

Review of multimodal treatment for type 2 diabetes: combining metabolic surgery and pharmacotherapy

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Abstract: Treating type 2 diabetes mellitus (T2DM) in patients with obesity remains a challenge for physicians, endocrinologists and surgeons, a fact supported by uncontroverted evidence from studies looking at mortality and associated morbidity. Metabolic surgery remains the most effective treatment for obesity and T2DM with evidence demonstrating an improvement or resolution of symptoms of T2DM and a reduction in a mortality and rates of cardiovascular events compared with pharmacotherapy alone. While these results are promising, two important limitations must be recognized and addressed. With regards to long-term remission of T2DM, the metabolic benefits of bariatric surgery appear to fatigue with time and a proportion of patients will not maintain normoglycaemia without pharmacotherapy. Second, there has been noteworthy progress in the development of several classes of medications for the treatment of T2DM which were unavailable when the original studies comparing the effects of bariatric surgery with pharmacotherapy were conducted.

Recognizing the need for further treatment following metabolic surgery for long-term disease control in conjunction with the availability of newer medications offering more effective, nonsurgical treatment presents a critical turning point in treatment treating obesity. While the traditional approach would be to determine the superiority (or non-inferiority) of these agents compared with surgery, clinicians and surgeons must acknowledge the limitations of this attitude towards treatment given evidence from fields such as cancer, where a combinational approach is the gold standard. Recent advances in pharmacotherapy, present not only a novel approach to medical therapy but a renewed impetus to investigate what can be achieved through multimodal care.

Keywords: antiobesity drugs, bariatric surgery, obesity, type 2 diabetes, weight-loss drugs, weight regain

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Introduction

Metabolic surgery is safe and effective

There is an ever growing, worldwide epidemic of patients in both developed and developing countries suffering from type 2 diabetes (T2DM) and given its inextricable link with obesity, weight control or reduction remains central to both prevention and treatment as well as long-term modification of the underlying disease process. Patients

are being diagnosed with T2DM at an increasingly young age, the implications of which are being seen at enormous personal and societal cost and marks a looming future health crisis. Although there has been significant progress recently in the development of several novel classes of pharmacological agents aimed at glycaemic control, medical treatment of T2DM in patients suffering from obesity has been met with limited success. A number of trials involving pharmacotherapy with

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or without lifestyle modification aimed specifically at improving outcomes in patients with obesity and T2DM through weight reduction have demonstrated a clinically significant weight loss of >5% is achievable; however, no studies to date have demonstrated a reduction in mortality despite improvements in cardiovascular risk factors including glycated haemoglobin (HbA1c), lipids or hypertension (HTN).^{1,2} Metabolic surgery is a very effective treatment for obesity with evidence from a meta-analysis of 136 studies including all types of commonly performed surgical procedures resulting in a mean absolute weight loss of -39.71 kg and a mean decrease in body mass index (BMI) of -14.20 kg/m² with a concomitant reduction or even resolution of obesity-related complications, including T2DM.³ Crucially, long-term data from the prospective case-control series, the Swedish Obese Subjects study established there was a reduction in all-cause mortality and decreased rates of fatal and nonfatal cardiovascular events in patients undergoing metabolic surgery in comparison with patients with obesity receiving standard care.^{1,4,5} Although data from numerous studies would suggest the superiority of surgical intervention as compared with medical treatment alone, an essential common element amongst all these trials that must be recognized is that they have drawn comparisons with drugs that have, in many cases since, been replaced with more effective versions of those previously used or even superseded by entirely new classes of pharmacological agents. Longer-term studies comparing surgical outcomes with patients managed medically with these novel medications are needed and a number are in progress; however, the shift in mindset with regards to management of obesity would suggest that the new direction of research should be focused on investigating what can be achieved through a combinational approach rather than viewing medical and surgical treatment as being mutually exclusive. In parallel with the increasing acceptance of metabolic surgery as a treatment for patients who have obesity, comes the recognition of its efficacy in managing obesity-related comorbidity, namely T2DM. Although the exact mechanisms underlying the improved glucose metabolism observed following metabolic surgery have yet to be fully elucidated, several studies have demonstrated an early alteration in gut hormone signalling resulting in an improvement in glycaemic control independent of weight loss.⁶⁻⁸

