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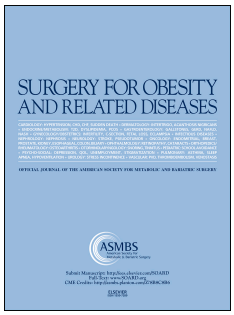

Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery compared to routine care: a population-based real-world UK cohort study

Pushpa Singh, Nicola J. Adderley, Anuradhaa Subramanian, Krishna Gokhale, Jonathan Hazlehurst, Rishi Singhal, Srikanth Bellary, Abd A. Tahrani, Krishnarajah Nirantharakumar

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Title: Glycaemic outcomes in patients with type 2 diabetes following bariatric surgery compared to routine care: a population-based real-world UK cohort study

Pushpa Singh[1,2], Nicola J Adderley[3], Anuradhaa Subramanian[3], Krishna Gokhale[3], Jonathan Hazlehurst[1,2], Rishi Singhal[4], Srikanth Bellary[2,5], Abd A Tahrani *[1,2,6], Krishnarajah Nirantharakumar* [2,3,7]

1Institute of Metabolism and Systems Research, University of Birmingham, UK

2 Department of Diabetes and Endocrinology, University Hospitals Birmingham NHS Foundation Trust, UK

3 Institute of Applied Health Research, University of Birmingham, UK

4 Department of Surgery, University Hospital Birmingham NHS Foundation Trust, UK

5 School of Life and Health Sciences, Aston University, UK

6 Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, U.K.

7 Midlands Health Data Research, U.K.

*AT and KN are joint senior authors and contributed equally to this manuscript.

Corresponding authors:

Professor K Nirantharakumar

Institute of Applied Health Research, University of Birmingham, Birmingham, B15 2TT, UK, Phone number- +447737773559

Email- K.Nirantharan@bham.ac.uk

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Abstract

Background: Clinical trials have shown that bariatric surgery (BS) is associated with better glycaemic control and diabetes remission in patients with type 2 diabetes (T2D) compared to routine care.

Objectives: We conducted a real world, population-based study examining the impact of BS on glycaemic control and medications in patients with T2D.

Methods and Settings: Retrospective matched-controlled cohort study, 1/1/1990–31/1/2018, using IQVIA Medical Research Data, a primary care electronic records database. Adults with body mass index (BMI) ≥30 kg/m2 and T2D who had BS (surgical) were matched for age, sex, BMI, and diabetes duration to two controls (with T2D and no BS).

Results: 1126 patients in the surgical and 2219 patients in the control group were analyzed. Mean (SD) age was 50.0 (9.3) years, 67.6% were women, baseline HbA1c was 7.8% (1.7) and diabetes duration was 4.7 (2.0-8.4) years.

Over a median (IQR) follow-up of 3.6 (1.7-5.9) years, a higher proportion of patients in the surgical group achieved HbA1c ≤6.0% than the control group (65.8% vs 22.8%). The surgical group showed a decrease in mean HbA1c of 1.5% (95%CI 1.4-1.7), 1.4% (1.2-1.5), and 1.3% (1.1-1.5) at 1-, 2- and 3-years' follow-up, respectively, while HbA1c increased in the control groups. The proportion of patients receiving glucose-lowering medications decreased in the surgical group (92.2% to 66.5%) but increased in the control group (85.3% to 90.2%).

Conclusions: BS is associated with significant improvement in glycaemic control, achievement of normal HbA1c, and reduced need for glucose-lowering therapy in patients with T2D.

Keywords: Bariatric surgery, Obesity, Diabetes, Glycaemic, HbA1c, Weight, Glucose lowering medications, adult

Highlights

- Bariatric surgery was associated with reduction in HbA1c compared to routine care
- Achieving and maintaining targeted HbA1c was more likely in surgical group despite lower number of glucose- lowering medications

Background:

Improving glycaemic control and achieving diabetes remission are important treatment aims in patients with type 2 diabetes. A 1% (11 mmol/mol) reduction in HbA1c is associated with a 21% decrease in deaths related to diabetes, a 14% decrease in myocardial infarction and a 37% decrease in risk of microvascular complications over a median of 10 years' follow-up [(1)]. Reduction in HbA1c has also been associated with a 24% decrease in annual average healthcare cost in the first year and a 17% decrease in the second year compared to patients who did not achieve HbA1c reduction [(2)].

Despite the development of several new classes of glucose lowering pharmacotherapy, only half of patients with type 2 diabetes achieve HbA1c targets of < 7.0% (53mmol/mol) and 64% are estimated to be achieving individualised glycaemic targets [(3)]. From the annual National Diabetes Audit (NADIA) in the UK, the percentage of patients achieving HbA1c ≤ 7.5% (58 mmol/mol) was 65.8% in 2011-12 and 66.8% in 2017-18 [(4)]. Hence, further treatment strategies to improve the achievement of glycaemic targets are needed. Weight loss is an important treatment strategy that can have a significant impact on glycaemic control, as shown by the DiRECT and LookAHEAD trials that utilised very low energy diet and intensive lifestyle interventions (including meal replacement) respectively [(5, 6)].

