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;44:116–124 | https://doi.org/10.2337/dc20-0571

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OBJECTIVE

To assess the impact of bariatric surgery (BS) on incident microvascular complications of diabetes-related foot disease (DFD), sight-threatening diabetic retinopathy (STDR), and chronic kidney disease (CKD) in patients with type 2 diabetes and obesity.

RESEARCH DESIGN AND METHODS

A retrospective matched, controlled population-based cohort study was conducted of adults with type 2 diabetes between 1 January 1990 and 31 January 2018 using IQVIA Medical Research Data (IMRD), a database of primary care electronic records. Each patient with type 2 diabetes who subsequently had BS (surgical group) was matched on the index date with up to two patients with type 2 diabetes who did not have BS (nonsurgical group) within the same general practice by age, sex, preindex BMI, and diabetes duration.

RESULTS

Included were 1,126 surgical and 2,219 nonsurgical participants. In the study population 2,261 (68%) were women. Mean (SD) age was 49.87 (9.3) years vs. 50.12 (9.3) years and BMI was 46.76 (7.96) kg/m^2 vs. 46.14 (7.49) kg/m^2 in the surgical versus nonsurgical group, respectively. In the surgical group, 22.1%, 22.7%, 52.2%, and 1.1% of patients had gastric band, sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB), and duodenal switch, respectively. Over a median follow-up of 3.9 years (interquartile range 1.8–6.4), BS was associated with reduction in incident combined microvascular complications (adjusted hazard ratio 0.53, 95% CI 0.43–0.66, $P <$ 0.001), DFD (0.61, 0.50–0.75, $P <$ 0.001), STDR (0.66, 0.44–1.00, $P =$ 0.048), and CKD (0.63, 0.51–0.78, $P <$ 0.001). Analysis based on the type of surgery showed that all types of surgery were associated with a favorable impact on the incidence of composite microvascular complications, with the greatest reduction for RYGB.

CONCLUSIONS

BS was associated with a significant reduction in incident diabetes-related microvascular complications.

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Received 19 March 2020 and accepted 7 October 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.13075748.

K.N. and A.A.T. are joint senior authors and contributed equally to this manuscript.

This article is featured in a podcast available at https://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

The rising levels of obesity and type 2 diabetes are major global health challenges. Vascular complications (microvascular and macrovascular) are the major causes of morbidity and mortality in patients with type 2 diabetes (1,2).

Worldwide, the cost of health expenditures due to diabetes has increased from U.S. dollars (USD) 232 billion in 2007 to USD 727 billion in 2017 and is estimated to rise further to USD 825 billion by 2030. The major portion of direct cost in diabetes management is spent in managing diabetes-related complications and its consequences (2). The cost of diabetes management had been estimated to be 20 times more in patients with four or more diabetes-related complications compared with patients with diabetes with no complications (2). In the U.K., diabetes accounts for 10% of the National Health Service budget, and 80% of this expense is spent dealing with diabetes-related complications mainly due to prolonged hospital stay, cardiovascular disease (CVD), kidney disease, and neuropathy (3).

Despite improved clinical management of type 2 diabetes over the last two decades, including new classes of glucose-lowering medication (dipeptidyl peptidase 4 inhibitor, sodium–glucose cotransporter 2 [SGLT2] inhibitor, glucagon-like peptide 1 agonist), the reduction in microvascular complications is far less compared with the reductions observed in CVD (4). Diabetes-related foot disease (DFD) is the leading cause for nontraumatic lower limb amputation in the developed world (5), sight-threatening diabetic retinopathy (STDR) is a leading cause of blindness at younger age (6), and diabetic nephropathy is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (7).

Obesity is an established risk factor for type 2 diabetes, hypertension, and hyperlipidemia (8). In addition, obesity is an independent risk factor for CKD (9), peripheral neuropathy (10–12), CVD (13), and mortality (14). A number of studies have shown that intentional weight loss is associated with improvements in glycemic control, blood pressure, hyperlipidemia, and other vascular risk factors (15,16). Among the several interventions for the treatment of obesity, bariatric surgery (BS) provides the most significant and sustainable weight loss and has a favorable impact on glycemic control and other vascular risk factors (17–19). We recently showed that BS in patients with and without type 2 diabetes was associated with a reduction in incident hypertension, CVD, and all-cause mortality compared with routine care (20). Hence, it would be expected that BS may also reduce the incidence of microvascular complications in patients with type 2 diabetes.

