The role of bariatric surgery in the treatment of type 2 diabetes mellitus

ABSTRACT
Medical treatments for patients with type 2 diabetes mellitus and class II and above obesity (body mass index greater than 35 kg/m²) are currently limited to treatment of diabetes and prevention of its vascular complications. Bariatric surgery is by far the most effective treatment not only for weight loss, but also for improvement or remission of diabetes. This editorial examines the current evidence for the impact of bariatric surgery on weight loss and type 2 diabetes.

KEYWORDS
Type 2 diabetes mellitus, bariatric surgery, diabetes remission, obesity

DECLARATION OF INTERESTS
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INTRODUCTION
Type 2 diabetes mellitus (T2D) is a significant healthcare challenge driven by the increasing prevalence of obesity.1,2 There are currently at least 2.6 million people with diabetes in the UK and the figure is predicted to rise to more than five million by 2025.3 Weight reduction in patients with T2D improves glycaemia and other cardiometabolic abnormalities and in some cases can result in diabetes remission.4,5 Lifestyle interventions, with or without the addition of weight loss medications, usually lead to modest weight loss, which is frequently not maintained.4,6 Currently, bariatric surgery is the most effective treatment for individuals with obesity complicated by T2D. Most procedures are generally performed laparoscopically as observed in the Longitudinal Assessment of Bariatric Surgery (LABS) study.7 Bariatric surgery is not only effective in weight reduction, it also results in greater improvement and remission of T2D. The most common procedures carried out in the National Health Service (NHS) are laparoscopic adjustable gastric banding (LAGB), laparoscopic Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG).

The International Diabetes Federation (IDF) has recommended bariatric surgery as a treatment option for individuals with T2D and a body mass index (BMI) ≥40 kg/m² because bariatric surgery is likely to result in significant improvement in T2D at a lower BMI. Improvement and remission of T2D after bariatric surgery are likely to be due to a combination of weight reduction mediated through alterations in appetite hormones and alterations in hormones regulating glycaemic control. Appetite hormones are a combination of weight loss and insulin resistance state.

Remission of diabetes after bariatric surgery

Remission or cure?
Glycaemic control improves significantly after bariatric surgery in T2D and glycaemia may return to a pre-diabetes level. However, these individuals are at risk of glycaemic deterioration in the future and may become...
diabetic again. This is supported by the Swedish Obese Subjects (SOS) study in which T2D remission rate was 36% at 10 years compared to 72% at two years follow-up. Moreover, T2D individuals who have achieved a pre-diabetes state (impaired fasting glucose [IFT] or impaired glucose tolerance [IGT] states) after bariatric surgery still have an increased risk in all-cause mortality as well as cardiovascular disease in the near future. Also, there is a paucity in the long-term data on microvascular complications after bariatric surgery in this group of individuals. Due to these reasons, the more appropriate medical terminology is remission of diabetes although the terminology ‘cure’ has also been used in the literature.

Definitions

There is no general consensus on the definition of diabetes remission. Because of this, the American Diabetes Association (ADA) released a consensus statement on the definition of diabetes remission in 2009. The statement suggested that remission can be partial, complete or prolonged depending on the duration of normality in glycaemic control without the need for anti-diabetic medications or procedures. Partial remission was defined as a fasting plasma glucose level of <7.0 millimoles per litre (mmol/L) or HbA1c <48 millimoles per mole (mmol/mol) (6.5%) for at least 12 months without the help of medications or procedures. Complete remission was defined as a fasting plasma glucose level of <5.6 mmol/L or glycated haemoglobin (HbA1c) <42 mmol/mol (6.0%) for at least 12 months, while prolonged remission was defined as complete remission achieved for at least five years without the need for medication or surgery. An HbA1c of 42 mmol/mol (6.0%) is still abnormal, representing impaired glucose tolerance (or pre-diabetes state). This HbA1c level, however, has a lower risk of diabetes microvascular complications used to define cut-off points for diabetes diagnosis.

Prior to the ADA statement, Buchwald et al. published two meta-analyses on T2D remission after bariatric surgery. Due to the absence of a universal definition at the time of publication, the authors formulated their own. They defined T2D remission as a fasting plasma glucose level of <5.7 mmol/L or HbA1c <43 mmol/mol (6.1%) without the help of hypoglycaemic medications. Currently there is no general international consensus on the definition of diabetes remission, so there is great diversity in reports of diabetes remission after bariatric surgery. However, the ADA consensus statement’s definition is now beginning to gain increasing popularity in the literature.