Bariatric surgery is the most successful intervention resulting in long term weight loss in patients with severe obesity [(7, 8)]. Several RCTs have shown that bariatric surgery in people with type 2 diabetes is associated with significant improvements in glycaemic control, reduction in insulin requirements and glucose lowering treatments, and diabetes remission. [(9-11)]. However, the uptake and accessibility of bariatric surgery in patients with type 2 diabetes remains low; in Europe, the number of bariatric surgeries per one million population was only 72 in Germany and 117 in England [(12, 13)]. Hence, it is important to examine the impact of bariatric surgery on glycaemic outcomes in a real world setting, especially given that real world studies have shown bariatric surgery was associated with a reduction in incident cardiovascular disease, microvascular complications, and mortality in patients with and without type 2 diabetes [(14, 15)].

Here we aimed to assess the impact of bariatric surgery on glycaemic control and the use of glucose lowering medications in patients with obesity and type 2 diabetes who underwent bariatric surgery compared to routine care in a real-world UK setting.

Method

Study design and data source

We conducted a retrospective cohort study between 1/1/1990 and 31/1/2018 utilising the IQVIA (Quintiles and Intercontinental Marketing Statistics company) Medical Research Data (IMRD-UK) database. General practices (primary care) from across the UK which use the Vision electronic health records software contribute data to IMRD. It uses de-identified data of over 15 million patients collected as a part of their routine primary care, covering nearly 6% of the UK population at a given time point [16]. It contains information on patient demographics, treatments, physical measurements, laboratory results, symptoms, and medical diagnoses. This database is specifically suitable for research relevant to conditions that are part of the Quality and Outcomes Framework (QOF), including type 2 diabetes, as the QOF scheme incentivizes primary care physicians for identification and management of these conditions, and so they are well recorded [17].

Practices were eligible for inclusion from a year after installation of electronic medical records software and achieving acceptable mortality reporting, a measure of data quality [18]. Patients registered with an eligible practice for at least one year were eligible for inclusion to ensure completeness of data.

Study population

We have used this dataset previously to assess the impact of bariatric surgery on incidence diabetes related microvascular complications in patients with obesity and type 2 diabetes (15). A participant selection flow chart has been presented as supplementary figure 1 in this paper (15). We included patients aged 18 to 75 years with type 2 diabetes. The surgical cohort was defined as patients with type 2 diabetes and a subsequent record of primary bariatric surgery [gastric banding (GB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), or duodenal switch (DS)] during the study period. Every patient in the exposed cohort was matched with up to 2 control patients (type 2 diabetes who did not undergo bariatric surgery) within the same general practice for age (± 2 years), sex, body mass index (BMI, ±2 kg/m^2) and diabetes duration (±3 years).

The date of bariatric surgery was assigned as the index date for exposed patients and the same date was assigned as index date to their matched control patients in order to minimise immortal time bias [19].

Patients in the surgical group along with their controls were excluded from the study if they met any of the following criteria at baseline: BMI < 30 kg/m^2, age > 75 years, prior record of gastric cancer, prior record of gastric balloon/endo-barrier/revisional bariatric surgery.

Eligible participants were followed up from the index date until the earliest occurrence of the following end points: a) patient left the practice; b) the practice ceased contributing to the database; c) patient died; and e) study end date (31/1/2018).

Outcome measures

The main outcomes of our study were: (1) mean change in HbA1c from baseline (yearly for up to 3 years); (2) risk (hazard ratio) of attainment or maintaining of glycaemic targets, defined as HbA1c ≤ 6.0% (42mmol/mol), ≤ 6.5% (48mmol/mol) and ≤ 7% (53mmol/mol) [9, 20], irrespective of their baseline HbA1c and use of glucose lowering medication; and (3) number and type of glucose lowering medications being used after bariatric surgery. We also assessed percentage weight loss in surgical and control group.

Statistical analysis

For outcome (1), HbA1c is expressed as a percentage (Diabetes Control and Complications Trial, DCCT unit). Change in HbA1c was defined as the difference between latest available HbA1c in each year after the index date (up to 3 years) and the baseline HbA1c. We disregarded HbA1c readings available within 28 days of index date as HbA1c measurements within 28 days of surgery may be the result of short-term effects of surgery. We used the independent sample t-test to compare change in HbA1c in the surgical and control groups. For the analysis of outcome (2), achieving target HbA1c, we used Cox proportional hazards regression analysis and calculated unadjusted and adjusted hazard ratios (HR) among patients who underwent bariatric surgery compared to their matched controls for each of the 3 glycaemic targets. We assessed achieving or maintaining glycaemic targets of ≤7% (53 mmol/mol), ≤ 6.5% (48mmol/mol) and ≤6 % (42 mmol/mol) based on earliest date after index date irrespective of baseline HbA1c and glucose lowering medications, as per the recommendations by ADA, NICE and studies examining diabetes remission after bariatric surgery [9, 20]. The proportional hazards assumption was checked using the Schoenfeld residuals test. The analysis was repeated in subsets of patients based on their insulin use status at baseline and the type of bariatric surgery they underwent. We did not perform analysis in the duodenal switch subgroup due to small numbers.

For outcome (3), glucose lowering medications included metformin, sulphonylurea, glinides, acarbose, thiazolidinediones, dipeptidyl peptidase 4 (DPP4) inhibitors, sodium-glucose transport-2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists/ analogue (GLP-1RA), and insulin. The proportion of patients who were prescribed each of these drugs at any time point before and after index date (pre- and post-surgery in the surgical group) are presented graphically.

