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REVIEW

Clinical insights into management options for recurrent type 2 diabetes and cardiovascular risk after metabolic-bariatric surgery

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Abstract *Aims:* Long-term clinical trials evaluating the effects of metabolic-bariatric surgery (MBS) on type 2 diabetes (T2D) demonstrate that a significant proportion of patients either fail to achieve remission or experience T2D recurrence over time. Furthermore, patients with recurrent T2D might require reinstitution of pharmacotherapy to control comorbidities (hypertension, dyslipidemia). This paper reviews therapeutic options in patients with T2D relapse.
Data synthesis: Although presently there is no recommended pharmacological strategy, the available data support GLP-1 analogues (GLP-1a) as the most suitable option to control hyperglycemia post-MBS. Beside their efficacy in lowering glycemia and body weight while preserving lean mass, GLP-1a exert cardiovascular/renal-protection and are also safe and well tolerated in surgical patients. In addition, the s.c. route of administration of these medications circumvents the problem of changes in oral drugs bioavailability following MBS. Of note, the available data refers to liraglutide and needs to be confirmed with weekly GLP-1a agents. Information regarding the impact of MBS on the pharmacokinetics of lipid lowering and anti-hypertensive drugs is scarce and inconclusive. The findings indicate that timing from intervention is particularly important because of adaptive intestinal mechanisms.
Conclusions: The recurrence of T2D following MBS is a clinically relevant issue. GLP-1a therapy represents the best option to improve glycemic and weight control with good tolerability. Long-term clinical trials will clarify the impact of these drugs on cardiovascular outcomes. A close monitoring of MBS patients is advised to guide drug dosage adjustments and ensure the control of cardiovascular risk factors.

1. Introduction

Metabolic-bariatric surgery (MBS) is widely recognized as the most effective treatment for long-term weight loss [1], improvement/remission of obesity-related diseases – primarily type 2 diabetes (T2D) – and reduction of total and

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cardiovascular (CV) mortality [2–7]. These beneficial outcomes have led to a rapid increase in the number of bariatric operations performed worldwide [8], with Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) accounting altogether for nearly 80% of all procedures, followed by adjustable gastric banding (AGB) and biliopancreatic diversion (BDP). Novel, minimally invasive bariatric procedures are under investigation with promising results [9].

Based on randomized clinical studies (RCTs) showing the superiority of MBS respect to lifestyle/medical treatment in achieving the remission of T2D [3], MBS has gained a distinct position in the algorithm of T2D treatment [10]. However, not all patients achieve T2D remission despite substantial weight loss, and others, who initially achieve remission, can present recurrence of T2D over the years. Indeed, up to 50% of operated patients experience T2D relapse during a 5- to 12-year follow-up [11], thus requiring reinstitution of pharmacological therapy to achieve normal glycemic control. At present there is no standard pharmacological regimen for the management of persistent/recurrent T2D; however, new data may help clinicians in the decision-making process, prioritizing some drugs over others.

Patients with persistent/recurrent T2D post-MBS might require pharmacologic support to meet the recommended clinical targets for the prevention of CV risk. In this regard, it is important to consider that the gastro-intestinal anatomical rearrangement following MBS can affect the absorption of oral drugs, and ultimately impact the efficacy of glucose lowering and cardioprotective therapy.

In this paper, we review the available literature on the clinical management of patients with persistent or recurrent T2D to help clinicians select the most appropriate therapeutic strategy to achieve an optimal control of both blood glucose and overall CV risk profile.

2. Remission and recurrence of type 2 diabetes after MBS

The remission of T2D following MBS ranges from 22 to 90%, depending on the type of surgery performed, the different definitions of remission (partial or complete) and the way this is estimated (cumulative or prevalent), the type of study (randomized or observational clinical study), and follow-up duration [2]. Notably, MBS also reduces the risk of diabetes-associated complications and CV mortality compared to usual medical care [12–18] and increases life expectancy by 6.1 years in nondiabetic and by 9.3 years in T2D patients [19].

