

Original article

Glycemic outcomes in patients with type 2 diabetes after bariatric surgery compared with routine care: a population-based, real-world cohort study in the United Kingdom

Pushpa Singh, Ph.D.^{a,b}, Nicola J. Adderley, Ph.D.^c, Anuradha Subramanian, M.Sc.^c,
Krishna Gokhale, M.Sc.^c, Jonathan Hazlehurst, Ph.D.^{a,b}, Rishi Singhal, M.D.^d,
Srikanth Bellary, M.D.^{b,e}, Abd A. Tahrani, Ph.D.^{a,b,f}, Krishnarajah Nirantharakumar, Ph.D.^{b,c,g,*}

^aInstitute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom

^bDepartment of Diabetes and Endocrinology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

^cInstitute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom

^dDepartment of Surgery, University Hospitals Birmingham, NHS Foundation Trust, Birmingham, United Kingdom

^eSchool of Life and Health Sciences, Aston University, Birmingham, United Kingdom

^fCentre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, United Kingdom

^gMidlands Health Data Research, Birmingham, United Kingdom

Received 5 April 2022; accepted 1 August 2022

Abstract

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

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

Setting and Methods: This was a retrospective, matched, controlled cohort study conducted between January 1, 1990, and January 31, 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: A total of 1126 patients in the surgical group and 2219 patients in the control group were analyzed. Mean (standard deviation) age was 50.0 (9.3) years, 67.6% were women, baseline glycosylated hemoglobin (HbA1C) was 7.8% (1.7 mmol/mol), and diabetes duration was 4.7 years (range, 2.0–8.4 years). Over a median (interquartile range) follow-up of 3.6 years (1.7–5.9 years), a higher proportion of patients in the surgical group achieved an HbA1C of $\leq 6.0\%$ than the control group (65.8% versus 22.8%). The surgical group showed a decrease in mean HbA1C of 1.5% (95% confidence interval [CI]: 1.4%–1.7%), 1.4% (1.2%–1.5%), and 1.3% (1.1%–1.5%) at 1-, 2-, and 3-year follow-up, respectively, whereas HbA1C increased in the control group. 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%).

Conclusion: BS is associated with significant improvement in glycemic control, achievement of normal HbA1C levels, and reduced need for glucose-lowering therapy in patients with

Abd A. Tahrani and Krishnarajah Nirantharakumar contributed equally to this article.

*Correspondence: Krishnarajah Nirantharakumar, Institute of Applied Health Research, University of Birmingham, Birmingham B15 2TT, United Kingdom.

E-mail address: K.Nirantharan@bham.ac.uk (K. Nirantharakumar).

T2D. (Surg Obes Relat Dis 2022;18:1366–1377.) © 2022 American Society for Metabolic and Bariatric Surgery. Published by Elsevier Inc. All rights reserved.

Keywords:

Bariatric surgery; Obesity; Diabetes; Glycemic; HbA1C; Weight; Glucose-lowering medications; adult

Improving glycemic control and achieving diabetes remission are important treatment aims in patients with type 2 diabetes (T2D). A 1% (11 mmol/mol) reduction in glycosylated hemoglobin (HbA1C) level is associated with a 21% decrease in deaths related to diabetes, a 14% decrease in myocardial infarctions, and a 37% decrease in the risk of microvascular complications over a median of 10 years of follow-up [1]. Reduction in HbA1C also has been associated with a 24% decrease in annual average healthcare cost in the first year and a 17% decrease in the second year compared with patients who did not achieve HbA1C reduction [2].

Despite the development of several new classes of glucose-lowering agents, only half of patients with T2D achieve HbA1C targets of $<7.0\%$ (53 mmol/mol), and 64% are estimated to be achieving individualized glycemic targets [3]. From the annual National Diabetes Audit (NADIA) in the United Kingdom (UK), the percentage of patients achieving an HbA1C level of $\leq 7.5\%$ (58 mmol/mol) was 65.8% in 2011–2012 and 66.8% in 2017–2018 [4]. Hence, further treatment strategies to improve the achievement of glycemic targets are needed. Weight loss is an important treatment strategy that can have a significant impact on glycemic control, as shown by the Diabetes Remission Clinical Trial (DiRECT) and the LookAHEAD Trial, which used a very low-energy diet and intensive lifestyle interventions (including meal replacement), respectively [5,6].

Bariatric surgery (BS) is the most successful intervention resulting in long-term weight loss in patients with severe obesity [7,8]. Several randomized controlled trials (RCTs) have shown that BS in people with T2D is associated with significant improvements in glycemic control, reduction in insulin requirements and glucose-lowering treatments, and diabetes remission [9–11]. However, the uptake and accessibility of BS in patients with T2D remain low; in Europe, the number of bariatric surgeries per 1 million population was only 72 in Germany and 117 in England [12,13]. Hence it is important to examine the impact of BS on glycemic outcomes in a real-world setting, especially given that real-world studies have shown that BS is associated with a reduction in incident cardiovascular disease, microvascular complications, and mortality in patients with and without T2D [14,15].

Here we report the impact of BS on glycemic control and the use of glucose lowering medications in patients with obesity and T2D who underwent BS compared with routine care in a real-world UK setting.