We also assessed the number of glucose-lowering medications pre- and post-bariatric surgery in the surgical and control groups. The number of glucose-lowering medications was categorised as no medication, monotherapy (one medication), dual therapy (two medications) and polypharmacy (≥ 3 medications).

Percentage weight loss (%WL) was calculated as change in weight (post-surgical weight defined as the latest available data after the index date - baseline weight) / baseline weight × 100. For the control group who had no surgery, weight change was calculated using a similar formula.

A two-tailed p-value <0.05 was considered statistically significant. All analyses were conducted using Stata version 15.

Covariates in the adjusted/multivariable model were selected based on biological plausibility and these included: age, sex, baseline BMI, ethnicity, social deprivation status, baseline HbA1c, diabetes duration and insulin use. BMI was categorised as < 35 kg/m^2, 35-40 kg/m^2 and > 40 kg/m^2. Social deprivation status was represented by Townsend deprivation quintile which is based on material deprivation within a population [21]. Ethnicity was categorised as White, Afro-Caribbean, South Asian and mixed. A missing category was used for missing data for BMI, Townsend quintile and ethnicity. Baseline HbA1c and diabetes duration were treated as continuous variables and insulin use as a binary variable.

Results

Baseline characteristics

The baseline characteristics of the 3345 participants included are summarised in Table 1. For the whole cohort, the mean age was 50 (9.3) years. Two thirds of the participants in the study (67.59%) were female. Baseline HbA1c was available for 1117 (99.2%) patients in surgical and 2184 (98.4%) in control group. The mean baseline HbA1c was similar in both groups (7.8%), but higher proportion of participants in the surgical group were prescribed insulin compared to the control group (270 (23.98%) vs 315 (14.20%)). The median follow-up was

3.4 years (1.6- 5.6) years in the surgical group and 3.7 (1.7- 6.1) years in the control group. Out of 1126 participants in surgical group, 249 (22.1%), 255 (22.7%), 610 (52.2%) and 12 (1.1%) of patients had GB, SG, RYGB and DS, respectively.

Mean HbA1c and change in glycaemic status

At 1 year from index date, mean (SD) HbA1c in the surgical (n=699) and control (n=1444) groups was 6.3% (1.3) vs 7.9% (1.8), respectively. In surgical group, there was a mean reduction in HbA1c of 1.5% (95% CI 1.7 to 1.4) whereas in the control group, there was a small increase in HbA1c of 0.1% (95% CI 0.0 to 0.2) resulting in difference in mean change between groups of 1.7 (95% CI 1.5 to 1.8) favouring the surgical group.

Participants who underwent surgical procedures achieved greater HbA1c reductions at 1 year compared to their matched controls, with a difference in mean HbA1c change of 1.0% (95% CI 0.7 to 1.3) in GB, 1.6% (1.3 to 1.9) in SG, 2.0% (1.7 to 2.2) in RYGB, and 3.2% (0.8 to 5.6) in DS compared to their respective control groups.

Reduction in HbA1c observed in the surgical group was maintained at 2 and 3 years while increase in HbA1c was noted in control group, with difference in mean change of 1.5 (95% CI 1.4 to 1.7) at 2 years and.1.6 (95% CI 1.4 to 1.8).at 3 years in favour of surgery. Above are summarised in Figure 1 a) and b).

Achieving glycaemic targets

At baseline, 132 (11.72%) patients in the surgical group and 219 (9.87%) patients in the control group had HbA1c ≤ 6.0% (42 mmol/mol). Over the median (IQR) follow-up of 1.8 (0.6- 4.3) years, 741 (65.8%) patients in the surgical group vs 506 (22.8%) in the control group achieved a HbA1c ≤ 6.0% . Compared to the control group, patients who had surgery were significantly more likely to achieve and maintain HbA1c ≤ 6% (adjusted HR 5.86 (95% CI 5.19 to 6.60), p<0.001) (Table 2). All surgical procedures were associated with higher HR of achieving target HbA1c ≤ 6.0% (42 mmol/mol) compared to their control group (Table 2). Analysing by insulin status showed similar results (Table 2).

Before index date, 328 (29.13%) patients in the surgical and 540 (24.34%) in the control group had HbA1c ≤ 6.5% and 483 (42.9%) patients in the surgical and 861 (38.81%) patients in the control group had HbA1c ≤ 7.0%. Over our study period, achieving or maintaining target HbA1c of ≤ 6.5% and ≤ 7.0% was greater in the surgical group irrespective of type of surgery and baseline insulin use (Table 2).

Change in medications

At baseline, the use of glucose lowering medications was similar in the surgical and control groups except that the percentage of patients on insulin (24.0% vs 14.2%) and GLP-1RA (25.6% vs 12.2%) were higher in the surgical group compared to the control group. This observation could be reflection of closer follow up provided to patients under weight management service. There were 88 (7.8%) patients in the surgical vs 326 (14.7%) in the control group without pharmacotherapy prescriptions at baseline (Table 3).

Over the study period, the proportion of patients on glucose lowering medications decreased in the surgical group from 92.2% at baseline to 66.5% at exit date, while in the control group, it increased 85.3% at baseline to 90.2% during the same period.