Unfortunately, T2D remission tends to decrease over time and the disease reemerges in 30–50% of patients during a 3–15 years follow-up [18,20–22], as shown in long-term studies. In the Swedish Obese Study (SOS), the average recurrence of T2D was 50% at 10 years and 70% at 15 years [12]. Arterburn et al. found that 35% of their cohort of RYGB patients relapsed within 5 years from surgery [2]. In the STAMPEDE study, 47% of patients undergoing RYGB or SG experienced relapse 5 years after surgery [21]. Mingrone et al. reported 67% relapse at 10 years in RYGB patients and 53% in patients treated with BDP/DS [22]. The risk of T2D relapse appears to be associated with some pre-operative factors such as duration of disease, degree of glucose control, number of glucose lowering agents [23,24] and, above all, the trajectory of post-surgery weight loss, with lower weight loss in the first year being associated with weight regain and higher 5-year T2D relapse [23]. There is evidence that at least one third of operated patients regain over 25% of the total weight lost within 2–5 years from surgery [25]. A reduction in energy expenditure consequent to the loss of lean mass [26] together with psychosocial and behavioral factors-such as mental health disorders, depression, alcohol and drug (ab)use- and food urges contribute to weight regain [27]. These observations emphasize the importance of intensified postoperative management, including psychological support, dietary adherence and the practice of physical exercise, as fundamental measures to ensure long-term weight maintenance.

Beside increasing the risk of T2D recurrence, weight regain has important consequences on patients' health, including the relapse of obesity-related co-morbidities and deterioration in quality of life [28] although an improvement in blood pressure and lipid profile can persist despite deterioration of glucose control suggesting that the time spent in remission has a "legacy effect" [24].

3. Clinical management of persistent or recurrent type 2 diabetes

In the frame of the pharmacological options for the management of persistent/recurrent T2D after MBS, clinicians should prioritize medications characterized by a considerable glucose-lowering effect, low hypoglycemia risk and a favorable impact on body weight. Below, we will examine possible therapeutic options starting with those agents for which there is more evidence of clinical efficacy (Table 1).

3.1. GLP1- analogues

GLP-1 analogues (GLP-1a) exert their glucose-lowering effects through a number of mechanisms, i.e., increased insulin secretion, suppressed glucagon secretion, slowed gastric emptying, increased satiety, reduced appetite and food intake, all of which contribute to decrease body weight, improve insulin sensitivity and glycemic control [29]. Interestingly, the reduction in body weight is due to a reduction in fat mass, especially visceral fat, with less effect on muscle mass [30]. Several studies have reported a significant increase in GLP-1 levels after malabsorptive or mixed procedures in patients with and without T2D [31,32] suggesting that such increase greatly contributes to the remission of T2D after MBS [33,34]. Another relevant observation is that in operated patients, the lack of increase in post-prandial GLP-1 response is associated with a poor T2D remission, providing a rationale for the use of GLP-1a for the management of recurrent/persistent T2D

Table 1 Overview of glucose lowering agents and clinical considerations for their use in patients with persistent/recurrent T2D after MBS.

Glucose lowering Agent	HbA1c	Body weight	CV protection	Renal protection	Concerns in patients following MBS	Evidence in patients following MBS[a]
GLP-1 analogues	↓↓	↓↓	↑↑	↑	More pronounced gastrointestinal side effects	Yes
DPP-4 inhibitors	↓	→	→	→	Modest improvement in glycemic control in case of moderate/severe hyperglycemia	Poor
SGLT-2 inhibitors	↓↓	↓	↑↑	↑	Increased risk of eDKA in perioperative phase Increased risk of dehydration Increased risk of Vit D deficiency	Poor
Metformin	↓	↓→	↑→	→	Increased toxicity risk (increased bioavailability) More pronounced gastrointestinal side effects Increased risk of Vit B_{12} deficiency	Poor
Sulfonylureas	↓↓	↑	→	→	Increased risk of hypoglycemia Increased risk of weight gain	No
Thiazolidinediones	↓↓	↑	↑	→	Increased risk of weight gain, fluid retention and bone fractures	No
Insulin	↓↓↓	↑↑	→	→	Increased risk of weight gain Increased risk of hypoglycemia	No

CV: cardiovascular; MBS: Metabolic-bariatric surgery; Vit: Vitamin; eDKA: euglycemic Diabetic Ketoacidosis.
One, two or three arrows indicate a mild, moderate or high increased/decreased (according to the direction) effect of the pharmacologic agent on the four variables listed in the columns, while the flat arrow indicates a neutral effect.
[a] Evidence refers to RCT for GLP-1a and to clinical studies for SGLT-2i and metformin.

after MBS. It should be also noted that the half-life of endogenous GLP-1 is only a few minutes whereas the exogenous administration of GLP-1a results in a greater and more prolonged exposure to high hormone levels with persistent metabolic effects.