Methods*Study design and data source*

We conducted a retrospective cohort study between January 1, 1990, and January 31, 2018, using the IQVIA (quintiles and intercontinental marketing statistics company) Medical Research Data (IMRD-UK) database. General practices (primary care) from across the UK that use the Vision Electronic Health Records Software (Surgical Information Systems, Inc, Alpharetta, Georgia) contribute data to IMRD. It uses deidentified data of more than 15 million patients collected as a part of its 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 T2D, because the QOF scheme incentivizes primary care physicians for identification and management of these conditions and so that they are well recorded [17].

Practices were eligible for inclusion from 1 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 1 year were eligible for inclusion to ensure completeness of data.

Study population

We have used this data set previously to assess the impact of BS on the incidence of diabetes-related microvascular complications in patients with obesity and T2D [15]. A participant selection flowchart was presented as Supplementary Fig. 1 in that article [15]. Included were patients aged 18–75 years with T2D. The surgical cohort was defined as patients with T2D and a subsequent record of primary BS (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 (patients with T2D who did not undergo BS) within the same general practice for age (± 2 years), sex, body mass index (BMI, ± 2 kg/m²), and diabetes duration (± 3 years). The date of BS was assigned as the index date for exposed patients and the same date was assigned as the index date for their

matched control individuals in order to minimize immortal time bias [19].

Patients in the surgical group along with their control individuals were excluded from the study if they met any of the following criteria at baseline: BMI $<30 \text{ kg/m}^2$, age >75 years, prior record of gastric cancer, and prior record of gastric balloon/endobarrier/revisional BS. Eligible participants were followed up from the index date until the earliest occurrence of the following end points: (1) patient left the practice; (2) the practice ceased contributing to the database; (3) the patient died; and (4) the study reached its end date (January 31, 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 maintenance of glycemic targets, defined as an HbA1C of $\leq 6.0\%$ (42 mmol/mol), $\leq 6.5\%$ (48 mmol/mol), and $\leq 7\%$ (53 mmol/mol) [9,20], irrespective of the baseline HbA1C and use of glucose lowering medication; and (3) number and type of glucose-lowering medications used after bariatric surgery. We also assessed percentage weight loss in the surgical and control groups.

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 the index date because HbA1C measurements within 28 days of surgery may be the result of the 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 a target HbA1C, we used Cox proportional hazards regression analysis and calculated unadjusted and adjusted hazard ratios (HRs) among patients who underwent BS compared to their matched control individuals for each of the 3 glycemic targets. We assessed achieving or maintaining glycemic targets of $\leq 7\%$ (53 mmol/mol), $\leq 6.5\%$ (48 mmol/mol), and $\leq 6\%$ (42 mmol/mol) based on the earliest date after the index date irrespective of baseline HbA1C and use of glucose-lowering medications, as per the recommendations by American Diabetes Association, National Institute for Health and Care Excellence, and studies examining diabetes remission after BS [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 BS they underwent. We did not perform an analysis in the DS subgroup because of the small numbers.

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

We also assessed the number of glucose-lowering medications before and after BS in the surgical and control groups. The number of glucose-lowering medications was categorized as no medication, monotherapy (1 medication), dual therapy (2 medications), and polypharmacy (≥ 3 medications).

Percentage weight loss (%WL) was calculated as change in weight (postoperative weight defined as [latest available data after the index date – baseline weight]/baseline weight $\times 100$). For the control group (which had no surgery), weight change was calculated using a similar formula.

A 2-tailed *P* value $<.05$ was considered statistically significant. All analyses were conducted using Stata version 15 (StataCorp LLC, College Station, Texas).

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 categorized as $<35 \text{ kg/m}^2$, $35\text{--}40 \text{ kg/m}^2$, and $>40 \text{ kg/m}^2$. Social deprivation status was represented by the Townsend deprivation quintile, which is based on material deprivation within a population [21]. Ethnicity was categorized 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.

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 (reference number 18THIN097). IMRD-UK incorporates data from The Health Improvement Network (THIN) and the Cegedim SA Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used deidentified data provided by patients as a part of their routine primary care.

Results

Baseline characteristics

The baseline characteristics of the 3345 participants included are summarized in Table 1. For the whole cohort,

the mean age was 50 years (9.3 years). Two thirds of the participants in the study (67.59%) were female. Baseline HbA1C was available for 1117 patients (99.2%) in the surgical group and 2184 patients (98.4%) in the control group. The mean baseline HbA1C was similar in both groups (7.8%), but a higher proportion of participants in the surgical group was prescribed insulin compared with the control group (270 patients [23.98%] versus 315 patients [14.20%]). The median (IQR) follow-up was 3.4 years (range, 1.6–5.6 years) in the surgical group and 3.7 years (range, 1.7–6.1 years) in the control group. Of the 1126 patients in the surgical group, 249 (22.1%), 255 (22.7%), 610 (52.2%), and 12 (1.1%) had GB, SG, RYGB, and DS, respectively.

Mean HbA1C and change in glycemic status

At 1 year from the index date, mean (standard deviation) HbA1C in the surgical group ($n = 699$) and control

group ($n = 1444$) was 6.3% (1.3%) versus 7.9% (1.8%), respectively. In the surgical group, there was a mean reduction in HbA1C of 1.5% (95% confidence interval [CI]: 1.7%–1.4%), whereas in the control group, there was a small increase in HbA1C of .1% (95% CI: .0%–.2%), resulting in a difference in mean change between groups of 1.7% (95% CI: 1.5%–1.8%) favoring the surgical group.