Even in the small percentage of patients who have absolute weight-loss failure (defined as a <0% reduction of BMI 10 years after surgery) the rates of resolution of comorbidity have been observed as similar to those with successful weight loss following Roux-en-Y gastric bypass (RYGB).⁹ Furthermore, the safety of metabolic surgery is well established with 30-day mortality rates of 0.16% according to 2009–2016 figures from the National Bariatric Surgery Registry which covers all bariatric surgery procedures performed within England.¹⁰ These figures are in keeping with data from the American registry, the American Society for Metabolic and Bariatric Surgery which reported a 30-day mortality of 0.11%.¹¹ Data from a worldwide registry would also suggest that in part, owing to the fact that 97.8% of procedures are performed laparoscopically, metabolic surgery is associated with a relatively short hospital length of stay, with 75.4% of those undergoing RYGB discharged after 2 days and 86.8% of sleeve gastrectomy (SG) discharged after 3 days.¹²

Metabolic surgery is an effective option for type 2 diabetes

Irrespective of the specific procedure performed, metabolic surgery has been demonstrated in several randomized controlled trials (RCTs) with short-term follow up to be superior to medical therapy, with respect to remission of diabetes and achieving glycaemic control. A 2004 meta-analysis including all types of widely employed methods of metabolic surgery found the diabetes remission rate within the surgically treated group was 76.8% with an associated improvement in HTN and hyperlipidaemia; however, the length of follow up of included studies was variable.³ An RCT comparing two forms of metabolic surgery, biliopancreatic-diversion (BPD) and RYGB with standard medical therapy, with either oral hypoglycaemic agents or insulin titrated to a target HbA1c < 7% for treatment of T2DM found a difference in the average percent change in HbA1c from baseline when comparing patients treated surgically *versus* those receiving standard medical care. At 2 years, those treated surgically achieved a greater reduction in HbA1c with patients undergoing BPD reaching an HbA1c of $4.95 \pm 0.49\%$ and $6.35 \pm 1.42\%$ in the RYGB group as compared with $7.69 \pm 0.57\%$ in the medically treated patients.¹³ Similarly, a trial investigating intensive medical treatment alone [aggressive combination

pharmacotherapy targeting hyperglycaemia and weight loss, including biguanides, thiazolidinediones, sulfonylureas, insulin, pramlintide and glucagon-like peptide 1 (GLP-1) agonists targeting an HbA1c < 6%, plus treatment of lipids and HTN according to American Diabetes Association (ADA) guidance] *versus* medical therapy, in addition to metabolic surgery, RYGB or SG, found that 12% of patients in the medically treated group *versus* 37% in the SG plus medication and 42% in the RYGB plus medication group achieved an HbA1c < 6% at the 12-month follow up.¹⁴ This improvement in HbA1c in the surgery plus medication group was accompanied by a decrease in the use of antihyperglycaemic agents as well as lipid- and blood-pressure-lowering medications, whereas the number of medications increased in the medically treated group. Not only has metabolic surgery been shown a highly effective treatment for established T2DM but evidence from a prospective cohort study demonstrated it also reduces the risk of patients with obesity from subsequently developing the disease.¹⁵

In light of this data, guidelines produced by both the ADA and International Diabetes Federation (IDF) recommend metabolic surgery as a treatment modality for T2DM in patients with BMI > 35 who fail to achieve adequate control with 'reasonable nonsurgical methods' and furthermore, advise it is considered in those with a BMI of 30–35 kg/m² or >27.5 kg/m² in those from an Asian background, if the metabolic response to treatment has been poor. Clinicians are encouraged to include metabolic surgery as part of the standard treatment algorithm for patients with T2DM and emphasize that it should not be regarded as a last resort, given the very low likelihood the majority of patients with severe obesity will achieve a sustained weight loss and resultant improvement in glycaemic control.^{16,17} Treatment options and strategies for management of T2DM are continuously evolving with an ever-increasing number of medications available. Given the complexity of the disease process of T2DM, ADA recommends not only a patient-centred, flexible approach but one that may change over time to reflect the progressive nature of the disease. A combinational approach with regards to pharmacotherapy is employed in a significant proportion of patients when glycaemic control is not achievable with a single agent. The current perception of the availability of treatment options must

progress beyond the present view to include a combinational approach whereby surgery is considered, as well as medical therapy, rather than instead of medical therapy or vice versa.¹⁸

In spite of these recommendations, metabolic surgery remains an underutilized strategy in the management of patients with T2DM, as only 1% of patients meeting the treatment criteria actually undergo any form of surgery.