In the surgical group, the percentage of patients taking metformin, sulphonylurea, DPP4 inhibitors, GLP-1RA and insulin decreased after the intervention compared to baseline. In the control group, the percentage of patients taking metformin, sulphonylurea, and insulin increased, with a significant increase in DPP4 inhibitor and GLP-1RA.

There was a reduction in thiazolidinediones, glinides and acarbose, and an increase in SGLT2 inhibitors in both groups during the study period.

The percentage of patients on no medication, monotherapy, dual therapy and polytherapy was similar in the surgical and control groups at baseline. After surgery/index date (and any point before exit date), the percentage of patients on no medication increased from 7.8 to 34.5% and there was a significant reduction in the proportion of patients on dual and polytherapy. In the control group, the percentage of patients on no therapy and monotherapy decreased after index date, and a significant increase in polytherapy was noted (31.9 % to 42.9%) (Figure 2).

Change in weight

Data on weight before and after index date was available for 1067 (94.8%) surgical and 1943 (87.6%) control participants. Over the median (IQR) follow-up of 3.2 years (1.4-5.4), the surgical group achieved a greater %WL (mean, 95% CI) of 21.6% (20.8% to 22.4%) compared to 4.6% (4.1% to 5.0%) in the control group.

A greater weight reduction was noted in the surgical group compared to their matched controls for all surgical procedures, %WL (mean (95% CI)): GB 14.6% (12.8% to 16.3%) vs 4.6% (3.6% to 5.5%); SG 20.6% (19.1% to 22.1%) vs 4.2% (3.2% to 5.2%); RYGB 25.0% (24.0% to 25.9%) vs 4.8% (4.2% to 5.3%); and DS 21.2% (14.5% to 28.1%) vs 1.7% (2.7% to 6.0%). Similarly, a greater weight reduction was noted in both insulin and non-insulin

users in the surgical compared to the control group, %WL: 22.6% (95% CI 21.2 to 24.1%) vs 4.1% (95% CI 2.8% to 5.4%) in insulin users and 21.3% (95% CI 20.4% to 22.2%) vs 4.6% (95% CI 4.2% to 5.1%) in non-insulin users.

Discussion

Our study provides real-world evidence of superior effect of bariatric surgery in people with type 2 diabetes and obesity. In our study, we found that patients undergoing bariatric surgery were more likely to meet glycaemic targets with less glucose lowering medications and achieve greater weight loss over median (IQR) follow-up of 3.6 (1.7- 5.9) years compared to routine care. These results occurred within the context of higher insulin prescriptions at baseline in surgical group. Higher percentage of participants on insulin in surgical group could be reflection of disease severity in surgical group and regular review under weight management service.

The possibility of diabetes cure or reversal has been identified as a top research priority by a Priority Setting Partnership project involving patients living with type 2 diabetes and their carers and multidisciplinary health care professionals [(22)]. Diabetes remission in the context of intensive lifestyle interventions has been investigated in several studies. The DiRECT trial using an integrated structured weight management programme based on low calorie diet showed diabetes remission rate of 36% over two years based on a diabetes remission definition of HbA1c ≤ 6.5% (48 mmol/mol) without glucose lowering agents,.[(23)] The LookAHead study defined diabetes remission (partial or complete remission of diabetes), as transition from meeting diabetes criteria to a prediabetes or nondiabetic level of glycemia (fasting plasma glucose <126 mg/dL and HbA1c ≤6.5% and off glucose- lowering medication). The study reported a remission rate of 7.3% (95% CI 6.2% to 8.4%) at four years' follow-up using an intensive lifestyle intervention [(6)]. While the results from above studies are highly encouraging, the remission rate reported following bariatric procedures are far greater. A meta-analysis of eight RCTs found bariatric surgery achieved higher remission rate compared to a non-surgical intervention with a risk ratio 5.41 (95% CI 2.47 to 11.85) over 1-2 years' follow-up, and 8.36 (2.71 to 25.85) over 3-5 years' follow-up [(24)]. A systematic review of RCTs comparing bariatric surgery vs non-surgical treatments concluded that the chance of diabetes remission was 22 times greater in the surgical compared to control group, with a relative risk 22.1 (95% CI 3.2 to 154.3) in a complete case analysis [(25)]. A RCT reported significant reduction in use glucose lowering medications including insulin in

surgical group compared to medical group over 5 years follow up [9].Population based cohort study included 3674 surgical patients and 1335 non- surgical patients. Over 6 years follow up 50% of patients in surgical group were on no glucose lowering medications and six times less likely to be on insulin treatment compared to non- surgical patients [26].

Our results support these findings and show that achieving HbA1c in the normoglycemic range is possible (for more than half of patients) within a real-world setting with bariatric surgery, while this was not observed in the routine care group using pharmacotherapy. Insulin use has been shown to be predictor of poorer glycaemic outcomes and diabetes remission in post bariatric surgery patients [27]. Despite higher insulin user in bariatric surgery at baseline in our study, more patients managed to achieve targeted glycaemic control in surgical group compared to routine care.