Currently, only one randomized double-blind, placebo-controlled trial – the GRAVITAS (GLP-1 Receptor Agonist interVentions for poor responders afTer bariatric Surgery) study – has evaluated the efficacy of liraglutide on glucose control and weight loss in patients with persistent or recurrent T2D [35]. In this study, 80 patients who had undergone Roux-en-Y gastric bypass or sleeve gastrectomy since at least one year were randomly assigned (2:1) to receive liraglutide (1·8 mg once daily) or placebo in addition to lifestyle measures. After 26 weeks, patients receiving liraglutide achieved a significant reduction in HbA1c (−13.3 mmol/mol, −1.22% from baseline) while a slight increase in HBA1c was observed in the placebo group. Liraglutide treatment was also associated with a greater reduction in body weight, with a mean difference of −4.23 kg versus placebo. Of note, 42% of patients receiving liraglutide achieved an HbA1c of <6.5% (<48 mmol/mol) compared with 13% of patients receiving placebo. The type of MBS did not affect the outcomes, although there was an imbalance in the number of participants undergoing RYGB. The results of the GRAVITAS trial are in line with previous retrospective studies demonstrating the effectiveness and tolerability of liraglutide in patients who did not reach weight and/or glycemic targets after MBS [36–38]. In the study by Gorgojo-Martinez et al. [38], patients with persistent/recurrent T2D treated with liraglutide at a dose of 1.6 ± 02 mg/day showed the same beneficial effects on glucose control and weight loss at 2 years than nonsurgical patients, demonstrating the efficacy of liraglutide in achieving glycemic targets after MBS.

Drug tolerability of GLP-1a in bariatric patients is an important issue, since post-meal GLP-1 concentration is already increased as a result of the surgical procedures, with potential exacerbation of the gastro-intestinal side effects in patients who frequently present alveus disorders. In this regard, the results of the GRAVITAS study are rather reassuring since the rate of side effects, such as nausea, constipation or diarrhea, was similar in the liraglutide and placebo groups and to that seen in previous studies in

diabetic patients given liraglutide 1.8 mg [39]. These side effects could be effectively limited by dose adjustment to the individual patient. Another important advantage of GLP-1a is the s.c. route of administration, which allows a stable drug concentration, at odds with orally administered drugs whose bioavailability can change after bariatric procedures. Recently, oral GLP-1 analogue (semaglutide) has become available and proved to be effective in lowering blood glucose and body weight. At present, no data is available on the use of this drug in post-MBS patients; however, because of possible changes in pharmacokinetics, s.c. GLP-1 analogues should be preferred to oral formulation. Finally, it is important to underline that GLP-1a treatment is associated with a significant reduction in major adverse CV and renal events in patients with T2D at moderate-to-high CV risk with a favorable risk–benefit profile [40]. The cardioprotective and nephroprotective effects of this class of drugs could be particularly useful in T2D patients with an unsatisfactory response to MBS who are, therefore, at persistently high cardiometabolic risk.

The literature on the use of GLP-1a in MBS patients refers to liraglutide, although similar benefits can be presumably achieved with weekly-administered GLP-1a, such as semaglutide and dulaglutide, which have shown similar or even higher efficacy on glucose control and weight loss than liraglutide, with similar safety and tolerability profile [41–43]. However, long-term, randomized clinical trials are warranted to assess the efficacy of weekly GLP-1a in patients with persistent/recurrent T2D post-MBS and to evaluate their impact on CV outcomes.

