

Association between preoperative glucose-lowering medication agents and the status of type 2 diabetes mellitus after bariatric surgery

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Abstract

Introduction: Bariatric surgery is an effective treatment for type 2 diabetes mellitus (T2DM) in patients with morbid obesity. This study investigates whether duration of diabetes and anti-diabetes therapy are associated with glycaemic control after surgery in a routine clinical setting.

Method: A cohort analysis of a prospectively maintained database was carried out for consecutive bariatric operations performed between April 2017 and March 2018 for patients with T2DM.

Results: A total 105 patients with T2DM underwent bariatric surgery (89 Roux-en-Y gastric bypass and 16 sleeve gastrectomy). Median follow-up was 19 months ([interquartile range] IQR 13-24 months). Median weight and body mass index (BMI) on the day of surgery were 125 kg (IQR 103.9-138.7) and 42.4 kg/m² (IQR 39-46.8), respectively. At follow-up, 68 patients (64.8%) had achieved remission of diabetes. Patients who were pre-operatively on more than one glucose-lowering medication were less likely to go into remission (odds ratio [OR] 0.13, 95% CI 0.04-0.44, $p=0.001$) compared to those that were on a single glucose-lowering medication agent. Pre-operative use of insulin therapy (OR 0.09, 95% CI 0.03-0.31, $p<0.001$) and SGLT2 inhibitors (OR 0.23, 95% CI 0.05-0.92, $p=0.038$) were significant negative predictors of remission. Type of operation ($p=0.34$), pre-operative BMI ($p=0.99$), and % total weight loss (TWL) ($p=0.83$) did not predict remission from T2DM after surgery.

Conclusions: Most patients who are medicated for T2DM can stop their glucose-lowering medication after bariatric surgery. Patients who are on multiple glucose-lowering medication agents or those dependent on insulin or SGLT2

inhibitors before bariatric surgery are less likely to undergo complete remission >12 months after bariatric surgery.

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Key words: diabetes mellitus, obesity, bariatric surgery

Introduction

Obesity rates are continuing to rise in both the developing and developed world.¹ This is driving a parallel pandemic of type 2 diabetes mellitus (T2DM), for which the therapeutic cornerstones are lifestyle modifications, such as diet and physical exercise, and glucose-lowering medications. Benefit from these conservative approaches is often modest, with clinically significant weight loss and its associated metabolic improvement being achieved only rarely in the long term.²

In recent decades, increasing attention has been paid to the role of bariatric surgery in the management of patients with T2DM. Through addressing various complementary pathogenetic mechanisms, bariatric surgery is now recommended as the most effective treatment for T2DM when other appropriate interventions have failed.³ Foremost of these effects are those on multi-organ insulin sensitivity, β -cell function, incretin response, and intestinal glucose metabolism.³ In addition, improvement in T2DM following surgery has been noted even before significant weight loss is achieved, signifying that glycaemic control is partially mediated by weight-independent factors.⁴

The aim of this study was to investigate the changes in glycaemic control after bariatric surgery for consecutive patients with diabetes who underwent surgery in our unit. Specifically, we explored the improvement in diabetes control according to two clinically relevant outcomes that are used in both primary and secondary care, namely improvement of glycated haemoglobin (HbA_{1c}) level and cessation of diabetic medication. In addition, the impact of glucose-lowering medication polytherapy was analysed, while considering important confounders such as duration of T2DM, body mass index (BMI) and weight loss.