Currently, the impact of BS on diabetes-related microvascular complications remains unclear. A meta-analysis of 10 studies (3 randomized controlled trials and 7 controlled studies) involving 17,532 patients found an overall reduction in the incidences of retinopathy and nephropathy, but not neuropathy, in the surgical arm compared with the nonsurgical arm, but there was heterogeneity in findings and in the definition of microvascular outcomes between the studies (21). Hence, there is lack of large, population-based studies examining the impact of BS on individual diabetes-related microvascular outcomes.

Our hypothesis was that BS is associated with a reduction in the incidence of microvascular complications compared with routine care in people with type 2 diabetes and obesity. We therefore conducted a population-based matched controlled cohort study to assess the impact of BS on incident microvascular complications in patients with type 2 diabetes. We also examined the findings stratified by individual bariatric procedures.

RESEARCH DESIGN AND METHODS

Study Design and Data Source

A retrospective matched controlled cohort study using the IQVIA Medical Research Data (IMRD) database was conducted. IMRD is an electronic primary care database that includes longitudinal patient records of >15 million patients, of which 3.7 million are currently active (contributing data to the database). The database covers ~6.2% of the U.K. population and has been shown to be representative of the U.K. demographic structure (22). IMRD contains demographic information, clinical diagnoses, procedures, laboratory results, medications, lifestyle information, and every consultation episode with primary care. IMRD (previously referred as The Health Improvement Network [THIN] database) has previously been used for research related to diabetes and vascular outcomes (23–27) and to assess effectiveness of bariatric surgery (20,28).

Study Population

Primary care practices were eligible for inclusion in the study if they had been using the Vision electronic records system for at least 1 year and had Acceptable Mortality Reporting (an indicator of the practice data quality) for at last 1 year before study entry (29). In addition, study participants must have been registered with an eligible practice for at least 1 year before study entry. The above-mentioned criteria were to ensure data extracted was high quality, with adequate documentation of concomitant diseases and treatments. The surgical cohort was adult patients (≥18 years) with obesity (BMI ≥30 kg/m^2) who had type 2 diabetes and a subsequent record of a primary BS, comprising gastric banding (GB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), or duodenal switch (DS). Each patient with type 2 diabetes who had BS (surgical group) was matched on the index date with up to two patients with type 2 diabetes who did not have BS (nonsurgical group) within the same general practice by age (±2 years), sex, preindex BMI (±2 kg/m^2), and diabetes duration (±3 years). Patients in the surgical group and their corresponding nonsurgical group were excluded from the study if they met any of the following criteria: had a BMI <30 kg/m^2, age >75 years, gastric balloon or endobarrier, or gastric cancer before BS or had been coded as type 1 diabetes (Supplementary Fig. 1).

Follow-up

The index date for the surgical cohort was the date of BS. For the nonsurgical population, the index date was assigned as the corresponding index date of their matched surgical patient to mitigate immortal time bias (30). Eligible participants were monitored from the index date until the earliest occurrence of the following end points: *1*) incidence of the outcome of interest; *2*) death; *3*) patient left the practice; *4*) the practice ceased contributing to the database; or *5*) study end date (31 January 2018).

Outcome Measures

The primary outcome measures were composite microvascular disease, DFD, STDR, and CKD. Outcomes were defined by a rigorous process of clinical Read code selection (31), reviewing them against existing literature, and ratifying through an expert panel of specialists in the field and primary care professionals.

DFD was defined as a composite of foot ulcer, gangrene, deformity, or amputation, moderate/high foot risk, peripheral vascular disease (PVD), or diabetes-related peripheral neuropathy (DPN) according to Read codes in the IMRD database, defined as DFD1. Moderate foot risk was defined as presence of DPN, deformity, or noncritical limb ischemia. High foot risk was defined as previous ulcer, amputation, more than two of the three parameters of DPN, deformity, or PVD (32,33). We considered alternative definitions for DFD in the analysis. DFD2 was defined as any of the components of DFD1, not including PVD/DPN codes. DFD3 was defined as any of the components of DFD2 without including moderate/high foot risk codes. In addition, we explored the risk of incident DPN and PVD separately as secondary outcomes.

