%-3% can be observed with SGLT2i in T2D, which starts with an early and rapid body water and fat loss up to around 8 weeks, followed by a slower rate of sustained fat loss[78]. The modest weight loss with SGLT2i is useful in patients with obesity. However, it is the cardiovascular (CV) and renal benefits of SGLT2i that makes this drug class exceptional. Large RCTs have shown that SGLT2i provides protection against major CV disease in those at high CV risk, reduce hospitalisations due to heart failure, reduce risk of kidney disease progression and acute kidney injury, and reduce CV and all-cause mortality[79,80]. Hence, SGLT2i are the preferred option for patients with T2D, regardless of whether they had bariatric surgery.

Given the progressive nature of T2D, insulin therapy remains the cornerstone of diabetes management. It addresses the β-cell failure seen in advanced diabetes and is used when adequate glycemic control cannot be achieved with other glucose-lowering agents alone. In general, East Asians with T2D have been shown to have a lower insulin-secreting capacity compared to their Caucasian counterparts[21]. Insulin therapy may be considered earlier in the treatment algorithm especially in those with poor glycemic control in the absence of significant weight regain. The main drawbacks of insulin therapy include hypoglycemia and weight gain, and these can be mitigated when insulin is used with insulin sensitisers or incretin-based therapies such as metformin or GLP-1RA[81]. Analysis from the Bariatric Outcomes Longitudinal Database showed that of the 3,318 patients with insulin-treated T2D who underwent RYGB, 62% could discontinue insulin at 12 months[82]. This leaves over one-third of patients who still require insulin therapy, albeit at lower doses.

Finally, management of hypertension and dyslipidemia should be given equal attention especially in those with established cardiovascular and renal diseases. In the immediate post-operative period, most anti-hypertensive and lipid-lowering medications can be temporarily stopped. With weight loss, hypertension, albuminuria and dyslipdiemia improve and may also go into remission or resolve. Regardless, attainment of blood pressure and lipid targets should be regularly assessed with re-initiation of medications as indicated [Table 1].

DISCUSSION

In patients with T2D, MBS provides better long-term glycemic control than conventional treatment, with reductions in diabetes medication use[13,32]. Significant reduction in adverse cardiovascular events, nephropathy and in mortality in people with T2D who had undergone MBS was observed in the long-term compared with those who were managed medically[83,84]. A large cohort study has showed that for every additional year of time spent in remission prior to relapse, the risk of microvascular disease was reduced by 19%. It is evident that trajectories of health and disease are significantly altered after MBS, and even transient remission can lead to lifelong benefits[85].

For every patient with T2D, an individualized goal of therapy balanced with the risk, benefits and outcome of each therapy including MBS should be discussed with the patient and treatment plans tailored in collaboration with the patient and the healthcare team. In the advent of long-term diabetes remission, patients with T2D should not be left unmonitored for diabetes complications as these may have been established or may still occur with time. Patients should not be promised a "cure" and a life free from monitoring as we do not have sufficient long-term data at present to advise so.

Management of residual diabetes and diabetes relapse requires careful evaluation to evaluate its cause. Insufficient weight loss or weight regain after MBS are risk factors for suboptimal diabetes control and should be addressed. Residual β-cell function is fundamental to maintaining diabetes remission and the natural progression of diabetes should always be borne in mind when considering T2D pharmacotherapy. A thorough multidisciplinary approach with a focus on lifestyle modification should be adopted. Comprehensive care based on standard diabetes guidelines should still be consistently applied in the post-bariatric setting, with greater emphasis on medications that can cause weight loss, without undue risk of hypoglycemia. Aggressive control of CV risk factors, in particular of blood pressure and lipids, use of cardio- and renoprotective therapy and ongoing assessment for diabetes micro- and macrovascular complications[47] should continue even in the event of long-term diabetes remission until further outcome data is available[15] [Table 1]. Metformin remains the first line option for T2D management. Preferential use of SGLT2i should be considered for patients with history of CV disease, heart failure or diabetes nephropathy. GLP-1 RA are generally also preferred in those with CV disease. In patients with weight

regain after MBS, use of incretin-based therapies with good weight loss data such as semaglutide or tirzepatide are preferred. Insulin therapy is recommended for patients with advanced diabetes with β-cell failure, or if satisfactory glycaemic control cannot be achieved with non-insulin agents. The tailoring of anti-diabetic pharmacotherapy is best considered in the light of the pathophysiologic factors in each individual. With T2D having such a complex pathophysiology, the various treatment modalities should be considered as complementary to rather than exclusive of each other. Initiation of treatments can be in tandem instead of sequentially which at times may perpetuate the treatment inertia frequently encountered in clinical practice.

Some unanswered questions remain. Anti-diabetic medications such as SGLT2i and GLP-1RA are used for the treatment of chronic kidney disease and heart failure, and for weight loss respectively. Defining diabetes remission with ongoing use of these medications remains unclear. Furthermore, the long-term outcome of diabetes complications on a background of sustained diabetes remission is currently unknown. MBS has been shown to be more effective than medical therapy for diabetes control and remission. However, most studies were conducted during the era prior to widespread use of GLP-1RA and SGLT2i which have potent effects on weight loss, glycemic control and metabolic improvements. Furthermore, the emergence of novel dual- and triple-hormone receptor agonists and gut-hormone based therapies as effective anti-diabetic and anti-obesity pharmacotherapy[70-72,86] which can potentially rival the glucose-lowering and weight loss outcomes of MBS, will re-shape our treatment approach to T2D and obesity-related diseases. Updated trials will be needed to substantiate the superiority of MBS over intensive medical therapy for T2D especially in the long-term, and assess the impact of adjunctive therapy of these novel pharmacotherapy with MBS which could well prove to be the most efficacious treatment for T2D. With the ultimate goal of diabetes treatment being to reduce diabetes complications and mortality, and to improve the quality of life in patients with T2D[43], further studies to evaluate these outcomes with additional incorporation of patient-reported outcome measures and cost-effectiveness are urgently needed.

CONCLUSION

T2D is a heterogeneous chronic metabolic disorder associated with increased morbidity and mortality. While MBS can help people with T2D and obesity attain diabetes remission, a substantial proportion remains with diabetes after surgery or experience diabetes relapse after remission. Holistic and personalized care of the patient remains the standard of care in all patients with T2D with or without remission.

Finally, it is important to remember that residual diabetes or diabetes relapse should not be considered as failure of MBS. Despite diabetes remission being an attainable end-point in many with T2D after MBS, it should not be the be-all and end-all goal of MBS as the ultimate goal of therapy is to prevent the burdensome complications of diabetes while optimizing quality of life in people with T2D.

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Authors' contribution

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