Methods

Patients

An analysis was carried out of consecutive prospectively recorded

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laparoscopic sleeve gastrectomies (LSG) and laparoscopic Roux-en-Y gastric bypasses (LRYGB) performed between April 2017 and March 2018 at our institution for T2DM patients requiring oral and injectable anti-hyperglycaemic drugs, insulin or both. The last recorded pre-operative HbA_{1c} was compared to HbA_{1c} measured at 12 months after bariatric surgery. The end point was remission of T2DM defined in two ways: an HbA_{1c} <48 mmol/mol or patients not needing to take anti-diabetic medications more than 12 months after surgery.⁵

Number and type of pre-operative medications, type of procedure, pre-operative BMI, %Total Weight Loss (TWL) and patient demographics were compared between those who achieved the outcome and those who did not. Patients who were taking more than one drug were labelled as being on 'polytherapy'. We examined the post-operative T2DM status for those on insulin, metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RA), sodium-glucose co-transporter 2 inhibitors (SGLT2i), or a combination of these.

Statistical analyses

All statistical analyses were undertaken using the Statistical Package for the Social Sciences (SPSS Mac OS version 25, Chicago, IL, USA). Chi-squared tests and Wilcoxon signed rank tests were used for categorical and continuous variables, respectively. The effect of the above-mentioned factors on remission of T2DM was calculated using a univariable binary logistic regression model, with statistical significance set at $p < 0.05$.

Results

A total of 105 patients were included with a pre-operative diagnosis of T2DM; 32 (30.5%) were males and 73 (69.5%) were females. The median age was 53 years (IQR 57-59) and the median duration of T2DM was six years (IQR 3-14) prior to surgery. The median pre-operative weight, BMI and HbA_{1c} levels were 119.9 kg (103.9–138.7), 42.4 kg/m² (39.0–46.8), and 51 mmol/mol (43–63), respectively. Forty-nine patients (46.7%) were on polytherapy (Table 1).

LRYGB was the most frequently performed procedure (89/105, 84.8%), while 16 patients underwent LSG (15.2%). Median follow-up was 19 months (IQR 13-24 months). Median percentage of TWL was 10.9% (IQR 8.2-12.7%). At follow-up, 68 (64.8%) patients were not on any medication for T2DM. Ninety patients (85.7%) had a post-operative HbA_{1c} of less than 48 mmol/mol. A significant improvement in HbA_{1c} levels after bariatric surgery was noted, with a fall from a median of 51.0 mmol/mol (IQR 43.0-63.0) to 40.0 mmol/mol (IQR 36.0-44.5) ($p < 0.001$). A subset analysis of 24 patients who were on insulin (with or without other anti-diabetic agents) demonstrated a fall in median HbA_{1c} levels from 61.5 mmol/mol (IQR 55.8-66.5) to 48.0 mmol/mol (IQR 43-60.0) ($p = 0.017$).

Patients who were on polytherapy prior to surgery were less likely to achieve the endpoints of HbA_{1c} <48 mmol/mol (OR 0.13, 95% CI 0.04-0.44, $p = 0.001$) or to be able to stop their medications more than 12 months after bariatric surgery (OR 0.22, 95% CI 0.09-0.54, $p = 0.01$) (Tables 2 and 3). Insulin (OR 0.09, 95% CI 0.03–0.31, $p < 0.001$) and SGLT2 inhibitors (OR 0.23, 95% CI 0.06-0.92, $p = 0.04$) were significant negative predictors of an HbA_{1c} <48

Table 1 Patient demographics and pre-operative diabetic medications

| n=105 | | N | % |
|-----------------------------------|--------|----|-------|
| Gender | Female | 73 | 69.5% |
| | Male | 32 | 30.5% |
| Age at surgery (years) | <50 | 35 | 33.3% |
| | 50-59 | 48 | 45.7% |
| | >60 | 22 | 21.0% |
| Metformin | No | 18 | 17.1% |
| | Yes | 87 | 82.9% |
| GLP-1 RA | No | 94 | 89.5% |
| | Yes | 11 | 10.5% |
| SGLT2i | No | 94 | 89.5% |
| | Yes | 11 | 10.5% |
| Insulin | No | 81 | 77.1% |
| | Yes | 24 | 22.9% |
| Other | No | 78 | 74.3% |
| | Yes | 27 | 25.7% |
| More than one diabetic medication | No | 56 | 53.3% |
| | Yes | 49 | 46.7% |