STDR was defined as preproliferative retinopathy (R2), proliferative retinopathy (R3), or maculopathy (M1); retinopathy treatment (photocoagulation/vitreous injection); or vision loss (24). In a sensitivity analysis, we excluded vision loss from the outcome definition, because this may have been caused by pathologies other than diabetes such as macular degeneration or cataract.

CKD was defined as estimated glomerular filtration rage (eGFR) <60 mL/min/1.73 m^2 or albuminuria (albumin-to-creatinine ratio [ACR] ≥3 mg/mmol) (34). In addition, we looked at eGFR <30 mL/min/1.73 m^2 and macroalbuminuria (ACR >30 mg/mmol) separately. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate the eGFR value from the creatinine value (35). In sensitivity analysis, we defined two consecutive values of eGFR <60 mL/min/1.73 m^2 and two consecutive ACR ≥3 mg/mmol as outcomes. In both analyses, patients who had the outcome measure of interest before the index date were excluded.

All outcomes defined above are assessed annually as part of the Quality and Outcomes Framework (QOF) scheme in primary care and are therefore likely to be accurate; this regular assessment also mitigates surveillance bias (36).

Statistical Analysis

Baseline characteristics are summarized as mean (SD) or median (interquartile range [IQR]) for continuous variables and proportions for categorical variables. Covariates in the adjusted/multivariable model were selected based on biological plausibility. These included age, sex, high BMI, smoking status, ethnicity, social deprivation status, hypertension status, diabetes duration, baseline HbA$_{1c}$, and medications, including ACE inhibitors, antilipid drugs, and insulin. BMI was categorized as <35 kg/m^2, 35–40 kg/m^2, and >40 kg/m^2. Smoking was categorized as smoker, nonsmoker, and former smoker. Social deprivation status was represented by the Townsend deprivation quintile, which is based on material deprivation within a population (31). Race/ethnicity was categorized as Caucasian, Afro-Caribbean, south Asian, or mixed. A missing category was used for missing data for BMI, Townsend quintile, smoking status, and race/ethnicity. Hypertension status and medications were handled as binomial variables and age, diabetes duration, and baseline HbA$_{1c}$ as continuous variables.

We calculated crude and adjusted hazard ratios (adjHRs) and 95% CIs for the occurrence (incident) of each outcome of interest in the surgical versus nonsurgical groups using a Cox proportional hazards regression model. Participants with the outcome of interest in the surgical or nonsurgical group at baseline were excluded from the respective analysis. For CKD analysis, we also excluded the patients on renal replacement therapy, defined as a patient with renal transplant or on dialysis at baseline.

The proportional hazards assumption was checked using the Schoenfeld residuals test. We adjusted for biologically plausible confounders as mentioned above.

Stratifying by type of surgery, we analyzed the outcome in participants undergoing GB, SG, and RYGB and their corresponding nonsurgical control group. We did not perform this analysis in the DS subgroup due to small numbers.

We know that beneficial effects of BS on weight loss and glycemic control lessen over time, so we reported the latest weight and HbA$_{1c}$ to avoid inflation of results in favor of surgery. Postsurgical weight was defined as latest weight available for the surgical or nonsurgical group after the index date and before the exit date. Percentage weight loss (%WL) was calculated as

$$\frac{\textit{postsurgical weight (latest available)} - \textit{baseline weight}}{\textit{baseline weight}} \times 100$$

For the nonsurgical group who had no surgery, weight change was calculated using latest weight after the index date and baseline weight. Independent sample *t* test was used to compare the %WL in surgical and nonsurgical groups. HbA$_{1c}$ was standardized as a percentage (Diabetes Control and Complications Trial [DCCT] unit). We calculated the change in HbA$_{1c}$ (latest HbA$_{1c}$ available after the index date minus baseline HbA$_{1c}$) and used the independent sample *t* test to compare the percentage difference between surgical and nonsurgical groups.