The effect of metabolic surgery is attenuated in the long term

Despite promising outcomes from studies with short-term follow up with regards to both weight loss and diabetes control following metabolic surgery, early enthusiasm has been somewhat tempered by follow-up data that have demonstrated a significant proportion of patients will not maintain sustained remission in the long term. In 2009, the ADA laid out clear guidance on the classification of remission of T2DM, stating that patients must have an HbA1c < 6% and fasting plasma glucose < 5.6 mmol/l at least 1 year after bariatric surgery without the need for any hypoglycaemic medication. The previous lack of consensus has made it difficult to compare outcomes between studies; however, application of these more stringent definitions in many studies leads to a sharp reduction in the number of patients who can be reported as achieving remission. Considering long-term remission, 5-year follow-up data from an RCT comparing medical treatment with two forms of bariatric surgery found that when the ADA criteria were applied, none of the medically treated patients could be considered to have been in remission at any point. Within the surgically treated groups, at 2 years, 75% undergoing RYGB and 95% undergoing BPD were considered to be in remission. Using the criteria for remission cited in the paper, which was an HbA1c < 6.5% off all medications, follow-up data at 5 years suggested 50% of the surgically treated patients and none of the medically treated patients were in remission; however, using the stricter ADA definition, in fact, none of the patients in either group met the criteria for remission.¹³ Similarly, data from the STAMPEDE trial comparing bariatric surgery with medical treatment found that at 5 years follow up, only 29% of those undergoing RYGB and 23% undergoing SG met the criteria for remission according to

ADA standards.¹⁴ In keeping with these findings, data from a study with 6-year follow up after RYGB or SG found that overall, approximately one in four patients will achieve remission and one in five will experience relapse after an initial period of remission.¹⁹

Furthermore, a number of studies with both short and long-term follow up have reported diabetes 'cure' or remission using varying definitions. This may have influenced reported outcomes. A single-centre retrospective review of 209 patients with T2DM undergoing metabolic surgery, SG, RYGB and adjustable gastric banding (AGB) found there was a significant difference in the reported rates of remission depending on the definition used, with 57.5% of those undergoing RYGB reported to have achieved remission with the previous definition *versus* 40.6% according to the ADA requirements.²⁰

The concept of multimodal treatment for type 2 diabetes

Taking into consideration data emerging from long-term follow-up studies demonstrating the significant proportion of patients who do not achieve sustained remission, the idea that surgery alone can effectively cure diabetes has been supplanted by the more realistic view of considering it as a method of achieving disease control. This is not to imply that the surgery itself is ineffective, rather, it reflects the inherent complexity of both diseases, obesity and T2DM. Patients undergoing metabolic surgery are significantly more likely to achieve glycaemic control; however, what is becoming increasingly evident is the need to shift the focus to a multimodal approach with regards to long-term management to maintain remission and normoglycemia following surgery.¹⁸

Adopting a multimodal approach to treatment

The concept of joint medical and surgical management of a number of complex diseases is hardly novel; however, it has yet to gain traction in management of obesity and related comorbidity despite mounting evidence of the limitations of either approach in isolation and the potential benefit of combinational therapy.^{21–23} It is not difficult to find examples in which this approach is the standard of care, such as the treatment of numerous forms of cancer or cardiovascular disease where a multimodal management is the gold

standard, with surgery often being used as the initial form of treatment to establish disease control and ongoing medical therapy/chemotherapy to achieve long-term maintenance. The reluctance to adopt this model of care is reflected in the relative paucity of research examining the potential of such an approach, with very few studies investigating the effects of pharmacotherapy in conjunction with bariatric surgery. Data from the STAMPEDE trial, in which patients undergoing metabolic surgery in addition to intensive medical therapy (aggressive combination pharmacotherapy targeting hyperglycaemia and weight loss, including biguanides, thiazolidinediones, sulfonylureas, insulin, pramlintide and GLP-1 agonists targeting an HbA1c < 6% plus treatment of lipids and HTN according to ADA guidance) were compared with those on intensive medical therapy alone, supports the potential benefit of a combinational approach, with 5-year follow-up data demonstrating 38% RYGB and 24% SG *versus* 5% in the medication group alone achieving sustained remission.¹⁴ It is worth noting that although the HbA1c of the SG and RYGB groups were similar at 5 years, the percentage of patients not taking any glucose-lowering medications was significantly higher in the RYGB group. This is an even more striking finding when considering patients in the RYGB group were also taking a higher average number of diabetes medications than the SG group at baseline. The improved glycaemic control associated with RYGB was also illustrated in a study comparing its effects on HbA1c and fasting glucose *versus* AGB. At 3 years, the nonrandomized study of 34 patients found that although the two groups had a similar improvement in HbA1c, only 17% of those undergoing AGB *versus* 72% following RYGB maintained a fasting glucose < 7 mmol/l without the need for any hypoglycaemic medications.⁶ Further studies comparing the effects of metabolic surgery alone *versus* surgery and intensive medical therapy are required to further investigate the efficacy of this combinational approach.