Participants who underwent surgical procedures achieved greater HbA1C reductions at 1 year than their matched control patients, with a difference in mean HbA1C change of 1.0% (95% CI: .7%–1.3%) in GB, 1.6% (95% CI: 1.3%–1.9%) in SG, 2.0% (95% CI: 1.7%–2.2%) in RYGB, and 3.2% (95% CI: .8%–5.6%) in DS compared with their respective control groups.

Reduction in HbA1C observed in the surgical group was maintained at 2 and 3 years, whereas an increase in HbA1C was noted in control group, with a difference in mean change of 1.5% (95% CI: 1.4%–1.7%) at 2 years

Table 1
Baseline characteristics of participants in the surgical group and the control (nonsurgical) group

Characteristic	Surgical group	Control group
Population, n	1126	2219
Age (yr), mean (SD)	49.87 (9.3)	50.12 (9.3)
Age categories (yr), n (%)		
<41	171 (15.19)	329 (14.83)
41–60	803 (71.31)	1568 (70.66)
61–maximum	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 (.27)	6 (.27)
Ethnicity, n (%)		
White	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 (.62)	10 (.45)
Other	2 (.18)	9 (.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 (yr), median (IQR)	4.7 (2.1–8.9)	4.6 (1.9–8.1)
HbA1C, %	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)

BMI = body mass index; SD = standard deviation.

and 1.6% (95% CI: 1.4%–1.8%) at 3 years in favor of surgery. Above results are summarized in Fig. 1.

Achieving glycemic targets

At baseline, 132 patients (11.72%) in the surgical group and 219 patients (9.87%) in the control group had an HbA1C $\leq 6.0\%$ (42 mmol/mol). Over the median (interquartile range [IQR]) follow-up of 1.8 years (.6–4.3 years), 741 patients (65.8%) in the surgical group versus 506 patients (22.8%) in the control group achieved an HbA1C of $\leq 6.0\%$. Compared with the control group, patients who had surgery were significantly more likely to achieve and maintain an HbA1C $\leq 6\%$ (adjusted HR = 5.86; 95% CI: 5.19%–6.60%; $P < .001$; Table 2). All surgical procedures were associated with higher HRs of achieving a target HbA1C of $\leq 6.0\%$ (42 mmol/mol) compared with the control group (Table 2). Analyzing by insulin status showed similar results (Table 2).

Before the index date, 328 patients (29.13%) in the surgical group and 540 patients (24.34%) in the control group had an HbA1c of $\leq 6.5\%$, and 483 patients (42.9%) in the surgical group and 861 patients (38.81%) in the control group had an HbA1C of $\leq 7.0\%$. Over our study period, achieving or maintaining a target HbA1C of $\leq 6.5\%$ and $\leq 7.0\%$ 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 percentages of patients on insulin (24.0% versus 14.2%) and on GLP-1RA (25.6% versus 12.2%) were higher in the surgical group than in the control group. This observation could be a reflection of the closer follow-up provided to patients under weight management service. There were 88 patients (7.8%) in the surgical group versus 326 patients (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, whereas in the control group it increased from 85.3% at baseline to 90.2% during the same period.

In the surgical group, the percentage of patients taking metformin, sulfonylurea, DPP4 inhibitors, GLP-1RAs, and insulin decreased after the intervention compared with baseline. In the control group, the percentage of patients taking metformin, sulfonylurea, and insulin increased, with a significant increase in DPP4 inhibitors and GLP-1RAs. There was a reduction in the use of thiazolidinediones, glinides, and acarbose and an increase in the use of SGLT2 inhibitors in both groups during the study period.

The percentages of patients on no medication, monotherapy, dual therapy, and polytherapy were similar in

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

Change in weight

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

A greater weight reduction was noted in the surgical group compared with their matched control patients for all surgical procedures: mean %WL for GB, 14.6% (95% CI: 12.8%–16.3%) versus 4.6% (95% CI: 3.6%–5.5%); for SG, 20.6% (95% CI: 19.1%–22.1%) versus 4.2% (95% CI: 3.2%–5.2%); for RYGB, 25.0% (95% CI: 24.0%–25.9%) versus 4.8% (95% CI: 4.2%–5.3%); and for DS, 21.2% (95% CI: 14.5%–28.1%) versus 1.7% (95% CI: 2.7%–6.0%). Similarly, a greater weight reduction was noted in both insulin users and those not using insulin in the surgical group versus the control group: %WL for insulin users, 22.6% (95% CI: 21.2%–24.1%) versus 4.1% (95% CI: 2.8%–5.4%), and for non insulin users, 21.3% (95% CI: 20.4%–22.2%) versus 4.6% (95% CI: 4.2%–5.1%).

Discussion

Our study provides real-world evidence of the superior effect of BS in people with T2D and obesity. In our study, we found that patients undergoing BS were more likely to meet glycemic targets with fewer glucose-lowering medications and achieve greater weight loss over a median (IQR) follow-up of 3.6 years (1.7–5.9 years) compared with those receiving routine care. These results occurred within the context of higher insulin prescriptions at baseline in the surgical group. The higher percentage of participants on insulin in the surgical group could be a reflection of disease severity in the 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 T2D and their caregivers and multidisciplinary healthcare professionals [22]. Diabetes remission in the context of intensive lifestyle interventions has been investigated in several studies. The DiRECT study using an integrated, structured weight management program based on a low-calorie diet showed a