We used Nelson-Aalen plots (nonparametric estimator) to present the cumulative hazard function for each outcome over 10-year periods. A two-tailed *P* value <0.05 was considered statistically significant. All analyses were conducted using Stata 15 software.

RESULTS

Baseline Characteristics

We included 1,126 surgical and 2,219 nonsurgical participants. Baseline characteristics are summarized in Table 1. Mean (SD) age was 50 (9.3) years, and 2,261 (67.59%) participants were women. Mean (SD) BMI was 46.76 (7.96) kg/m^2 vs. 46.14 (7.49) kg/m^2, and mean (SD) HbA$_{1c}$ was 7.78% (1.82) vs. 7.82% (1.69) for surgical versus nonsurgical participants, respectively. Median (IQR) diabetes duration was 4.72 (2.17–8.93) vs. 4.63 (1.91–8.19) years in surgical versus nonsurgical participants. Most of the study population (88.9% of the surgical and 82.1% of the nonsurgical) was not recorded as active smokers. Insulin was prescribed for 270 surgical (23.98%) versus 315 of the nonsurgical participants (14.20%). The prevalence of microvascular complications at baseline was similar in the surgical and nonsurgical groups.

Table 1—Baseline characteristics of participants in the surgical and nonsurgical groups

	Surgical	Nonsurgical
Population, *n*	1,126	2,219
Age categories, years, *n* (%)		
<41	171 (15.19)	329 (14.83)
41–60	803 (71.31)	1,568 (70.66)
61-max	152 (13.50)	322 (14.51)
Mean (SD)	49.87 (9.3)	50.12 (9.3)
Sex, *n* (%)		
Male	366 (32.50)	718 (32.36)
Female	760 (67.50)	1,501 (67.64)
BMI categories, kg/m^2, *n* (%)		
<35	57 (5.06)	121 (5.46)
35–39.9	165 (14.65)	344 (15.50)
≥40	901 (80.02)	1,748 (78.77)
Missing	3 (0.27)	6 (0.27)
Mean (SD)	46.76 (7.96)	46.14 (7.49)
Smoker categories, *n* (%)		
Nonsmoker	563 (50.00)	1,189 (53.58)
Smoker	125 (11.10)	395 (17.80)
Former smoker	438 (38.90)	633 (28.53)
Missing	0 (0)	2 (0.09)
Drinker categories, *n* (%)		
Nondrinker	315 (27.98)	625 (28.17)
Drinker	688 (61.10)	1,403 (63.23)
Former drinker	74 (6.57)	92 (4.15)
Missing	49 (4.35)	99 (4.46)
Race/ethnicity, *n* (%)		
Caucasian	620 (55.06)	1,094 (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)	1,013 (45.65)
Townsend, *n* (%)		
1 (least deprivation <20%)	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 >80%)	160 (14.21)	414 (18.66)
Missing	150 (13.32)	310 (13.97)
Baseline comorbidities		
Mental health conditions, *n* (%)		
Anxiety	310 (27.53)	526 (23.70)
Depression	616 (54.71)	1,001 (45.11)
Cardiovascular diseases, *n* (%)		
Hypertension	620 (55.06)	1,239 (55.84)
Atrial fibrillation	26 (2.31)	47 (2.12)
Heart failure	16 (1.42)	46 (2.07)
Ischemic heart disease	74 (6.57)	165 (7.44)
Stroke/transient ischemic attack	30 (2.66)	70 (3.15)
Obstructive sleep apnea	243 (21.58)	175 (7.89)
Diabetes duration, median (IQR)	4.72 (2.17–8.93)	4.63 (1.91–8.19)
Insulin user, *n* (%)	270 (23.98)	315 (14.20)
Baseline microvascular complications		
Any microvascular complication (DFD3/STDR/CKD)	649 (57.64)	1,220 (54.98)
DFD1	350 (31.08)	633 (28.53)
DFD2	212 (18.83)	371 (16.72)
DFD3	61 (5.42)	106 (4.78)
DPN	155 (13.77)	291 (13.11)
PVD	126 (11.19)	226 (10.18)
STDR	57 (5.06)	151 (6.80)
CKD	481 (42.72)	865 (38.98)

CKD, eGFR <60 mL/min/1.73 m^2 or ACR ≥3; DFD1, ulcer or gangrene or deformity or amputation or moderate/high foot risk or DPN/PVD; DFD2, ulcer or gangrene or deformity or amputation or moderate/high foot risk; DFD3, ulcer or gangrene or deformity or amputation.