3.2. Other therapeutic options

SGLT-2 inhibitors (SGLT-2i) lower blood glucose (0.5–0.6% reduction in HbA1c) by inhibiting tubular glucose reabsorption [44,45] and provide additional clinical benefits, such as low risk of hypoglycemia, moderate weight loss and reduction in blood pressure consequent to a decrease in circulating volume induced by osmotic diuresis [46]. In addition, as demonstrated in several CV outcome trials, SGLT-2i reduce the risk of hospitalization due to heart failure, the incidence of major CV events and slow down the progression of renal disease [47]. To date, only one randomized clinical study has investigated the effect of SGLT-2i in patients with T2D relapse allocated to placebo or canaglifozin in a 1:2 ratio for 6 months [48]. Canagliflozin treatment was associated with a greater reduction in HbA1c, blood glucose, body weight, and uric acid compared with placebo. Moreover, the canagliflozin group showed an improvement in body composition, expressed through a reduction in android adiposity and truncal fat with preservation of lean mass. Unfortunately, the pharmacokinetics of canagliflozin was not specifically investigated. On the whole, these findings indicate some benefits of SGLT-2i in terms of weight loss and glucose outcomes although the small sample size and the preliminary nature of the data require further studies. Some safety concerns with the SGLT-2i use in MBS patients must be considered. First, some case reports have documented the occurrence of euglycemic ketoacidosis (eDKA) among T2D patients on SGLT2i undergoing BS [49–52]. However, these events occurred in patients who were in the perioperative phase, which is known to be characterized by metabolic instability due to surgical stress, calorie and carbohydrate restriction and reduced fluid intake. Reassuringly, no eDKA event was observed during a 6-month study by Kashyap et al. [48]. In order to prevent this potentially lethal side effect, SGLT-2i discontinuation is warranted well in advance (1 week) of surgical intervention, resuming them [53], if necessary, under conditions of metabolic stability and adequate carbohydrate intake. Another issue is about the increased risk of dehydration in MBS patients, as a consequence of their well-known difficulties in maintaining an adequate daily water intake [54]. Finally, SGLT-2i treatment has been associated with reduced 1,25-dihydroxyvitamin D3 levels [55], a finding that deserves a special remark in MBS patients who are at high risk of vitamin and micronutrient deficiency [56]. Two recent meta-analyses showed no increased risk of bone fractures or reduction in bone mineral density in T2D patients treated with SGLT-2i compared to placebo [57,58]; rather, they showed a beneficial effect against bone fractures with treatment length $\leq$52 weeks [57]. However, given the short duration of the studies examined and the low number of bone-fracture events, long-term RCTs are needed to confirm these findings.

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are able to prolong the half-life of circulating GLP-1 by blocking the enzyme responsible for its degradation, with consequent increase in the levels and activity of endogenous GLP-1 [59]. DPP-4i do not cause hypoglycemia and are characterized by an excellent tolerability and a neutral effect on body weight. Few studies have evaluated these drugs in the bariatric setting and no data is available on their pharmacokinetics. Svane et al. showed a modest reduction in glycemic peak without changes in glucose AUC and 120-min glucose levels in non-diabetic RYGB patients after premeal administration of 100 mg sitagliptin vs placebo [60]. Similarly, a 4-week randomized trial assessing the efficacy and safety of sitagliptin (100 mg daily) in 32 subjects with persistent/recurrent T2D after RYGB showed a small improvement in glucose and fructosamine concentrations not accompanied by improvement in β-cell function [60]. Overall, the data available indicate that, by virtue of an excellent safety profile and optimal tolerance, DPP-4i could be a useful option in patients with recurrent T2D after MBS; however, they are likely to be insufficient as monotherapy in case of moderate/severe hyperglycemia.