Central to the success of adopting a joint approach to management of patients with T2DM who have obesity are clearly defined therapeutic targets and endpoints. Evidence from the UK Prospective Diabetes Study (UKPDS) has established that even a period of normoglycaemia can improve long-term mortality and a reduction in diabetes-related endpoints and cardiovascular events.²⁴ The lasting benefits of a period of glycaemic

control on overall mortality are supported by evidence from the SOS study which demonstrated that despite a 10-year remission rate of only 36%, the long-term benefits in terms of reduced risk of cardiovascular events persisted in the group undergoing metabolic surgery.¹

Adjuvant pharmacotherapy

In spite of recommendations from the IDF recommending that metabolic surgery should be seen as complementary to medical therapy for the reduction of microvascular and cardiovascular risk, the use of adjuvant pharmacotherapy is rarely implemented. Studies looking specifically at the use of medications in conjunction with metabolic surgery are limited; however, there are good data supporting the use of pharmacotherapy as monotherapy with several trials demonstrating improvements in glycaemic control and cardiovascular risk factors. With respect to novel approaches to the management of patients with T2DM undergoing metabolic surgery, in terms of adjuvant pharmacotherapy, therapeutic options can be broadly divided into two categories: antiobesity medications (AOMs) and antidiabetic medications.

Antiobesity medications

AOMs have long been available; however, their use has been limited by the widely held perception that they are unsafe and ineffective. Given the withdrawal of previously approved medications including sibutramine and fenfluramine and the limited efficacy of drugs such as orlistat, this view is understandable, although not informed by the evidence currently available in support for newly available medications. In recent years, there has been significant progress with the development of several new classes of medications that have been shown as safe, with good tolerability, and effective in not only reducing weight but improving glycaemic control and cardiovascular risk factors in patients with T2DM. The identification of lower percentage excess weight loss or weight regain as risk factors for long-term diabetes recurrence presents clinicians with an additional treatment target, and recent advances in weight-loss pharmacotherapy have vastly improved therapeutic options.

There have been a number of smaller trials investigating the use of several weight-loss agents in the context of poor weight loss or weight regain

following bariatric surgery which have demonstrated not only tolerability but efficacy in producing further reductions in weight. Although most have not specifically focused on diabetic endpoints, unsurprisingly, given the population being studied, many included patients with T2DM and have demonstrated significant weight loss which has potential implications for disease control.

The majority of studies investigating the use of adjunctive weight-loss medications have for the most part been retrospective or very small prospective studies involving a variety of agents. The largest study to date was a retrospective, multi-centre analysis of 317 patients using 15 different agents following SG or RYGB, where they found that 50% of patients were able to lose >5% of total weight; however, topiramate was the only medication shown to produce a statistically significant weight loss with patients twice as likely to lose >10%.²⁵ Another retrospective study using four different agents (phentermine, phentermine/topiramate, lorcaserin and naltrexone/bupropion) in 209 patients found 37% of patients were able to lose >5% of their total weight after 1 year of treatment.²⁶

A recent prospective study investigating the use of 3 mg liraglutide in 2092 patients with obesity, of whom 188 had already undergone bariatric surgery, found that in those completing >16 weeks of treatment, 23% lost >10% of their weight from baseline and there was no observed difference between the groups who were postmetabolic surgery and those managed with medications alone.²⁷

The availability of prospective trials investigating the use of rescue pharmacotherapy following bariatric surgery is limited, with only five published to date, most involving small numbers of patients.^{28–32} The agents used in the studies were varied and one included fenfluramine which has since been withdrawn. It is difficult to draw conclusions from these studies due to their significant limitations. The larger retrospective studies, while unable to explain the indication for prescribing AOMs in the postoperative period, necessarily, would suggest that these medications are well tolerated, with only mild–moderate gastrointestinal (GI) side effects, and produce clinically meaningful weight loss, warranting the need to develop larger RCTs to investigate their potential for use in the wider population.^{33–40}