Of the 1,126 participants in the surgical group, 249 (22.1%), 255 (22.7%), 610 (52.2%), and 12 (1.1%) patients had GB, SG, RYGB, and DS, respectively.

Weight Change

Data on weight before and after the index date were available for 1,067 surgical (94.8%) and 1,943 nonsurgical (87.6%) participants. Over the median (IQR) follow-up of 2.8 years (1.2–4.9) in the surgical group and 3.4 years (1.5–5.6) in the nonsurgical group, the surgical group achieved a greater mean (SD) %WL of 21.6% (13%) compared with 4.6% (9.7%) in the nonsurgical group.

Participants who underwent surgery lost more weight compared with their matched nonsurgical participants for all surgical procedures: GB, 14.6% (13.9%) vs. 4.6% (10.3%), $P < 0.001$; SG, 20.6% (11.5%) vs. 4.2% (10.1%), $P < 0.001$; RYGB, 25.0% (12.0%) vs. 4.8% (9.1%), $P < 0.001$; and DS, 21.2% (10.8%) vs. 1.7% (9.3%), $P < 0.001$.

Glycemic Control

HbA_{1c} values before and after the index date were available for 1,043 surgical (93%) and 1,958 nonsurgical (88%) participants. Over the median (IQR) follow-up period of 2.6 years (1–4.9) in the surgical group versus 3.1 years (1.2–5.5) in the nonsurgical group, participants in the surgical group achieved a mean reduction in HbA_{1c} of 1.3% (95% CI 1.2–1.5) (14.2 mmol/mol [13.1–16.4]), while in the nonsurgical group, HbA_{1c} increased by 0.2% (95% CI 0.1–0.3) (2.2 mmol/mol [1.1–3.3]). The mean HbA_{1c} reduction difference between the surgical and nonsurgical cohorts was 1.5% (95% CI 1.4–1.7) (16.4 mmol/mol [15.3–18.5]). Participants receiving any of the surgical procedures achieved greater HbA_{1c} reductions compared with the nonsurgical group, with a mean reduction difference of 1% (95% CI 0.7–1.3) (10.9 mmol/mol [7.6–14.2]) in GB, 1.4% (1.1–1.7) (15.3 mmol/mol [12.0–18.5]) in SG, 1.8% (1.6–2.0) (19.6 mmol/mol [17.4–21.8]) in RYGB, and 2.4% (0.8–4.0) (26.2 mmol/mol [8.7–43.6]) in DS.

Composite Microvascular Disease

BS was associated with 47% reduction in the hazard of developing composite microvascular complications versus nonsurgical (adjHR 0.53; 95% CI 0.43–0.66) over the median follow-up period of 2.2 years (IQR 1–4.4).

Analysis based on the type of surgery showed that all types of surgery were associated with favorable impact on the incidence of composite microvascular complications. The adjHRs and follow-up duration in each surgical procedure can be found in Table 2.

Diabetes-Related Foot Disease, Peripheral Neuropathy, and PVD

BS was associated with reduction in the hazards of incidence DFD1 by 39% ($P < 0.001$). Analysis based on the type of surgery showed that all types of surgery were associated with favorable impact on the incident of DFD1; however, this reached statistical significance only in the RYGB and GB groups but not in the SG group (Table 2). BS was associated with reduction in incidence DFD2 by 37% ($P < 0.001$) and DPN by 28% ($P = 0.037$). There was nonsignificant reduction in hazards of DFD3 and PVD in the surgical group versus the nonsurgical group in adjusted analysis (Table 3).