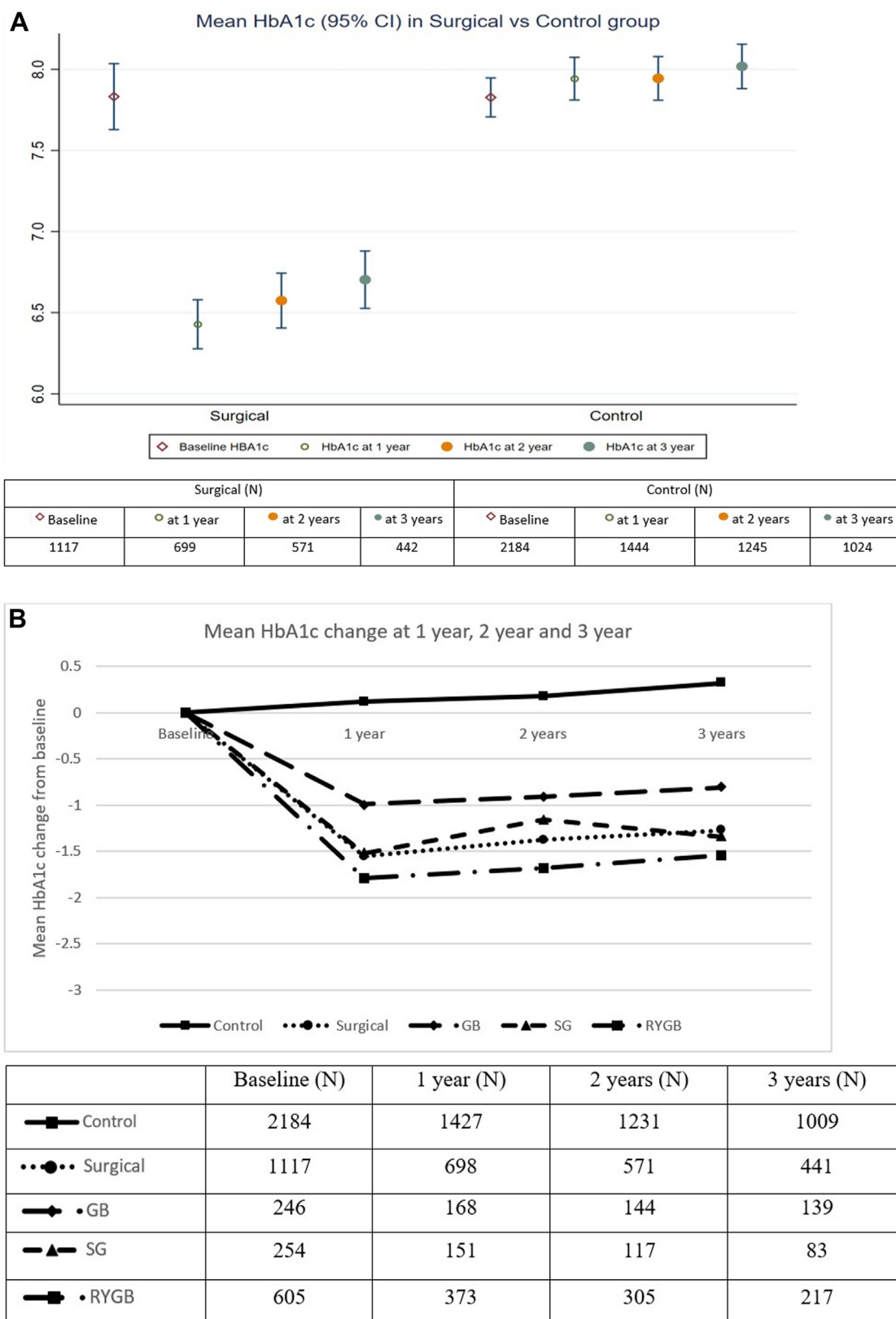


Fig. 1. (A) Mean (standard deviation) HbA1C level in surgical group versus control group. (B) Mean HbA1C change from baseline in surgical group versus control group. GB = gastric band; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy.