Lorcaserin

The BLOOM-DM study was a randomized, placebo-controlled trial of 604 patients with T2DM comparing the use of 10 mg once daily or 10 mg twice daily lorcaserin *versus* placebo.⁴¹ At the trial conclusion at 1 year, 44.7%, 37.5% and 16.1% of patients lost >5% baseline body weight, respectively. A similar reduction in HbA1c was observed with 52.2%, 50.4% and 26.3% achieving a level of <7% at 52 weeks, respectively. Although not limited to patients with T2DM, the CAMELLIA-TIMI 61 study followed up 12,000 patients suffering from overweight or obesity with established cardiovascular disease or multiple cardiovascular risk factors over a period of 3.3 years and found no statistically significant difference in the rate of cardiovascular events.⁴² This finding is noteworthy from a safety perspective as there had been a number of concerns regarding cardiovascular safety, as lorcaserin is a member of the same drug class as the weight-loss medication, fenfluramine, which was withdrawn due to its link to development of valvular defects. There was a statistically significant reduction in weight with 38.7% of those taking lorcaserin achieving a weight loss of >5% as compared with 14.6% in the placebo arm. With regards to diabetes specifically, the use of lorcaserin was associated with a 19% reduction in the risk of incident diabetes in the prediabetic population and by 23% in those who did not have diabetes. There was also a statistically significant improvement in HbA1c in patients with diabetes, with a decrease of 0.33% from baseline at 1 year.

Naltrexone/bupropion

The 2013 COR-Diabetes trial was a double-blind, placebo-controlled study investigating the use of naltrexone 32 mg/bupropion 360 mg slow release in 505 patients with T2DM which found a statistically significant reduction in both baseline HbA1c and body weight over a 56-week follow-up period.⁴³ Within the treatment group, 20.7% reached an HbA1c < 6.5% *versus* 10.2% in the placebo arm and 44.5% achieved a clinically significant weight loss of >5% *versus* 18.9% in the placebo arm. At present, there are no published data on the cardiovascular outcomes of naltrexone/bupropion; however, a 2016 trial of 9000 patients investigating the cardiovascular safety of naltrexone/bupropion was terminated when interim results were made public in a patent filing made by the drug company sponsoring the trial.

Phentermine/topiramate

A 56-week phase II trial of 130 patients with T2DM and compared the use of once-daily phentermine/topiramate (15 mg/92 mg) plus lifestyle modification *versus* placebo plus lifestyle modification and found a reduction in HbA1c of -1.6% from baseline in the treatment arm *versus* -1.2% in the placebo group.⁴⁴ The phentermine/topiramate group was also found to have a -9.4% weight loss from baseline as compared with -2.7% in the placebo group. The study authors undertook a *post hoc* subgroup analysis of patients from the similar CONQUER study which was a 56-week double-blind, placebo-controlled study of patients with BMI 27–45 kg/m² taking phentermine/topiramate (7.5 mg/46 mg or 15 mg/92 mg) as compared with placebo. A subset of 388 patients were identified as having T2DM at baseline and were included in the analysis.⁴⁵ At 56 weeks, 21% of the patients in the lower-dose phentermine/topiramate group achieved an HbA1c < 6.5% and 37% in the high-dose group, compared with 17% of those given placebo.

Antidiabetic medications

GLP-1 analogues

There have been a number of GLP-1 analogues that have received approval for use in the management of T2DM, acting as glucose-lowering agents, but studies have also demonstrated patients receiving these medications achieve reductions in body weight, as well as an improvement in cardiovascular risk factors such as blood pressure and lipids. The primary action by which these medications mediate effect with regards to glucose homeostasis is by stimulating insulin secretion, which occurs in a glucose-dependent manner, reducing the risk of hypoglycaemia with a concomitant inhibition of glucagon secretion. Of these agents, three currently available have been shown to produce a significant reduction in the overall risk or major cardiovascular events in studies with medium-term follow up. Data from the STAMPEDE trial suggest that in comparison with intensive medical treatment alone, including GLP-1 agonists, these medications, as part of a medical treatment plan, in conjunction with bariatric surgery, are more effective for glycaemic control.¹⁴ Given the tendency in bariatric surgery to compare medication alone *versus* surgery, what is not known is whether GLP-1 agonists plus surgery would still be beneficial *versus* surgery alone.