STDR

Over the median follow-up of 3.5 years (IQR 1.6–5.7), BS was associated with a 34% reduction in incidence of STDR ($P = 0.048$). In a sensitivity analysis excluding low vision/blindness in the outcome definition, we found a 42% reduction in incidence of STDR in the surgical group compared with the nonsurgical group, ($P = 0.021$) (Table 2). Stratifying by the type of BS showed that there was a statistically significant decrease in incident STDR in the GB cohort versus their nonsurgical counterparts, but no association was observed in the SG or RYGB groups (Table 2).

CKD

Over the median follow-up of 2.7 years (IQR 1.1–4.9), there was a 37% reduction in incident CKD in the surgical group compared with the nonsurgical group ($P < 0.001$) (Table 2). An examination of the data based on the type of BS showed that all types of surgery were associated with favorable impact on incident CKD, but this was statistically significant in RYGB and SG but not in GB (Table 2).

No significant association was observed between BS and incident eGFR <60 mL/min/1.73 m^2 or <30 mL/min/1.73 m^2 (Table 4).

Table 2—Incidence of composite microvascular complications and DFD, STDR, and nephropathy in total population and subgroup analyses

	Composite microvascular complications		DFD1		STDR		CKD	
	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical
Population, *n*	477	999	776	1,586	1,069	2,068	645	1,354
Outcome events, *n* (%)	116 (24.3)	420 (42.0)	125 (16.1)	396 (25.0)	34 (3.2)	96 (4.6)	113 (17.5)	385 (28.4)
Person-years	1,478.6	2,768.3	2,681.7	5,271.4	4,014.3	8,205.3	2,108.4	4,378.2
Crude IRR	78.45	151.72	46.61	75.12	8.47	11.7	53.6	87.94
Follow-up, years	2.4 (1–4.4)	2.1 (1–4.3)	3.0 (1.3–5.2)	2.8 (1.3–5.0)	3.3 (1.5–5.5)	3.6 (1.5–5.9)	2.7 (1.1–4.9)	2.7 (1.1–5.0)
Crude HR (95% CI), *P* value	0.52 (0.42–0.64), <0.001		0.62 (0.51–0.76), <0.001		0.72 (0.49–1.07), 0.105		0.61 (0.49–0.75), <0.001	
AdjHR (95% CI), *P* value	0.53 (0.43–0.66), <0.001		0.61 (0.50–0.75), <0.001		0.66 (0.44–1.00), 0.048		0.63 (0.51–0.78), <0.001	
Gastric banding								
Population, *n*	133	240	188	366	240	465	165	308
Outcome events, *n* (%)	49 (36.8)	127 (52.9)	39 (20.7)	119 (32.5)	12 (5.0)	36 (7.7)	51 (30.9)	121 (39.3)
Person-years	514.4	845.9	895.3	1,521.9	1,223.4	2,399.5	692.5	1,287.2
Crude IRR	95.25	150.13	43.56	78.19	9.81	15	73.65	94
Follow-up, years	3.5 (1–6.2)	2.7 (1.3–5.6)	4.3 (2–7.2)	3.8 (1.8–6.3)	4.9 (2.3–7.5)	5.2 (2.6–7.5)	4.1 (1.4–6.5)	3.7 (1.8–6.4)
Crude HR (95% CI), *P* value	0.64 (0.46–0.89), 0.008		0.55 (0.39–0.80), 0.001		0.65 (0.34–1.25), 0.194		0.77 (0.55–1.06), 0.112	
AdjHR (95% CI), *P* value	0.65 (0.46–0.91), 0.013		0.53 (0.36–0.78), 0.001		0.49 (0.24–0.99), 0.048		0.77 (0.55–1.09), 0.144	
Sleeve gastrectomy								
Population, *n*	104	206	165	335	241	456	147	283
Outcome events, *n* (%)	21 (20.2)	73 (35.4)	27 (16.4)	76 (22.7)	6 (2.5)	12 (2.6)	17 (11.6)	65 (23)
Person-years	299.07	439.21	484.73	926.2	782.32	1,521.87	425.9	756.58
Crude IRR	70.22	166.21	55.7	82.06	7.67	7.89	39.92	85.91
Follow-up, years	2.3 (1–4.0)	1.6 (0.7–3.6)	2.4 (0.9–4.3)	2.3 (1–4.1)	2.8 (1.3–5)	2.8 (1.2–4.9)	2.2 (1–4.2)	2 (0.9–4.0)
Crude HR (95% CI), *P* value	0.45 (0.27–0.73), 0.001		0.69 (0.44–1.07), 0.098		1 (0.376–2.69, 0.989		0.47 (0.27–0.80), 0.005	
AdjHR (95% CI), *P* value	0.49 (0.29–0.83), 0.008		0.70 (0.44–1.11), 0.13		1.41 (0.49–3.99), 0.523		0.52 (0.29–0.91), 0.023	
Gastric bypass								
Population, *n*	236	542	413	869	577	1,123	329	748
Outcome events, *n* (%)	44 (18.6)	220 (40.6)	57 (13.8)	201 (23.1)	16 (2.8)	48 (4.3)	44 (13.4)	197 (26.3)
Person-years	656.1	1,446.46	1,277.87	2,775.225	1,978.4	4,206.25	979.26	2,288.854
Crude IRR	67.06	152.1	44.61	72.43	8.087	11.41	44.93	86.07
Follow-up, years	2.2 (1–4.2)	1.9 (0.9–4.1)	2.6 (1.3–4.4)	2.8 (1.3–4.8)	3.0 (1.5–5.0)	3.5 (1.6–5.6)	2.5 (1–4.4)	2.5 (1–4.8)
Crude HR (95% CI), *P* value	0.44 (0.32–0.61), <0.001		0.61 (0.46–0.82), 0.001		0.72 (0.41–1.27), 0.255		0.52 (0.38–0.72), <0.001	
AdjHR (95% CI), *P* value	0.42 (0.30–0.59), <0.001		0.58 (0.43–0.79), 0.001		0.63 (0.35–1.16), 0.137		0.51 (0.36–0.71), <0.001	