Results from systematic review, meta-analyses and pooled data

In 2009, a meta-analysis of 621 studies by Buchwald et al. was published in which 29 were randomised controlled trials (RCT) and only ten of these were considered class one evidence. Results from these ten studies were then published in two categories: diabetes remission achieved in two years or more than two years. At two years, the greatest remission was achieved following gastric bypass (about 81%) compared to the gastric band (55%). Results from more than two years showed a reduction in diabetes remission rate with the gastric bypass (70.9%) and a higher rate with the gastric band (58.3%). A further meta-analysis by Buchwald et al. in 2004 involved 136 studies with 19,388 patients. Most of them were case series with only one RCT in the analysis. The greatest diabetes remission was reported after gastric bypass surgery (83.8%) followed by gastroplasty (68.2%) and finally the gastric band (47.8%). Dixon et al. performed a review of diabetes remission after LAGB in a total of 35 studies with only one RCT. After approximately one year, a weighted average or 52.3% achieved diabetes remission. Remission was lower at 24 months or longer (37.6%).

Recent randomised controlled trials

There are limited published RCTs examining the effect of bariatric surgery on diabetes remission. The sample sizes for these RCTs are relatively small. Despite this, the results are statistically significant because of the high effectiveness of bariatric surgery in glycaemic change, at least in the short term.

Mingrone and colleagues recently compared diabetes remission rates between gastric bypass (n=20), biliopancreatic diversion (n=20) and medical therapy (n=20) in an RCT. Remission was defined as a fasting glucose level of <5.6 mmol/L and a HbA1c of <48 mmol/mol (6.5%) for at least one year without anti-diabetes medications. The greatest remission percentage occurred after biliopancreatic diversion (95%) followed by gastric bypass (75%) and medical therapy (0%). This equates to a relative risk of 7.5 (95% confidence interval [CI]: 1.97 to 28.61) in the gastric bypass group and 9.5 (95% CI: 2.54 to 35.51) in the biliopancreatic diversion group for diabetes remission.

An RCT performed in Australia comparing intensive lifestyle intervention (ILI) (n=30) to LAGB (n=30) found that the remission rate (defined as HbA1c <44 mmol/mol [6.2%] and a fasting glucose level of <7.0 mmol/L) after two years was 73% in LAGB compared to 13% in the ILI group. The mean difference in reduction in the glycated haemoglobin between LAGB (−1.81%) and ILI (−0.38%) was 1.43% (95% CI: 2.10 to 0.80). Although the
majority of the LAGB patients achieved weight reduction in this study, one patient did not. Both the RCTs above demonstrate the greater effect of bariatric surgery when compared to lifestyle intervention on glycaemic control. A recent Taiwanese study examined the impact of gastric bypass (n=30) and sleeve gastrectomy (n=30). Diabetes remission was defined as a fasting glucose level of <7.0 mmol/L or glycated haemoglobin of less than 48 mmol/mol (6.5%), without the use of medication. Greater remission was found in the gastric bypass group (93%) compared to the gastric sleeve (47%). The mean reduction in glycated haemoglobin in gastric bypass recipients (4.2%) was also higher compared to gastric sleeve recipients (3.0%).

**Remission of type 2 diabetes based on ADA criteria**

Recently, Pournaras et al. compared their results using the ADA and Buchwald et al. definitions. They reported their results from three bariatric centres: one in Norway and two in the UK. A total of 209 patients were followed up for 23 months and it was found that overall, 34.4% achieved complete remission and 13.4% achieved partial remission based on the ADA guidelines. This is compared to 49.3% achieving complete remission based on the definition used by Buchwald and colleagues. Patients who underwent gastric bypass surgery had the highest success rate compared to LSG (1.6 to 3.12 times higher) and LAGB (2.2 to 5.8 times higher) in diabetes remission.

**Type 2 diabetes remission in the long term**

Long-term remission of T2D was assessed by the Swedish Obese Subjects (SOS) study, a non-randomised prospective observational study. Remission of diabetes for SOS was defined as a fasting plasma glucose level of <7.0 mmol/L or a fasting capillary glucose level of <6.1 mmol/L. Participants were followed up for ten years after bariatric surgery. The majority of the participants received either a gastroplasty or a gastric band (95%). At two years, the diabetes remission rate was 72% and this decreased to 36% at ten years. This study suggests that diabetes remission may not be sustained in half of the patients over time and reinforces the importance of long-term follow-up, including assessments for complication in patients with diabetes who undergo bariatric surgery.