In our study, 70.3% and 79.9% of patients in the surgical group achieved HbA1c of ≤ 6.5% and ≤ 7.0%, respectively over a median follow up period of 3.4 years. Reduction in HbA1c was noted in all surgical groups and was highest in the RYGB group followed by SG and GB. RYGB and SG are the two commonly performed bariatric procedures and their beneficial impact on glycaemic control is well evident (9, 10). Although it is difficult to ascertain if one is better than the other, there is some indication that RYGB may be slightly better with respect to glycaemic outcomes. A prospective study conducted on 18 RYGB patients and 15 SG patients analysed the glycaemic effect over 12 months follow up period (28). The study reported effect on glycaemic control was similar in both group at follow up of 2 days, 3 weeks and 1 year follow up (28). However, few other systematic reviews found similar result as ours. A systematic review identified 10 RCTs, 705 patients with type 2 diabetes who had RYGB or SG with follow up 1 to 5 years (29). Meta-analysis of these studies found rate of diabetes remission was higher in patients undergoing RYGB compared to SG with relative risk of 1.20 (1.00- 1.45, p=0.047) in studies with 1 year follow up and 1.06 (0.94- 1.20, p= 0.34) in studies with 2-5 years follow up (29).Another systematic review and meta-analysis of 10 RCT, 778 patients with type 2 diabetes allocated to RYGB or SG and at least 12 months follow up found that RYGB was associated with higher likelihood of achieving diabetes remission compared to SG at 1 year and 5 years follow up with relative risk of 1.34 and 1.18 respectively (30).

The proportion of patients achieving the targeted HbA1c was higher in our study than those noted in RCTs (9, 10). These differences could be because 29.1% and 42.9% of patients in

our study had HbA1c ≤ 6.5% and ≤ 7.0%, respectively at baseline while all patients in both the RCTs (9, 10) had HbA1c > 7.0%. %. Good glycaemic status in surgical group was noted despite being on less glucose lowering medications. Percentage of patients on SGLT2I and GLP1-RA medication reduced in surgical group in post operative period. RCT GRAVITAS (GLP-1 Receptor Agonist Intervention for poor responders after bariatric surgery) by Miras et al showed adjuvant effect of Liraglutide on diabetes management of patients who underwent RYGB or SG [31]. Patients on liraglutide managed to achieve reduction in HbA1c and weight over 26 weeks follow up [31]. Continuation of GLP1-RA and SGLT2I class of medications in surgical group could have resulted in further reduction in HbA1c and better outcomes. We also noted 22.8%, 42.63% and 57.82% patients in control group managed to achieve and/ or maintain the target HbA1c of 6.0%, 6.5% and 7.0% respectively. This could be result of increasing use of newer medications in general. In our study cohort, the percentage of patients in control group receiving a prescription for GLP1-RA increased from 12.17% to 23.07% and those receiving SGLT2I increased from 3.15% to 15.86% over the study period.

In our study, we found that all classes of medications were used post bariatric surgery, most commonly metformin and sulphonylurea. The use of sulphonylurea is surprising, considering their impact on weight and hypoglycaemia. It is possible that the continued use of sulphonylurea is driven by national guidelines for the management of type 2 diabetes that are not specific to post bariatric surgery [32]. The effect of bariatric surgery on glycaemic status is well evidenced in clinical studies. However, the guidance on choice and titration of glucose lowering medications post bariatric surgery is currently not well defined [33, 34]. The clinical practice guideline for management of patients undergoing bariatric surgery published 2019 recommends discontinuation of all insulin secretagogues like sulphonylurea and meglitinides, SGLT2I and thiazolidinediones and reduction in insulin dose in immediate post operative patients [34]. Metformin and/or incretin-based therapies has been advised for glycaemic management in immediate postoperative patients [34]. Use of rapid acting insulin analogue before meals and long-acting insulin analogue administered subcutaneously have also been recommended for achieving glycaemic targets in post operative stage [34]. However, the guidance on long term residual diabetes management is lacking.

The mechanism behind glycaemic improvement after bariatric surgery is complex and incompletely understood. The likely mechanisms include changes in beta cell function, insulin sensitivity, gluconeogenesis, glucose uptake and utilization in peripheral organs

driven by neurohormonal changes in the gut brain axis and weight loss. Weight loss leads to reductions in ectopic fat in pancreas, liver and muscle which could contribute to improvement in insulin sensitivity [35]. Bariatric surgery has been associated with changes in hormones [36], bile acid metabolism, gut microbiome, taste and smell senses [37], intestinal enteroplasticty, and vagus nerve function [35, 38] which contribute in creating low calorie absorption environment and good glycaemic control.

Limitations and strengths

Our findings should be interpreted within certain limitations. The IMRD-UK database is a validated primary care data source and had been used by our team and other researchers in numerous studies [14, 39-41]. Because of the retrospective nature of the study and the limited data on some covariates, residual confounding cannot be excluded. Compared to other studies, our study had a shorter period of follow up. This limited our ability to look at outcomes beyond 5 years. On the other hand, our study looked at real-world data and the large sample size allowed us to explore the effect in different types of bariatric surgery. Further, our study included patients with type 2 diabetes on insulin as well as non-insulin users, thus enabling us to analyse the outcomes in these two groups separately. The findings or our study add to the growing evidence of the beneficial impact of bariatric surgery on glycaemic status and glucose lowering medications.