Table 2
Achieving targeted HbA1C in the surgical group and the control group

Factor		HbA1C $\leq 6\%$ (42 mmol/mol)		HbA1C $\leq 6.5\%$ (48 mmol/mol)		HbA1c $\leq 7.0\%$ (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)		.7 (.3–1.9)	2.7 (1.1–5.1)	.5 (.3–1.1)	1.8 (.6–4.0)	.4 (.2–.8)	1.1 (.4–3.0)
HR (95% CI),	Unadjusted	4.90 (4.36–5.49), <.001		3.52 (3.21–3.87), <.001		2.85 (2.62–3.11), <.001	
	Adjusted	5.86 (5.19–6.60), <.001		3.94 (3.57–4.34), <.001		2.98 (2.73–3.26), <.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 (.5–3.7)	3.1 (1.1–5.4)	.8 (.3–2.5)	2.5 (.9–4.7)	.5 (.3–1.3)	1.6 (.6–4.0)
HR (95% CI),	Unadjusted	3.48 (2.50–4.86), <.001		3.54 (2.72–4.6), <.001		3.35 (2.68–4.20), <.001	
	Adjusted	3.98 (2.83–5.60), <.001		3.75 (2.87–4.90), <.001		3.55 (2.82–4.46), <.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)		.6 (.3–1.4)	2.7 (1.1–5.1)	.4 (.2–.8)	1.7 (.6–3.8)	.4 (.2–.7)	1 (.4–2.7)
HR (95% CI),	Unadjusted	5.88 (5.19–6.66), <.001		4.07 (3.67–4.51), <.001		3.09 (2.81–3.40), <.001	
	Adjusted	6.21 (5.46–7.06), <.001		3.99 (3.59–4.43), <.001		2.92 (2.64–3.22), <.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 (.6–4.1)	3.6 (1.4–6.5)	.8 (.4–2.1)	2.5 (.7–5.6)	.6 (.3–1.2)	1.2 (.5–3.8)
HR (95% CI),	Unadjusted	2.87 (2.26–3.62), <.001		2.38 (1.96–2.89), <.001		2.12 (1.77–2.53), <.001	
	Adjusted	3.50 (2.72–4.49), <.001		2.59 (2.11–3.18), <.001		2.27 (1.89–2.72), <.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)		.6 (.3–1.2)	2.3 (1.0–4.4)	.5 (.2–.9)	1.6 (.6–3.3)	.4 (.2–.7)	1 (.4–2.4)
HR (95% CI),	Unadjusted	6.55 (5.06–8.47), <.001		4.35 (3.56–5.33), <.001		3.04 (2.53–3.65), <.001	
	Adjusted	8.29 (6.29–10.92), <.001		4.77 (3.84–5.922), <.001		3.12 (2.56–3.78), <.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)		.6 (.3–1.5)	2.7 (1.7–4.9)	.4 (.2–.9)	1.7 (.6–3.9)	.4 (.2–.7)	1.1 (.4–2.9)
HR (95% CI),	Unadjusted	5.71 (4.88–6.68), <.001		4.04 (3.55–4.60), <.001		3.25 (2.89–3.66), <.001	
	Adjusted	7.32 (6.19–8.66), <.001		4.98 (4.33–5.73), <.001		3.69 (3.26–4.19), <.001	

IQR = interquartile range; HR = hazard ratio; CI = confidence interval.

*IRR = Crude incidence rate = Rate per 1000 person years, adjusted for age, sex, baseline body mass index, ethnicity, Townsend quintile, baseline HbA1C, diabetes duration, and insulin use.

diabetes remission rate of 36% over 2 years based on a diabetes remission definition of an HbA1C level $\leq 6.5\%$ (48 mmol/mol) without glucose-lowering agents [23]. The LookAHEAD study defined diabetes remission (partial or

complete remission) as transition from meeting diabetes criteria to a prediabetes or nondiabetic level of glycemia (fasting plasma glucose <126 mg/dL and HbA1C $\leq 6.5\%$ and off glucose-lowering medication). The study reported

Table 3
Change in glucose-lowering medications before and after index date in the surgical group and the control group

Medication	Surgical group		Control group	
	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 (.36)	38 (1.71)	8 (.36)
Sulfonylurea	475 (42.18)	160 (14.21)	852 (38.40)	904 (40.74)
Acarbose	31 (2.75)	8 (.71)	32 (1.44)	14 (.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 receptor 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)

DPP4 = dipeptidyl peptidase 4; SGLT2 = sodium-glucose transporter 2; GLP-1 = glucagon-like peptide 1.

a remission rate of 7.3% (95% CI: 6.2%–8.4%) at 4 years of follow-up using an intensive lifestyle intervention [6]. While the results from these studies are highly encouraging, the remission rates reported following BS procedures are far greater. A meta-analysis of 8 RCTs found that BS achieved a higher remission rate than a nonsurgical intervention with risk ratios of 5.41 (95% CI: 2.47–11.85) over 1–2 years of follow-up and 8.36 (95% CI: 2.71–25.85) over 3–5 years of follow-up [24]. A systematic review of RCTs comparing BS versus nonsurgical treatments concluded that the chance of diabetes remission was 22 times greater in the surgical group than in the control group, with a relative risk of 22.1 (95% CI: 3.2–154.3) in a complete case analysis [25]. An RCT reported a significant reduction in the use of glucose-lowering medications including insulin in the

surgical group compared with the medical group over 5 years of follow-up [9]. A population-based cohort study included 3674 surgical patients and 1335 nonsurgical patients. Over 6 years of follow-up, 50% of patients in the surgical group were on no glucose-lowering medications, and they were 6 times less likely to be on insulin treatment than the nonsurgical patients [26].

Our results support these findings and show that achieving an HbA1C in the normoglycemic range is possible (for more than half of patients) within a real-world setting with BS, whereas this was not observed in the routine-care group using pharmacotherapy. Insulin use has been shown to be a predictor of poorer glycemic outcomes and diabetes remission in post-BS patients [27]. Despite higher insulin user in BS patients at baseline in