Metformin is a first-line agent for the treatment of T2D and is effective both as monotherapy and in combination with other glucose-lowering medications. Beside a mild weight loss effect, metformin improves insulin sensitivity and does not cause hypoglycemia as it does not stimulate insulin secretion [61]. Despite the widespread use of metformin, few clinical studies have assessed its use in patients with persistent/recurrent T2D after MBS. An unexpected 50% increase in the absorption and bioavailability of metformin has been demonstrated after RYGBP,

probably due to transporter upregulation and/or to adaptive villous hyperplasia [62]; therefore, a reduction in metformin dose should be considered especially in MBS patients with renal dysfunction. The gastrointestinal side effects of metformin (nausea, diarrhea, abdominal pain, bloating etc.) could be troublesome in bariatric patients, especially in those undergoing malabsorptive procedures; in this regard, the slow-release formulations of metformin, characterized by a lower rate of gastrointestinal side effects, should be preferred. Moreover, there is evidence that the long-term use of metformin is associated with low levels of vitamin B12 and, in some reports, of vitamin D and magnesium [63]. Considering that MBS patients are at high risk of micronutrients and vitamin deficiency [56], metformin-treated patients should undergo regular monitoring of vitamin status and, possibly, vitamin B12 replacement.

Sulfonylureas stimulate insulin secretion in a glucose-independent way by blocking potassium-ATP channels in the beta cells [64]; therefore, they increase the risk of hypoglycemia and do not preserve beta-cell function. Moreover, sulfonylureas are associated with weight gain thus hampering weight loss after MBS. Because of these effects, no study has been conducted on the use of sulfonylureas in bariatric patients.

Thiazolinideniones exert an effective insulin sensitizing action, along with beta-cell protection [65], However, their use is associated with weight gain, fluid retention and bone fractures – all features that make thiazolidinediones a poor therapeutic option in MBS patients.

Insulin represents a valid option in patients with recurrent T2D poorly respondent to other glucose-lowering agents, however, the increased risk of hypoglycemia and weight gain do not make insulin a first-line option in these patients. However, in case of failure of other glucose-lowering drugs more suitable for MBS subjects, different insulin regimens such as basal, basal-plus or basal-bolus can be implemented according to individual needs. Pre-meal insulin may be more difficult to adjust because of the accelerated gastric emptying.

4. Management of CVD risk factors in T2D patients undergoing MBS: is pharmacokinetics of oral drugs an additional challenge?

Although many T2D patients are able to discontinue pharmacologic treatment after MBS, some of them might need to resume anti-hypertensive and lipid lowering drugs to meet the therapeutic targets. However, the anatomical changes in the gastrointestinal tract consequent to MBS may profoundly impact the bioavailability of oral medications [66–68]. Here, we focus our attention on those medications frequently prescribed in T2D patients for the control of CV risk, including atorvastatin, fenofibrate, acetylsalicylic acid (ASA), anticoagulants, and beta blockers. The main findings are summarized in Table 2.

Limited data is available on the pharmacokinetics of statins after MBS and refers exclusively to atorvastatin. As known, atorvastatin is largely metabolized in the intestine and in the liver by the enzymes CYP3A4 and CYP3A5 and, therefore, has a low oral bioavailability [69]. Skottheim et al. found a high variability in atorvastatin pharmacokinetics in 12 obese subjects after RYGBP, with the area under the plasma atorvastatin concentration [AUC(0–8 h)] ranging from a threefold decrease to a twofold increase [70–72]. In a subsequent study [72], the Authors found an increased atorvastatin bioavailability (twofold higher AUC0-8 h) in 10 patients undergoing biliopancreatic diversion with duodenal switch (BPD-DS) at 4–8 weeks after surgery compared to pre-surgery, suggesting that the increased atorvastatin disposition after MBS is the result of two counteracting events, i.e. a reduced intestinal absorbing area and, in the meanwhile, a decreased activity of the metabolizing enzymes. Of interest is also the finding by Jakobsen et al. that plasma atorvastatin levels increased in most patients at 3–8 weeks after RYGBP and BPD-DS but decreased in the long-term (21–39 months), indicating that atorvastatin bioavailability might change over time probably due to intestinal adaptation with large inter- and intraindividual variations [71]. Summing up, the bioavailability of atorvastatin increases in the first weeks

Table 2 Summary of the available evidence on the pharmacokinetics of some oral drugs for the management of CV risk factors after MBS.