Conclusion

Bariatric surgery was associated with a large reduction in HbA1c in patients with type 2 diabetes and obesity compared to routine care. It was also associated with a reduction in polypharmacy. Bariatric surgery is an effective treatment for patients with type 2 diabetes and obesity and can result in HbA1c in the normoglycemic range. Taken together with the findings of this study, increased utilization of bariatric surgery for those who are eligible can be seen to reduce the burden of type 2 diabetes.

Ethics

Use of IQVIA Medical Research Data (IMRD-UK) is approved by the UK Research Ethics Committee (reference number: 18/LO/0441); in accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (reference number: 18THIN097). IMRD-UK incorporates data from The Health Improvement Network (THIN), A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care.

Copyright Statement

Author contributions:

AAT, PS and KN had the original idea for the study. PS, AAT, and KN designed the study. KG undertook data extraction. PS designed and performed the analysis, which was reviewed by KN, AS and NA. PS, AS, KN and AAT contributed to the data analysis and interpretation. PS wrote the first draft of the paper, which was revised and edited by NA, SB, KAT, RS, KG, AAT and KN. PS, AAT and KN affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. PS and KN had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: There are no potential conflicts of interest relevant to this article.

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Competing Interest:

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Table1: Baseline characteristics of participants in surgical and control (non-surgical) groups

	Surgical	**Control**
Population, n	**1126**	**2219**
Age, years, Mean (SD)	49.87 (9.3)	50.12 (9.3)
Age Categories, years, n (%)		
<41	171 (15.19)	329 (14.83)
41-60	803 (71.31)	1568 (70.66)
61-max	152 (13.50)	322 (14.51)
Sex, n (%)		
Male	366 (32.50)	718 (32.36)
Female	760 (67.50)	1501 (67.64)
BMI, kg/ m^2, Mean (SD)	46.76 (7.96)	46.14 (7.49)
BMI Categories, kg/m^2, n (%)		
30-34.9	57 (5.06)	121 (5.46)
35-39.9	165 (14.65)	344 (15.50)
≥40	901 (80.02)	1748 (78.77)
Missing	3 (0.27)	6 (0.27)
Ethnicity, n (%)		
White Caucasian	620 (55.06)	1094 (49.30)
Black Afro-Caribbean	25 (2.22)	37 (1.67)
South Asian	32 (2.84)	56 (2.52)
Mixed Race	7 (0.62)	10 (0.45)
Other	2 (0.18)	9 (0.41)
Missing	440 (39.08)	1013 (45.65)
Townsend quintile, n (%)		
1 (Least deprived)	185 (16.43)	250 (11.27)
2	178 (15.81)	290 (13.07)
3	219 (19.45)	463 (20.87)
4	234 (20.78)	492 (22.17)
5 (Most deprived)	160 (14.21)	414 (18.66)
Missing	150 (13.32)	310 (13.97)
Diabetes Status		
Diabetes duration (years), Median (IQR)	4.7 (2.1- 8.9)	4.6 (1.9- 8.1)
Mean HbA1c, Mean (SD)	7.8 (1.8)	7.8 (1.7)
Insulin user n (%)	270 (23.98)	315 (14.20)
No glucose lowering medication n (%)	88 (7.82)	326 (14.69)