GLP-1 RA=glucagon-like peptide-1 receptor agonist; SGLT2i=sodium glucose co-transporter-2 inhibitor

Table 2 Univariate analyses for prediction of HbA_{1c} <48mmol/mol

| | Odds ratio | 95% CI | | p-value |
|-----------------------|------------|--------|-------|---------|
| Polytherapy | 0.13 | 0.04 | 0.44 | 0.001 |
| Insulin | 0.09 | 0.03 | 0.31 | <0.001 |
| SGLT2i | 0.23 | 0.06 | 0.92 | 0.04 |
| Metformin | 0.51 | 0.14 | 1.82 | 0.30 |
| GLP-1 RA | 0.57 | 0.07 | 4.82 | 0.61 |
| Type of operation | 2.81 | 0.34 | 22.94 | 0.34 |
| BMI | 1.00 | 0.42 | 2.36 | 0.99 |
| Total Weight Loss (%) | 1.09 | 0.51 | 2.34 | 0.83 |

HbA_{1c}=glycated haemoglobin; SGLT2i=sodium glucose co-transporter-2 inhibitor; GLP-1 RA=glucagon-like peptide-1 receptor agonist; BMI=body mass index

Table 3 Univariate analyses for prediction of not requiring medical therapy postoperatively

| | Odds ratio | 95% CI | | p-value |
|-----------------------|------------|--------|------|---------|
| Polytherapy | 0.22 | 0.09 | 0.54 | 0.01 |
| Insulin | 0.14 | 0.05 | 0.37 | <0.001 |
| SGLT2i | 0.27 | 0.07 | 0.99 | <0.05 |
| Metformin | 0.90 | 0.31 | 2.64 | 0.85 |
| GLP-1 RA | 0.62 | 0.18 | 2.19 | 0.46 |
| Type of operation | 1.53 | 0.52 | 4.51 | 0.45 |
| BMI | 1.09 | 0.27 | 4.38 | 0.85 |
| Total Weight Loss (%) | 2.36 | 0.77 | 2.28 | 0.30 |

SGLT2i=sodium glucose co-transporter-2 inhibitor; GLP-1 RA=glucagon-like peptide-1 receptor agonist

mmol/mol or of not requiring medical therapy after one year (OR 0.14, 95% CI 0.05 – 0.37, $p < 0.001$ and OR 0.27, 95% CI 0.07 – 0.99, $p < 0.05$, respectively). LRYGB (as compared to LSG), higher pre-operative BMI and higher %TWL were found to have a positive trend toward T2DM remission rates after surgery, but these results were statistically not significant. Patients with longer duration of

T2DM pre-operatively were less likely to achieve remission after surgery (OR 11.20, 95% CI 1.41–88.84, $p=0.02$) as measured by an $HbA_{1c} >48\text{mmol/mol}$.

Discussion

Achieving remission from T2DM after primary bariatric surgery is multifactorial. This study aimed to assess the effect of pre-operative glucose-lowering medications on status of T2DM after surgery. The results of this study showed that patients with T2DM who are offered bariatric surgery are less likely to go into remission or to be able to stop their medications if they are taking more than one glucose-lowering medication. This may be reflective of the severity of T2DM in this group of patients, with increasing number of glucose-lowering medications required to overcome poor glycaemic control. One possible mechanism for this poor control could be higher levels of beta cell dysfunction, which remains beyond the remit of bariatric surgery to overcome.⁶