Data are median (IQR) for follow-up. AdjHR, adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration, baseline HbA_{1c}, and medications, including ACE inhibitors, antilipid drugs, and insulin. Crude HR, unadjusted HR. DFD1, ulcer/gangrene/deformity/amputation/moderate or high foot risk/peripheral neuropathy/PVD; IRR, incidence rate ratio/1,000 person-years.

Table 3—Incidence of DFD2 and DFD3, peripheral neuropathy, and PVD

	DFD2		DFD3		DPN		PVD	
	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical	Surgical	Nonsurgical
Population, *n*	914	1,848	1,065	2,113	971	1,928	1,000	1,993
Outcome events, *n* (%)	147 (16.1)	453 (24.5)	29 (2.7)	64 (3.0)	58 (6.0)	157 (8.1)	29 (3.0)	81 (4.1)
Person-years	3,314.8	6,488.0	4,028.9	8,457.09	3,590.71	7,308.73	3,642.73	7,667.25
Crude IRR	44.35	69.82	7.2	7.57	16.15	21.48	7.96	10.56
Follow up, years	3.3 (1.5–5.4)	3.0 (1.4–5.3)	3.3 (1.6–5.5)	3.6 (1.6–6.0)	3.2 (1.5–5.4)	3.4 (1.5–5.7)	3.2 (1.5–5.4)	3.5 (1.6–5.6)
Crude HR (95% CI), *P* value	0.63 (0.53–0.76), <0.001		0.96 (0.62–1.48), 0.841		0.75 (0.55–1.01), 0.06		0.75 (0.49–1.15), 0.185	
AdjHR (95% CI), *P* value	0.63 (0.52–0.76), <0.001		0.87 (0.55–1.37), 0.538		0.72 (0.52–0.98), 0.037		0.70 (0.45–1.09), 0.113	

Data are median (IQR) for follow-up. AdjHR, adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration, baseline HbA_{1c} and medications, including ACE inhibitors, antilipid drugs and insulin. Crude HR, unadjusted HR. DFD2, amputation/ulcer/gangrene/deformity/moderate/high foot risk; DFD3, amputation/ulcer/gangrene/deformity; IRR, incidence rate ratio/1,000 person-years.