Table 2: Achieving targeted HbA1c in surgical and control groups

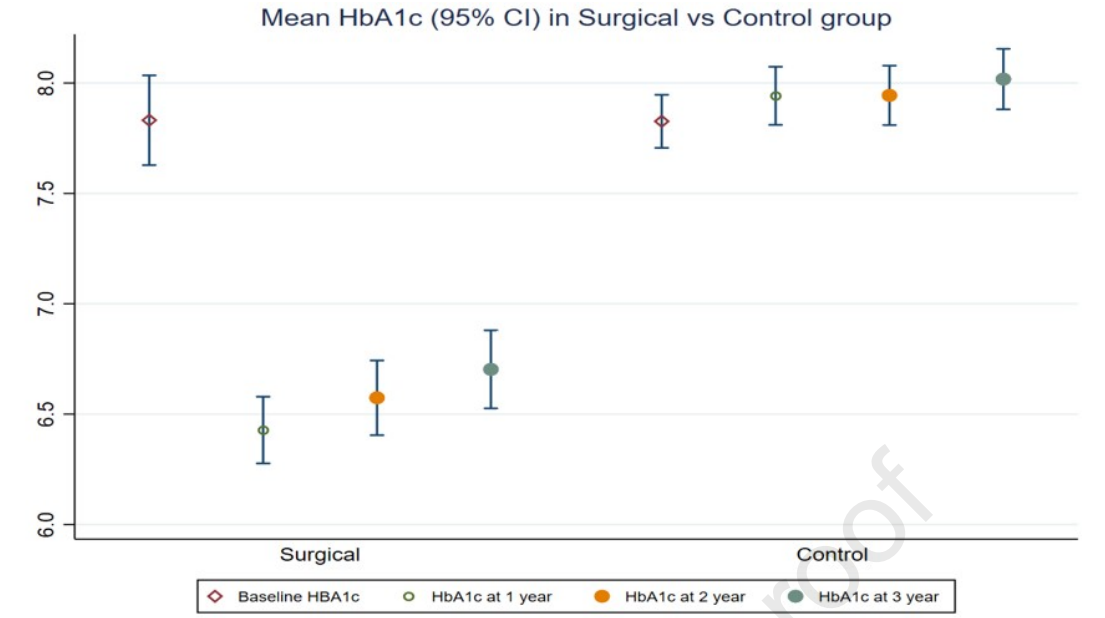
		HBA1c ≤ 6 (42mmol/mol)		HBA1c ≤ 6.5 (48 mmol/mol)		HBA1c ≤ 7.0 (53 mmol/mol)	
		Surgical	Control	Surgical	Control	Surgical	Control
Total Population		**1126**	**2219**	**1126**	**2219**	**1126**	**2219**
Outcome events, n (%)		741 (65.81)	506 (22.80)	897 (79.66)	946 (42.63)	980 (87.03)	1283 (57.82)
Person-years		1179.55	7421.33	1227.48	5883.31	908.79	4469.07
Crude Incidence Rate*		416.39	68.18	730.77	160.69	1078.36	287.08
Follow-up years, Median (IQR)		0.7 (0.3- 1.9)	2.7 (1.1- 5.1)	0.5 (0.3- 1.1)	1.8 (0.6- 4.0)	0.4 (0.2- 0.8)	1.1 (0.4- 3.0)
HR (95% CI), p-value	Unadjusted	4.90 (4.36- 5.49), <0.001		3.52 (3.21- 3.87), <0.001		2.85 (2.62- 3.11), <0.001	
	Adjusted	5.86 (5.19- 6.60), <0.001		3.94 (3.57- 4.34), <0.001		2.98 (2.73- 3.26), <0.001	
On Insulin		270	315	270	315	270	315
Outcome events, n (%)		115 (42.59)	50 (15.87)	172(62.70)	84 (26.67)	211 (78.15)	123 (39.05)
Person-years		640.38	1067.41	475.13	952.24	342.60	796.95
Crude Incidence Rate*		179.58	46.84	362	88.21	615.89	154.34
Follow-up years, Median (IQR)		1.3 (0.5- 3.7)	3.1 (1.1-5.4)	0.8 (0.3- 2.5)	2.5 (0.9- 4.7)	0.5 (0.3- 1.3)	1.6 (0.6- 4.0)
HR (95% CI), p-value	Unadjusted	3.48 (2.50- 4.86), <0.001		3.54 (2.72- 4.6), <0.001		3.35 (2.68- 4.20), <0.001	
	Adjusted	3.98 (2.83- 5.60), <0.001		3.75 (2.87- 4.90), <0.001		3.55 (2.82- 4.46), <0.001	
Not on Insulin		856	1904	856	1904	856	1904
Outcome events, n (%)		626 (73.13)	459 (23.95)	725 (84.70)	862 (45.27)	769 (89.84)	1160 (60.92)
Person-years		1139.18	6353.92	752.34	4931.07	566.19	3672.12
Crude Incidence Rate*		549.52	71.77	963.66	174.81	1358.2	315.89
Follow-up years, Median (IQR)		0.6 (0.3- 1.4)	2.7 (1.1- 5.1)	0.4 (0.2- 0.8)	1.7 (0.6- 3.8)	0.4 (0.2- 0.7)	1 (0.4- 2.7)
HR (95% CI), p-value	Unadjusted	5.88 (5.19- 6.66), <0.001		4.07 (3.67- 4.51), <0.001		3.09 (2.81- 3.40), <0.001	
	Adjusted	6.21 (5.46- 7.06), <0.001		3.99 (3.59- 4.43), <0.001		2.92 (2.64- 3.22), <0.001	
Gastric Band		249	492	249	492	249	492
Outcome events, n (%)		143 (57.43)	140 (28.46)	186 (74.70)	235 (47.76)	211 (84.74)	308 (62.60)
Person-years		652.74	2075.4	450.23	1644.53	303.48	1221.87
Crude Incidence Rate*		219.08	67.46	413.12	142.9	695.27	252.07
Follow-up years, Median (IQR)		1.5 (0.6- 4.1)	3.6 (1.4- 6.5)	0.8 (0.4- 2.1)	2.5 (0.7- 5.6)	0.6 (0.3- 1.2)	1.2 (0.5- 3.8)
HR (95% CI), p-value	Unadjusted	2.87 (2.26- 3.62), <0.001		2.38 (1.96- 2.89), <0.001		2.12 (1.77- 2.53), <0.001	
	Adjusted	3.50 (2.72- 4.49), <0.001		2.59 (2.11- 3.18), <0.001		2.27 (1.89- 2.72), <0.001	
Sleeve Gastrectomy		255	497	255	497	255	497
Outcome events, n (%)		173 (67.84)	93 (18.71)	209 (81.96)	195 (39.24)	220 (86.27)	279 (56.14)
Person-years		316.27	1435.30	212.16	1135.16	172.05	869.38
Crude Incidence Rate*		546.99	64.79	985.12	171.8	1278.68	320.92
Follow-up years, Median (IQR)		0.6 (0.3- 1.2)	2.3 (1.0- 4.4)	0.5 (0.2- 0.9)	1.6 (0.6- 3.3)	0.4 (0.2- 0.7)	1 (0.4- 2.4)
HR (95% CI), p-value	Unadjusted	6.55 (5.06- 8.47), <0.001		4.35 (3.56- 5.33), <0.001		3.04 (2.53- 3.65), <0.001	
	Adjusted	8.29 (6.29- 10.92), <0.001		4.77 (3.84- 5.922), <0.001		3.12 (2.56- 3.78), <0.001	
Gastric bypass		610	1206	610	1206	610	1206
Outcome events, n (%)		418 (68.52)	267 (22.14)	494 (80.98)	505 (41.87)	538 (88.20)	680 (56.38)
Person-years		797.77	3850.68	553.68	3058.41	423.93	2345.38
Crude Incidence Rate*		523.96	69.34	892.21	1165.12	1269.07	289.93
Follow-up years, Median (IQR)		0.6 (0.3- 1.5)	2.7 (1.7- 4.9)	0.4 (0.2- 0.9)	1.7 (0.6- 3.9)	0.4 (0.2- 0.7)	1.1 (0.4- 2.9)
HR (95% CI), p-value	Unadjusted	5.71 (4.88- 6.68), <0.001		4.04 (3.55- 4.60), <0.001		3.25 (2.89- 3.66), <0.001	
	Adjusted	7.32 (6.19- 8.66), <0.001		4.98 (4.33- 5.73), <0.001		3.69 (3.26- 4.19), <0.001	