Liraglutide

The SCALE Diabetes trial was a multicentre randomized, placebo-controlled, parallel-group trial over 56 weeks including 846 patients that demonstrated a significant reduction in weight in patients receiving 3.0 or 1.8 mg liraglutide *versus* placebo, with all groups receiving dietary and lifestyle interventions.⁴⁶ A clinically significant reduction in weight of >5% was seen in 54.3% in the 3 mg liraglutide group, 40.4% in the 1.8 mg liraglutide group and 21.4% in the placebo group. There was also a significant reduction in HbA1c of -1.3% in the 3.0 mg treatment group and -1.1% in the 1.8 mg group *versus* -0.3% in the placebo group. Furthermore, this improved glycaemic control with high-dose liraglutide given at 1.8 mg daily was shown in the LEADER trial, an RCT of nearly 10,000 patients to result in a significant reduction in the risk of death from cardiovascular causes as well as a reduction in the risk of nonfatal cardiovascular events as compared with placebo. Over a follow-up period of 3.8 years, fewer patients in the liraglutide group reached the primary endpoint of death from cardiovascular causes with a hazard ratio (HR) of 0.87.⁴⁷ Results from two studies looking specifically at the use of liraglutide in patients following bariatric surgery with persistent T2DM are promising. A 2016 retrospective cohort study of 164 patients, 15 who had previously undergone bariatric surgery demonstrated both groups achieved a statistically significant weight loss and decrease in HbA1c after 2 years of treatment, with no difference between the groups.³³ The GRAVITAS trial, a randomized, double-blind, placebo-controlled trial investigated the use of 1.8 mg liraglutide in patients following either RYGB or SG found a -1.3% decrease in HbA1c compared with placebo after 26 weeks of treatment, with no differences in outcomes depending on the type of surgery.²⁸

Semaglutide

SUSTAIN is an ongoing series of phase III trials looking at the use of semaglutide in patients with T2DM. The trials consistently demonstrated a significant reduction in body weight and HbA1c when compared with placebo or other agents, including insulin, gliptins, GLP-1 agonists (exenatide, dulaglutide). The SUSTAIN-6 trial included 3297 patients with T2DM with cardiovascular risk factors over a 2.1-year follow-up period.⁴⁸ In comparison with placebo, the authors found that 6.6% of patients taking semaglutide

(0.5 or 1 mg weekly) suffered cardiovascular death, nonfatal myocardial infarction (MI) or nonfatal stroke as compared with 8.9% in the placebo group. Further trials comparing semaglutide with canagliflozin and liraglutide have completed recruitment and results are awaited.

Dulaglutide

Comparison between dulaglutide and semaglutide in the SUSTAIN-7 trial demonstrated that patients taking semaglutide had a greater reduction in HbA1c, as well as more achieving >5% weight loss.⁴⁹ In trials comparing dulaglutide with glargine, metformin and sitagliptin, it produced a greater reduction in HbA1c, and results from the REWIND study looking at cardiovascular outcomes has demonstrated a reduction in the risk reaching the composite primary endpoint of nonfatal MI, nonfatal stroke or death from cardiovascular causes [HR 0.88; 95% confidence interval (CI) 0.79–0.99; $p=0.026$], although not in all-cause mortality.⁵⁰

SGLT-2 inhibitors

Sodium–glucose transporter 2 (SGLT-2) inhibitors act by a mechanism distinct from that of metabolic surgery. Two agents have been demonstrated to not only achieve the primary goal of improving glycaemic control but have also shown to result in a reduction in weight and cardiovascular risk. A recent randomized controlled trial investigating the effect of a third commonly used agent, dapagliflozin, on cardiovascular endpoints demonstrated no significant effect on major adverse cardiovascular events as compared with placebo but a reduced rate of cardiovascular death or hospitalization for heart failure (4.9% *versus* 5.8%; HR 0.83; 95% CI 0.73–0.95; $p=0.005$).⁵¹

There have been reports of patients taking SGLT-2 inhibitors suffering diabetic ketoacidosis in the early postoperative period; however, this is limited to a number of case reports.⁵²

Canagliflozin

Canagliflozin produces clinically significant weight loss in patients with T2DM. A pooled analysis of data from four placebo-controlled phase III trials including more than 2000 patients with T2DM found that 33% of patients on

300 mg and 25% on 100 mg canagliflozin daily experienced a clinically significant weight loss of >5% as compared with 6% in the placebo group.⁵³ Moreover, the CANVAS trial including nearly 10,000 patients with T2DM at high risk for cardiovascular disease demonstrated a statistically significant reduction in the risk of reaching the primary outcome which was a composite of death from cardiovascular causes, nonfatal MI and nonfatal stroke.⁵⁴ Over a mean follow-up period of 188.2 weeks, the rate of the primary outcome occurring in the canagliflozin group was lower than with placebo, occurring in 26.9 versus 31.5 patients per 1000 patient-years. In spite of the apparent promising cardioprotective effects of canagliflozin, the authors also noted those in the treatment arm were at a greater risk of requiring an amputation, most likely at the level of a toe or metatarsal. The recent CREDENCE study investigating the use of canagliflozin on renal outcomes in 4401 patients with T2DM and nephropathy found that in comparison with placebo, the relative risk of the primary endpoint, which was a composite measure of end-stage kidney disease occurring, was 30% lower as compared with placebo.⁵⁵ In contrast to the earlier CANVAS trial, they found no difference in the rates of amputations.