Oral drug	Evidence from available studies in patients following MBS	General suggestions for clinical management[a]	Strength of suggestions
Atorvastatin	Increased bioavailability in the first weeks after MBS; further possible changes in the long-term	Regular monitoring of lipid profile for dose adjustment	Weak
Fenofibrate	Unaltered disposition after RYGB	No dose adjustment for pharmacokinetic issues is required after RYGB	Weak
Acetylsalicylic acid	Increased absorption and disposition after RYGBP	No adjustment of the standard daily dose is required after RYGB	Weak
Anticoagulants	Modified pharmacokinetic of warfarin; pharmacokinetic of rivaroxaban and apixaban does not change	Dosage of warfarin should be decreased in the first weeks after MBS and increased afterward; no dose adjustment is required for rivaroxaban and apixaban	Weak
Beta blockers	Modified pharmacokinetic of propranolol; pharmacokinetic of atenolol does not change	Atenolol should be preferred	Weak

CV: cardiovascular; MBS: metabolic-bariatric surgery; RYGB: Roux-en-Y gastric bypass.
[a] Given the poor available evidence, each suggestion should be carefully weighted taking into account the individual characteristics.

after MBS; major uncertainties exist in the long-term, raising the need to regularly monitor lipid profile in operated patients for dose adjustment.

Being a lipophilic drug, the absorption of fenofibrate is highly *dependent on bile salts concentration* [73]; contrary to expectations, the disposition of fenofibrate was unaltered in patients undergoing RYGBP [74]. Since dyslipidemia improves considerably after weight loss, it is advisable to monitor lipid levels until weight loss stabilizes and to discontinue therapy if appropriate [75]. In patients at high CV risk or previous CVD events, the dose of the lipid-lowering drugs should be determined according to the therapeutic targets for each risk category and the potential side effects [75].

Acetylsalicylic acid (ASA) is a weak acid quickly absorbed in the stomach by passive diffusion. A significant increase in ASA absorption and exposure has been reported after RYGBP [76], suggesting that the absorption of ionized ASA can also take place in the jejunum because of an accelerated gastric emptying [76,77]. Despite the significant increase in ASA exposure after RYGBP, no change in the standard dose of 80 mg is advised after this specific intervention [76].

Concerning anticoagulant drugs, no change in the pharmacokinetics of rivaroxaban and apixaban after MBS has been demonstrated and, therefore, no dose adjustment is required [78]; in contrast, the dosage of warfarin should be decreased in the immediate post-operative period (3–4 weeks) and increased afterward [79]. No information is available on the bioavailability of other anticoagulant drugs, such as dabigatran and edoxaban after MBS.

Few studies have assessed the pharmacokinetics of antihypertensive drugs following MBS. Wójcicki et al. investigated the pharmacokinetics of propranolol (lipophilic compound) and atenolol (hydrophilic compound) after a single oral dose of 80 and 100 mg, respectively, in patients undergoing partial gastric resection [80]. While the pharmacokinetics of propranolol significantly differed from that of control subjects with lower propranolol plasma levels occurring in operated patients, the pharmacokinetics of atenolol did not reveal any significant difference compared to controls [80]. A possible explanation is that the partial gastric resection negatively influences pancreatic function, thus impairing lipid absorption. On this basis, the Authors conclude that if a beta blocker therapy is necessary after MBS, a hydrophilic compound like atenolol should be preferred.

To sum up, MBS influences the pharmacokinetics of some drugs commonly prescribed for the prevention and/or treatment of CV risk factors. Most studies have been performed in the immediate post-operative period leaving some uncertainty on drugs bioavailability in the long term. These considerations, together with large inter-individual variability, prompt for a close monitoring of CV risk factors and medication use to ensure the achievement of the therapeutic goals.

5. Conclusions

Long term studies demonstrate that 30–50% of patients who initially experience remission of T2D after MBS present re-emergence of the disease during 3–15 years of follow-up. The available literature supports the use of GLP-1a as the most suitable option to control hyperglycemia also in light of their beneficial effects on body weight, CV and renal outcomes. Of clinical relevance is also the observation that the safety and tolerability of GLP-1a in operated patients are similar to those of nonsurgical patients. In addition, the subcutaneous route of administration of GLP-1a circumvents the problem of the pharmacokinetic changes of orally administered medications. Since the bioavailability of oral medications can be altered, MBS patients should be regularly monitored to ensure that the desired therapeutic goals for all CV risk factors are achieved.

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