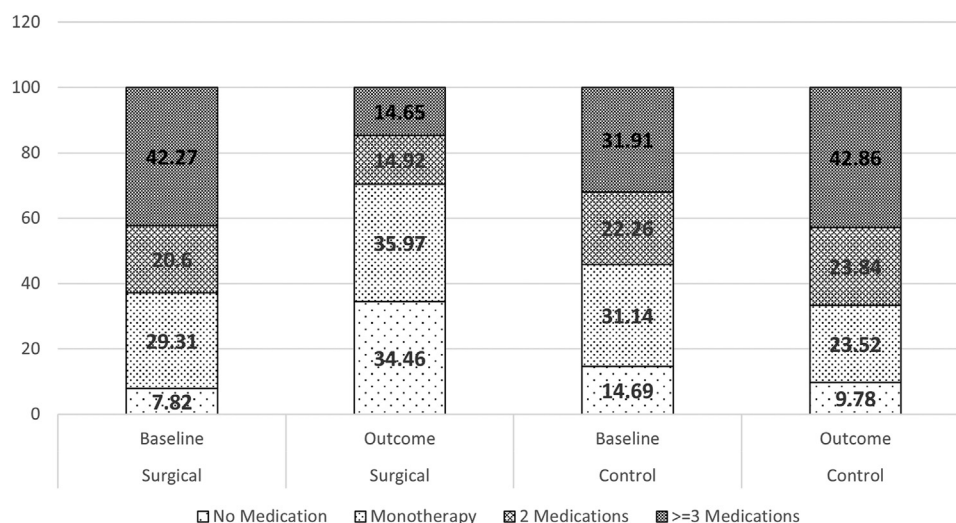


Fig. 2. Percentage of patients on glucose-lowering medications before and after the index date (pre- and postoperatively) in the surgical group and the control group.

our study, more patients managed to achieve targeted glycemic control in surgical group than in the routine-care group.

In our study, 70.3% and 79.9% of patients in the surgical group achieved an HbA1C of $\leq 6.5\%$ and $\leq 7.0\%$, 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 the SG and GB groups. RYGB and SG are the 2 commonly performed BS procedures, and their beneficial impact on glycemic 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 glycemic outcomes. A prospective study conducted on 18 RYGB patients and 15 SG patients analyzed the glycemic effect over 12 months of follow-up [28]. The study reported that the effect on glycemic control was similar in both group at follow-ups of 2 days, 3 weeks, and 1 year [28]. However, few other systematic reviews found similar result as ours. A systematic review identified 10 RCTs involving 705 patients with T2D who had RYGB or SG with follow-ups of 1–5 years [29]. A meta-analysis of these studies found that the rate of diabetes remission was higher in patients undergoing RYGB compared with SG with relative risks of 1.20 (95% CI: 1.00–1.45; $P = .047$) in studies with 1 year of follow-up and of 1.06 (95% CI: .94–1.20; $P = .34$) in studies with 2–5 years of follow-up [29]. Another systematic review and meta-analysis of 10 RCT involving 778 patients with T2D allocated to RYGB or SG and at least 12 months of follow-up found that RYGB was associated with a higher likelihood of achieving diabetes remission compared with SG at 1 and 5 years of follow-up with relative risks of 1.34 and 1.18, respectively [30].

The proportion of patients achieving the targeted HbA1C was higher in our study than in those RCTs [9,10]. These differences could be because 29.1% and 42.9% of patients in our study had HbA1C levels $\leq 6.5\%$ and $\leq 7.0\%$, respectively, at baseline, whereas all patients in both the RCTs [9,10] had HbA1C levels $> 7.0\%$. Good glycemic status in the surgical group was noted despite being on fewer glucose-lowering medications. The percentages of patients on SGLT2 inhibitors and on GLP1-RA medication decreased in the surgical group in the postoperative period. An RCT by Miras et al. [31] (GRAVITAS [GLP-1 Receptor Agonist Intervention for Poor Responders after Bariatric Surgery]) showed the adjuvant effect of liraglutide on diabetes management in patients who underwent RYGB or SG. Patients on liraglutide managed to achieve reductions in HbA1C and weight over 26 weeks of follow-up [31]. Continuation of GLP1-RA and SGLT2 inhibitor medications in the surgical group could have resulted in further reduction in HbA1C and better outcomes. We also noted that 22.8%, 42.63%, and 57.82% patients in the control group managed to achieve and/or maintain the target HbA1C levels of 6.0%, 6.5%, and 7.0% respectively. This

could be the result of increasing use of newer medications in general. In our study cohort, the percentage of patients in the control group receiving a prescription for GLP1-RA increased from 12.17% to 23.07%, and those receiving an SGLT2 inhibitor increased from 3.15% to 15.86% over the study period.

In our study, we found that all classes of medications were used after BS (most commonly, metformin and sulfonylurea). The use of sulfonylurea is surprising, considering its impact on weight and hypoglycemia. It is possible that the continued use of sulfonylurea is driven by national guidelines for the management of T2D that are not specific to the post-BS situation [32]. The effect of BS on glycemic status is well evidenced in clinical studies. However, the guidance on choice and titration of glucose-lowering medications after BS is currently not well defined [33,34]. The clinical practice guideline for the management of patients undergoing BS published 2019 recommends discontinuation of all insulin secretagogues such as sulfonylurea and meglitinides, SGLT2 inhibitors, and thiazolidinediones and reduction in insulin dose in the immediate postoperative period [34]. Metformin and/or incretin-based therapies have been advised for glycemic management in the immediate postoperative period [34]. Use of a rapid-acting insulin analogue before meals and a long-acting insulin analogue administered subcutaneously also has been recommended for achieving glycemic targets in the postoperative period [34]. However, guidance on long-term residual diabetes management is lacking.

The mechanism behind glycemic improvement after BS is complex and incompletely understood. The likely mechanisms include changes in beta-cell function, insulin sensitivity, gluconeogenesis, glucose uptake and use in peripheral organs driven by neurohormonal changes in the gut–brain axis, and weight loss. Weight loss leads to reductions in ectopic fat in the pancreas, liver, and muscle that could contribute to improvement in insulin sensitivity [35]. BS has been associated with changes in hormones [36], bile acid metabolism, gut microbiome, taste and smell senses [37], intestinal enteroplasticity, and vagus nerve function [35,38] that contribute in creating a low-calorie-absorption environment and good glycemic control.