Empagliflozin

The 2015 EMPA-REG OUTCOME trial of 7020 patients with T2DM classified as being at high risk for cardiovascular events compared patients receiving 10 or 25 mg empagliflozin with placebo over a median follow-up period of 3.1 years.⁵⁶ The investigators found the primary outcome, which was a composite endpoint of death from cardiovascular causes, nonfatal MI or nonfatal stroke, occurred in 10.5% of the pooled empagliflozin group as compared with 12.1% of those receiving placebo. Within the empagliflozin group, the rate of death from cardiovascular causes was 3.7% compared with 5.7% in the placebo group, equating to a relative risk reduction of 38%. A *post hoc* analysis from the same study looking specifically at the potential renal protective effects of empagliflozin included patients with established kidney disease (estimated glomerular filtration rate <59 ml/min per 1.73 m²) and found incidents or worsening of nephropathy in 12.7% of the empagliflozin group compared with 18.8% in the placebo group.⁵⁷

Discussion

Timing and indications for treatment

There is a growing perception that metabolic surgery shares several similarities to operations for benign disease. Initially, surgery may be very successful in inducing disease remission but the durability of the changes it effects may fatigue with time. In the context of metabolic surgery, this is evidenced by studies examining long-term rates of T2DM remission that have widely shown a significant rate of relapse, often after two or more years, despite an initial period of good glycaemic control.¹³ The physiological changes underlying both the improvement in glycaemic control in the postoperative period, as well as those involved in subsequent disease relapse, are incompletely understood, reflecting the fact that they are likely the result of several mechanisms and physiological pathways. Although weight-related parameters such as lower percentage of total excess weight loss and weight regain have been identified as predictors of diabetes relapse, weight-independent factors also appear to play a significant role. Longer duration of diabetes has been demonstrated not only to be a predictor of which patients will experience initial remission but also, those most likely to relapse. In patients with a duration of diabetes less than 5 years, 76% maintained partial or complete disease control 5 years postoperatively compared with 21% with a duration of diabetes over 5 years.¹⁹ This finding likely reflects how underlying residual β -cell function is a critical factor that should be considered when discussing the timing of treatment, as early intervention is more likely to result in better long-term disease control. Although patients with a longer duration of disease are less likely to maintain long-term remission, glycaemic control is overall improved. Despite the well-recognized legacy benefit of a period of good glycaemic control as demonstrated by the UKPDS trial, what remains to be seen is whether the employment of additional therapeutic options in the form of medical management is required to maintain disease control and ultimately improve long-term outcomes. Moreover, it is perhaps in these patients who may benefit most from the addition of pharmacotherapy to maintain disease control and remission; however, RCTs investigating this approach are lacking.

In developing the concept of adopting a multimodal treatment approach to patients suffering

from T2DM and obesity comes a number of practical questions regarding its implementation beyond the choice of pharmacological therapies alone. One of the most important considerations in any treatment algorithm comes the indication for initiation of treatment as well as where intervention should occur within the timeline of an evolving disease process. As evidenced by the ADA guidelines on pharmacological treatment for T2DM, while they make broad recommendations, there are no clear-cut answers as to how patients should be treated; rather, general principles that should be applied. As there are few studies at present investigating the application of a multimodal approach, the same pragmatic view of patient-led or -centred care must be employed. Irrespective of the timing of joint intervention initiation, developing a multidisciplinary overview of both surgical and medical treatment options individualized to the patient from the earliest point possible should be a key aspect of care. As seen with any other chronic relapsing or remitting disease, treatment options must be revisited and reconsidered throughout the evolution of disease process.^{21–23} The question of timing with regards to initiation of treatment in any multimodal treatment approach is critical. Given the long-term data illustrating the high rate of relapse of disease following bariatric surgery, the question remains whether clinicians should routinely continue medications in the postoperative period or wait for the reappearance of markers of disease and utilize medication as rescue therapy. Drawing parallels with the treatment of other diseases such as cancer in which multimodal therapy is routinely employed, the use of medical therapy is most often used in conjunction with surgery, planned from the outset with a multidisciplinary approach in which second-line medical treatment is employed in patients not responding to initial treatment or becoming refractory to first-line therapies, rather than waiting for disease recurrence when there is a well-recognized rate of relapse.²²