**BARIATRIC SURGERY AND CARDIO-METABOLIC RISK**

Management of T2D also includes blood pressure (BP) and lipid control as part of cardiovascular risk reduction. Apart from better glycaemic control, bariatric surgery also results in improvement in blood pressure control as well as lipid profile. A recent systematic review of 52 studies published from 1950 to 2010 consists of 16,867 patients. The mean follow-up period was 34 months. Results showed that after bariatric surgery, there was a 15 millimetres of mercury (mm Hg) drop in systolic BP. Resolution of hypertension and lipid profile was similar in LAGB (58% and 60% respectively) and RYGB (60% and 57% respectively). These results differed from Buchwald et al. as they reviewed studies published from 1990 to 2003 and reported a greater resolution in gastric bypass recipients (75.4%) compared to LAGB (38.4%).

A systematic review on LSG examined 33 studies from 2000 to 2011 of which one study was an RCT. Resolution of hypertension was defined as discontinuation of any anti-hypertensive medications. There were a total of 3,997 patients. Resolution of hypertension occurred in 58% of patients after 12 months. In the SOS study, resolution of hypertension was defined as BP of less than 140/90 mm Hg. Thirty-four per cent of patients achieved resolution of hypertension at two years but this was reduced to 19% at ten years.

A systematic review performed by Buchwald and colleagues demonstrated that weight loss surgery resulted in improvements in lipids profile. Improvements of hyperlipidaemia, hypercholesterolaemia and hyper-triglyceridaemia were greater after RYGB (96.9%, 94.9% and 91.2% respectively) compared to LAGB (58.9%, 78.0% and 77% respectively). Other studies have shown between 18% and 38% reduction in triglycerides level, and between 13% and 30% improvements in high-density lipoprotein (HDL)-cholesterol level after bariatric surgery. Significant changes are not seen in LDL-cholesterol level after surgery except in one study which showed a reduction of between 17% and 65%. Long-term improvements in lipid profiles were shown in the SOS study. Resolution of hyper-triglyceridaemia (defined as level <1.7 mmol/L) was achieved by 62% of participants at two years and 46% at ten years. Resolution of low HDL-cholesterol (defined as level HDL >1.0 mmol/L) was similar at two and ten years (76% and 73% respectively) after surgery.

**BARIATIC SURGERY AND QUALITY OF LIFE**

Several studies have reported that quality of life of patients improved after bariatric surgery. This includes improvement in general quality of life, weight related quality of life, physical activity, depression scores and self-esteem. Because of greater weight reduction after bariatric surgery, problems with excess skin could arise. This could lead to recurrent infections and discomfort. Unfortunately, body contouring surgery is not offered as part of the NHS service and patients should be warned of this possible adverse effect prior to bariatric surgery.
SAFETY OF BARIATRIC SURGERY

With improved surgical technique, patient selection and preparation, bariatric procedures have mortality rates similar to common operations such as laparoscopic cholecystectomy, which has a mortality rate of up to 0.2%. Although the gastric bypass appears to be more successful in diabetes remission, it is associated with a higher mortality and complication risk. The 30-day perioperative mortality rate for gastric bypass (up to 0.4%) is at least four times higher when compared to the gastric band (up to 0.1%). At two years, the gastric band mortality rate (0.0%) continues to be lower compared to the bypass (0.4%). Recipients of the gastric bypass and sleeve are also at risk of nutritional deficiencies. The problems that might occur after the gastric band are usually due to mechanical failure of the band or lack of dietary adherence by patients, causing excessive vomiting, oesophageal dilatation, dysmotility and band slippage. Operative technique has however been optimised to reduce risk of band slippage.

CONCLUSION AND UNRESOLVED QUESTIONS

In obese diabetic patients, bariatric surgery results in significant weight reduction and great success in the remission in T2D mellitus in the short and medium-term. More data are still needed for assessing the long-term outcomes. The majority of bariatric procedures are carried out laparoscopically and the mortality and complications rates are usually very low. However, in those aged 60 years and above, perioperative risks and mortality rates appear to be higher. A thorough multidisciplinary assessment of patients is therefore important to weigh up risks and benefits prior to surgery.

Obesity and T2D are major challenges to the NHS. The choice of anti-obesity medication is limited and some anti-diabetes medications induce weight gain as an adverse effect. Compared to lifestyle interventions, glycaemic control, cardiometabolic risk and quality of life are more likely to be improved with bariatric surgery. Moreover, bariatric surgery has been shown to be cost-effective. Ongoing and planned studies will ensure that better study designs are implemented which will strengthen the evidence-base for the use of bariatric surgery in cases of obesity complicated by T2D.

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