In keeping with published literature,⁷ the current study has confirmed that bariatric surgery leads to an improvement in HbA_{1c} levels but that insulin is a significant setback for remission. This is consistent with findings from other studies in the literature.^{8,9} In a retrospective cohort study of 505 patients, remission rates were greater in patients who were not taking insulin pre-operatively (53.8% vs 13.5%, $p<0.001$).¹⁰ Similarly, another study found that patients with severe obesity receiving insulin were less likely to achieve remission after one year compared with those on oral glucose-lowering medication agents (50% v 93%).¹¹ The current study contributes to the existing literature as it contains data from the UK, which generally has a higher rate of obesity compared to many other countries, and the BMI of this patient group tends to be higher than their counterparts in Europe according to The Organisation for Economic Co-operation and Development (OECD).¹²

In this study, longer duration of T2DM pre-operatively was noted to be a significant negative predictor of remission. According to a cohort study of 8,526 patients, remission of T2DM after primary bariatric surgery was inversely associated with duration of T2DM (OR 0.87, 95% CI 0.85–0.89, $p<0.001$).¹³ These findings support the fact that long-standing T2DM has a detrimental effect on both the function and number of pancreatic beta cells which cannot be reversed with bariatric surgery.¹⁴ One postulated mechanism is glucotoxicity-mediated beta cell apoptosis that could result in elevated blood glucose levels through insulin hyposecretion.⁶ This, in turn, causes further progressive beta cell decline.⁶ It is therefore not surprising that achieving significant remission in patients with significant pre-existing metabolic deterioration, secondary to chronic hyperglycaemia, is difficult at best.

This study adds to the evidence that bariatric surgery is an effective method for achieving remission from T2DM. Existing literature shows that it is superior to conventional medical therapy in this regard.^{15,16} Such changes may be attributable to the positive effect of weight loss on insulin sensitivity in the liver and peripheral tissues.^{17,18}

This study has some limitations: the follow-up duration is



Key messages

- Nearly 2/3 of patients with obesity and diabetes mellitus will achieve remission of diabetes following bariatric surgery
- Patients taking insulin or SGLT2 inhibitors are less likely to undergo remission of diabetes mellitus
- The type of surgery does not seem to influence the rate of remission of diabetes mellitus

short, largely because our bariatric services were not able to follow up patients referred from distant geographic locations. Although a minimum follow-up period of 12 months was used to address this issue, it has to be appreciated that the efficacy of both medical and surgical treatments for patients with obesity with T2DM evolves over time, with many studies reporting improvements in remission after 10 years.^{19,20} Equally, it is well recognised that a significant proportion of those who experience remission in the early period after surgery suffer a relapse on longer-term follow-up.^{21,22} The eligibility criteria of our study did not include individuals undergoing other primary bariatric operations such as gastric band and intra-gastric balloon insertion. Furthermore, the relatively small sample size and lack of comparison with a non-surgical obese control group are further limitations of the study.

Bariatric surgery is an effective treatment option in patients with obesity with T2DM. This study shows that patients on polytherapy and those with longer duration of T2DM are less likely to achieve remission compared to those on single anti-diabetic drugs and with a shorter duration of diabetes. Patients on insulin and SGLT2 inhibitors are less likely to undergo remission after bariatric surgery compared to those who are not taking these agents. Further studies involving larger sample sizes and longer follow-up are warranted to validate our findings, as well as underpin other predictors of remission from T2DM in patients with obesity, to help optimise patient selection and improve metabolic outcomes after bariatric surgery.

Conflict of interest None declared.

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Authors' contributions HR prepared the first draft of this manuscript. RM analysed the data, performed a detailed and systematic review of the literature and contributed to the writing up of the manuscript. MTA and TR conceived the idea of writing the manuscript, contributed to the design, and revised it critically. All co-authors participated in the development of the recommendations and reviewed and approved the final manuscript.

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ERRATUM

Use of a simplified local guideline improves "front door" management of diabetes and hyperglycaemia in people admitted to hospital with COVID-19

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In the printed issue of the article above, the author Mei Lan Kwok was omitted from the list of authors. The correction has been made and the online version has been updated and can be viewed at <https://bjd-abcd.com/index.php/bjd/article/view/905>