The aim of metabolic surgery in patients with T2DM has long been focused on establishing normoglycemia without the use of any additional medications and indeed, as previously discussed, the vast majority of studies show this is achievable in the short term. Given this data, the use of adjunctive pharmacotherapy in postoperative patients is not without its challenges if the aim is achieving tight glycaemic control, given the

clearly demonstrated increased mortality risk as demonstrated by the ACCORD study.⁵⁸ These reasonable concerns have to be counterbalanced by consideration of the potential benefit legacy effect of a period of normoglycaemia, even if not sustained long term, as evidenced in the UKPDS trial.²⁴ As much as the concept of having a single agent that suits all patients suffering from T2DM is rarely applicable, the same applies to the pharmacological treatment of patients with obesity and T2DM; however, given the number of different classes and subgroups of medications available, this presents the opportunity to provide an individualized approach to treatment. Considering the broad categorization of pharmacotherapy as AOMs or antidiabetic medications offers an initial starting point with the identification of patients with either suboptimal weight loss/regain or weight loss as expected and residual diabetic symptoms. Adopting such an approach with either weight loss or glycaemic-control targets could potentially allow for the initiation of adjunctive therapy while decreasing the potential risk of hypoglycaemia.

Although metabolic surgery has proven a highly effective treatment for obesity and obesity-related comorbidity, including T2DM, data emerging from long-term studies have demonstrated that the duration of the improvement in glycaemic control may be limited. The significant proportion of patients who experience a relapse of T2DM is not suggestive of treatment failure; rather, it reflects that metabolic surgery is a form of functional benign surgery. Treatment is aimed at the management of a chronic and often progressive disease and the metabolic benefits of surgery may become attenuated with time, requiring further intervention in order to maintain disease control. Recognizing the chronic nature of both diseases involved requires the adoption of a life-long management strategy and accepting that some treatments, including surgery may have a limited duration of being highly efficacious but the benefits conferred by consistent glycaemic control may be prolonged or sustained with the addition of adjunctive therapies.

Given the significant recent advances in the development of several novel classes of powerful antidiabetic medications which also have implications for weight loss, there is a need to ensure that there are RCTs to determine the benefit of these medications, in addition to bariatric

surgery as compared with surgery alone. For many of these medications, we have evidence demonstrating improved glycaemic control when combined with bariatric surgery compared with medication alone but what remains to be seen is whether they provide benefit beyond surgery alone. Long-term studies are also needed to determine their effect on cardiovascular and mortality-related endpoints and whether the addition of antidiabetic or weight-loss pharmacotherapy can improve long-term diabetes control and remission. With the agents currently available and the latest evidence for their use, medication alone in comparison with bariatric surgery will likely be insufficient to produce long-term weight loss and diabetes control. Focus of research should be directed towards investigating what can be achieved through a combinational approach to treatment, moving away from direct comparisons with medication *versus* surgery. Improving outcomes with pharmacotherapy may actually lead to more metabolic surgery as better outcomes become a realistic target in the same way improved chemotherapy has allowed more patients to be considered for surgery with certain types of cancer. Given the rapid and significant advances in pharmacotherapy with the development of entirely novel classes of drugs in recent years, medication may prove to be as effective, or more so, than bariatric surgery in the future. If this were to occur, we may need to consider returning to trials comparing pharmacotherapy *versus* surgery to determine their superiority for weight loss and diabetes control in certain patients.

This challenges the current view on surgery and its role in the treatment of T2DM and should prompt clinicians to reconsider the aims of treatment. The goal of metabolic surgery in the context of treating T2DM needs to be reframed, moving away from the idea of cure to a more realistic view of inducing remission with surgery and longer-term maintenance with medical management. Given the improvements in morbidity and mortality conferred by a period of sustained normoglycemia, metabolic surgery should be seen as one aspect of a multimodal approach in which adjunctive pharmacotherapy can be used to optimize long-term effects. Surgery is by far the most effective method at present to achieve remission of T2DM, but the effects may be enhanced by using medication to maintain remission.

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DJP and CWIR were responsible for critical revision.

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