IRR= Crude Incidence Rate/1000 person-years; HR= Hazard ratio

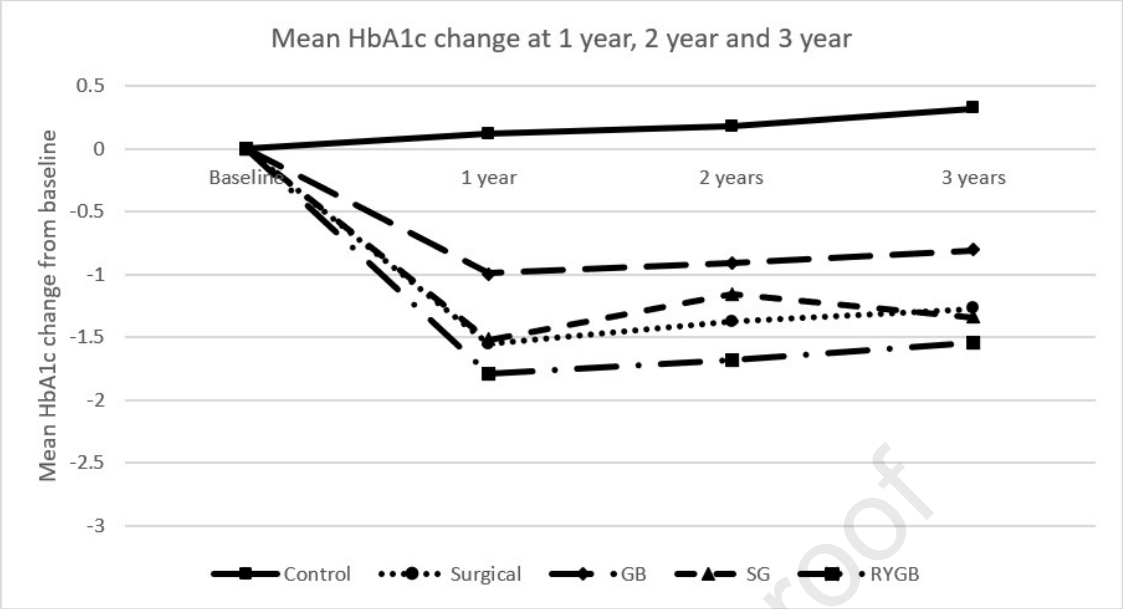
Adjusted for age, sex, baseline BMI, ethnicity, Townsend quintile, baseline HbA1c, diabetes duration and insulin us

Table 3: Change in glucose lowering medications before and after index date in surgical and control groups.

	Surgical		Control	
	Before N (%)	After N (%)	Before N (%)	After N (%)
Metformin	1024 (90.94)	683 (60.66)	1863 (83.96)	1881 (84.77)
Glitazones	332 (29.48)	67 (5.95)	547 (24.65)	373 (16.81)
Glinides	26 (2.31)	4 (0.36)	38 (1.71)	8 (0.36)
Sulphonylurea	475 (42.18)	160 (14.21)	852 (38.40)	904 (40.74)
Acarbose	31 (2.75)	8 (0.71)	32 (1.44)	14 (0.63)
DPP4 inhibitor	178 (15.81)	102 (9.06)	325 (14.65)	641 (28.89)
SGLT2 inhibitor	53 (4.71)	71 (6.31)	70 (3.15)	352 (15.86)
GLP-1 agonist	288 (25.58)	109 (9.68)	270 (12.17)	512 (23.07)
Insulin	270 (23.98)	136 (12.08)	315 (14.20)	429 (19.33)
No treatment	88 (7.82)	388 (34.46)	326 (14.69)	217 (9.78)



Surgical (N)				Control (N)			
Baseline	at 1 year	at 2 years	at 3 years	Baseline	at 1 year	at 2 years	at 3 years
1117	699	571	442	2184	1444	1245	1024



	Baseline (N)	1 year (N)	2 years (N)	3 years (N)
Control	2184	1427	1231	1009
Surgical	1117	698	571	441
GB	246	168	144	139
SG	254	151	117	83
RYGB	605	373	305	217