Limitations and strengths

Our findings should be interpreted within certain limitations. The IMRD-UK database is a validated primary care data source that has 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 with other studies, our study had a shorter period of follow-up. This limited our ability to look at outcomes beyond 5 years. In contrast, our study looked at

real-world data, and the large sample size allowed us to explore the effect in different types of BS. Further, our study included patients with T2D on insulin as well as nonusers of insulin, thus enabling us to analyze the outcomes in these 2 groups separately. The findings of our study add to the growing evidence of the beneficial impact of BS on glycaemic status and the use of glucose-lowering medications.

Conclusion

Bariatric surgery was associated with a large reduction in HbA1C in patients with T2D and obesity compared with patients undergoing routine care. It also was associated with a reduction in polypharmacy. BS is an effective treatment for patients with T2D and obesity and can result in achieving HbA1C levels in the normoglycemic range. Given the findings of this study, it is apparent that the increased use of BS for those who are eligible can be seen to reduce the burden of T2D.

Disclosures

K. Nirantharakumar received funding from AstraZeneca, United Kingdom (RSBD20464) and reports fees from Sanofi, United States and Boehringer Ingelheim outside the submitted work. A.A. Tahrani reports grants from Novo Nordisk, personal fees from Novo Nordisk, nonfinancial support from Novo Nordisk, personal fees from Eli Lilly, nonfinancial support from Eli Lilly, personal fees from Janssen, personal fees from AstraZeneca, nonfinancial support from AstraZeneca, nonfinancial support from Impeto Medical, nonfinancial support from Resmed, nonfinancial support from Aptiva, personal fees from Boehringer Ingelheim, nonfinancial support from Boehringer Ingelheim, personal fees from Bristol Myers Squibb, nonfinancial support from Bristol Myers Squibb, personal fees from Napp Pharmaceuticals, nonfinancial support from Napp Pharmaceuticals, personal fees from Merck Sharp & Dohme, nonfinancial support from Merck Sharp & Dohme, personal fees from Nestle, personal fees from Gilead, United Kingdom, grants from Sanofi, and personal fees from Sanofi outside the submitted work. A.A. Tahrani is currently an employee of Novo Nordisk. This work was performed before A.A. Tahrani had become a Novo Nordisk employee, and Novo Nordisk had no role in this project. S. Bellary has received consultation and/or lecture fees from Sanofi Aventis, Astra Zeneca, Eli Lilly, Boehringer Ingelheim, Napp Pharmaceuticals, and Merck Sharp & Dohme and grants and personal fees from Novo Nordisk Ltd, Denmark. outside the submitted work. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

IMRD is a registered trademark of Cegedim SA in the United Kingdom and other countries. References made to the IMRD database is intended to be descriptive of the data asset licensed by IQVIA.

References

- [1] Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321(7258):405–12.
- [2] Bansal M, Shah M, Reilly B, Willman S, Gill M, Kaufman FR. Impact of reducing glycated hemoglobin on healthcare costs among a population with uncontrolled diabetes. *Appl Health Econ Health Policy* 2018;16(5):675–84.
- [3] Edelman SV, Polonsky WH. Type 2 diabetes in the real world: the elusive nature of glycemic control. *Diabetes Care* 2017;40(11):1425–32.
- [4] NHS Digital. National diabetes audit, 2016–17. Report 1: care processes and treatment targets [Internet]. 2018 Mar 14 [cited 2020 Feb 1];[42 p.]. Available from: <https://www.hqip.org.uk/wp-content/uploads/2018/03/National-Diabetes-Audit-2016-17-Report-1-Care-Processes-and-Treatment-T....pdf>. Accessed February 1, 2020.
- [5] Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;391(10120):541–51.
- [6] Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012;308(23):2489–96.
- [7] O'Brien PE, Hindle A, Brennan L, et al. Long-term outcomes after bariatric surgery: a systematic review and meta-analysis of weight loss at 10 or more years for all bariatric procedures and a single-centre review of 20-year outcomes after adjustable gastric banding. *Obes Surg* 2019;29(1):3–14.
- [8] Golzarand M, Toolabi K, Farid R. The bariatric surgery and weight losing: a meta-analysis in the long- and very long-term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults. *Surg Endosc* 2017;31(11):4331–45.
- [9] Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes: 5-year outcomes. *N Engl J Med* 2017;376(7):641–51.
- [10] Mingrone G, Guidone C, Iaconelli A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5-year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 2015;386(9997):964–73.
- [11] Courcoulas AP, Belle SH, Neiberg RH, et al. Three-year outcomes of bariatric surgery vs lifestyle intervention for type 2 diabetes mellitus treatment: a randomized clinical trial. *JAMA Surg* 2015;150(10):931–40.
- [12] Borisenko O, Colpan Z, Dilleman B, Funch-Jensen P, Hedenbro J, Ahmed AR. Clinical indications, utilization, and funding of bariatric surgery in Europe. *Obes Surg* 2015;25(8):1408–16.
- [13] Dixon JB. Regional differences in the coverage and uptake of bariatric-metabolic surgery: a focus on type 2 diabetes. *Surg Obes Relat Dis* 2016;12(6):1171–7.
- [14] Singh P, Subramania A, Adderley N, et al. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population-based cohort study. *Br J Surg* 2020;107(4):432–42.
- [15] Singh P, Adderley N, Subramanian A, et al. The impact of bariatric surgery on incident microvascular complications in patients with type 2 diabetes: a matched controlled population-based retrospective cohort study. *Diabetes Care* 2021;44(1):116–24.
- [16] IQVIA [Internet]. c2018-22 [2019; cited 2019 Dec 3]. THIN-HES privacy notice. Available from: <https://www.iqvia.com/locations/united-kingdom/information-for-members-of-the-public/medical-research-data>. Accessed September 29, 2020.
- [17] Doran T, Fullwood C, Gravelle H, et al. Pay-for-performance programs in family practices in the United Kingdom. *N Engl J Med* 2009;355(4):375–84.

- [18] Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf* 2009;18(1):76–83.
- [19] Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010;340:b5087.
- [20] American Diabetes Association. Standards of medical care in diabetes—2020. *J Clin Appl Res Educ* 2019;38(1):10–38.
- [21] Townsend P, Phillimore P, Beattie A. Health and deprivation. *Nurs Stand* 1988;2(17):34.
- [22] Finer S, Robb P, Cowan K, Daly A, Robertson E, Farmer A. Top ten research priorities for type 2 diabetes: results from the Diabetes UK–James Lind Alliance Priority Setting Partnership. *Lancet Diabetes Endocrinol* 2017;5(12):935–6.
- [23] Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;7(5):344–55.
- [24] Wu GZ, Cai B, Yu F, et al. Meta-analysis of bariatric surgery versus non-surgical treatment for type 2 diabetes mellitus. *Oncotarget* 2016;7(52):87511–22.
- [25] Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013;347:f5934.
- [26] Imtiaz R, Doumouras AG, Hong D, Anvari M, Shah BR. Long-term impact of bariatric surgery on glycemic control and glucose-lowering therapy for people with type 2 diabetes: population-based cohort study. *Surg Obes Relat Dis* 2021;17(6):1049–56.
- [27] Singh P, Adderley NJ, Hazlehurst J, et al. Prognostic models for predicting remission of diabetes following bariatric surgery: a systematic review and meta-analysis. *Diabetes Care* 2021;44(11):2626–41.
- [28] Wallenius V, Dirinck E, Fändriks L, Maleckas A, Roux CW, Thorell A. Glycemic control after sleeve gastrectomy and Roux-En-Y gastric bypass in obese subjects with type 2 diabetes mellitus. *Obes Surg* 2018;28(6):1461–72.
- [29] Borgeraas H, Hofso D, Hertel JK, Hjelmestaeth J. Comparison of the effect of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 2020;21(6):e13011.
- [30] Castellana M, Procino F, Biacchi E, et al. Roux-en-Y gastric bypass vs sleeve gastrectomy for remission of type 2 diabetes. *J Clin Endocrinol Metab* 2021;106(3):922–33.
- [31] Miras AD, Pérez-Pevida B, Aldhwayan M, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019;7(7):549–59.
- [32] NICE, Guideline N. Type 2 diabetes in adults: management, NICE; 2017. Available from: <https://www.nice.org.uk/guidance/ng28>. Accessed November 8, 2017.
- [33] Thorell A, Hagström-Toft E. Treatment of diabetes prior to and after bariatric surgery. *J Diabetes Sci Technol* 2012;6(5):1226–31.
- [34] Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures—2019 update: cosponsored by the American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. *Surg Obes Relat Dis* 2020;16(2):175–247.
- [35] Wilson R, Aminian A, Tahrani AA. Metabolic surgery: a clinical update. *Diabetes Obes Metab* 2021;23(Suppl 1):63–83.
- [36] Pucci A, Batterham RL. Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different. *J Endocrinol Invest* 2019;42(2):117–28.
- [37] Zakeri R, Batterham RL. Potential mechanisms underlying the effect of bariatric surgery on eating behaviour. *Curr Opin Endocrinol Diabet Obes* 2018;25(1):3–11.
- [38] Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. *Diabetes Care* 2016;39(6):893–901.
- [39] Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. *BMJ* 2018;361:k1717.
- [40] Subramanian A, Adderley NJ, Tracy A, et al. Risk of incident obstructive sleep apnea among patients with type 2 diabetes. *Diabetes Care* 2019;42(5):954–63.
- [41] Caleyachetty R, Thomas GN, Toulis KA, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. *J Am Coll Cardiol* 2017;70(12):1429–37.

Editorial comment

Comment on: Glycemic outcomes in patients with type 2 diabetes after bariatric surgery compared with routine care: a population-based, real-world cohort study in the United Kingdom

Applications of interventions in the real world do not always have the same results as found initially in the controlled settings of clinical trials [1]. Multiple randomized studies have demonstrated that bariatric surgery is the most effective treatment for obesity and, moreover, leads to improvement and often resolution of type 2 diabetes [2]. Using a large primary care patient database, Singh et al. [3] examined real-world outcomes of bariatric surgery for type 2 diabetics in the United Kingdom. They find that bariatric surgery leads to superior diabetes outcomes compared with a nonsurgical cohort. With a median follow-up of just over 3 years, 66%

of patients who underwent bariatric surgery achieved a hemoglobin A1C (HbA1C) level of $\leq 6\%$ compared to 23% in the nonsurgical cohort. Furthermore, the percentage of patients on no glycemic medications increased from 8% to 33% after surgery, while the percentage of patients on no therapy declined from 15% to 10% in the nonsurgical control patients.

While not surprising, this study confirms that in a large population setting, bariatric surgery is a superior treatment for type 2 diabetes versus medical management, leading to metabolic improvements of similar magnitude to those