There was a 40% reduction in incident albuminuria in the surgical group compared with the nonsurgical group ($P < 0.001$) and a 64% reduction in macroalbuminuria ($P = 0.009$) (Table 4).

In a sensitivity analysis, the observed association of BS with reduction in incidence microalbuminuria, defined with two consecutive measurements, ACR ≥3 mg/mmol persisted with an adjHR of 0.52 (95% CI 0.37–0.72). But no association of BS and incidence eGFR <60 mL/min/1.73 m^2 (two consecutive results) was found.

Nelson-Aalen Cumulative Hazard Estimates for Study Outcomes

The cumulative hazard estimates for the study outcomes over a 10-year period can be found in Supplementary Fig. 2.

Table 4—Incidence of eGFR <60 mL/min per 1.73 m^2, eGFR <30 mL/min per 1.73 m^2, ACR ≥3 mg/mmol, and ACR >30 mg/mmol and sensitivity analysis

	eGFR		ACR	
	Surgical	Nonsurgical	Surgical	Nonsurgical
Population, *n*	963	1,931	737	1,510
	eGFR <60		ACR ≥3	
Outcome events, *n* (%)	67 (6.96)	174 (9.01)	109 (14.79)	372 (24.64)
Person-years	3,482.7	7,405.5	2,525.8	5,001.2
Crude IRR	19.24	23.5	43.16	74.38
Follow-up, years	3.4 (1.5–5.5)	3.5 (1.5–5.6)	2.9 (1.3–5.5)	2.8 (1.1–5.1)
Crude HR (95% CI), *P* value	0.82 (0.62–1.1), 0.181		0.58 (0.47–0.72), <0.001	
AdjHR (95% CI), *P* value	0.81 (0.62–1.11), 0.21		0.60 (0.48–0.75), <0.001	
	eGFR <30		ACR >30	
Outcome events, *n* (%)	8 (0.8)	28 (1.5)	8 (1.1)	48 (3.2)
Person-years	3,693.9	7,826.8	2,907.4	6,200.2
Crude IRR	18.14	22.23	2.75	7.74
Follow-up, years	3.7 (1.7–6.0)	3.7 (1.7–6.0)	3.5 (1.6–5.7)	3.8 (1.6–6.1)
Crude HR (95% CI), *P* value	0.63 (0.29–1.37), 0.242		0.36 (0.17–0.76), 0.007	
AdjHR (95% CI), *P* value	0.74 (0.32–1.70), 0.48		0.36 (0.17–0.77), 0.009	
Sensitivity analysis	Two consecutive eGFR <60		Two consecutive ACR ≥3	
Population, *n*	963	1,931	924	1,795
Outcome events, *n* (%)	67 (7.0)	174 (9.0)	46 (5.0)	168 (9.4)
Person-years	3,482.7	7,405.5	3,419.7	6,675.1
Crude IRR	19.24	23.50	13.45	25.17
Follow-up, years	3.2 (1.5–5.3)	3.5 (1.4–5.6)	3.3 (1.5–5.4)	3.3 (1.4–5.6)
Crude HR (95% CI), *P* value	0.83 (0.62–1.09), 0.181		0.53 (0.39–0.74), <0.001	
AdjHR (95% CI), *P* value	0.83 (0.62–1.11), 0.21		0.52 (0.37–0.72), <0.001	

Data are median (IQR) for follow-up. AdjHR, adjusted for age, sex, smoking status, baseline BMI category, ethnicity, Townsend quantile, hypertension, diabetes duration, baseline HbA_{1c} and medications, including ACE inhibitors, antilipid drugs and insulin; Crude HR, unadjusted HR; IRR, incidence rate ratio/1,000 person-years.

The figure illustrates the association between BS and the reduction in incident composite microvascular complications, DFD1, STDR, and CKD. The impact of BS on incident DFD1 and CKD was apparent within the first 2–3 years postsurgery, whereas the impact on STDR took longer to become apparent (5–6 years).

CONCLUSIONS

Our study provides real-world population-based data showing that BS was associated with significant reduction in incident composite microvascular complications, DFD, STDR, CKD, and DPN, in patients with type 2 diabetes compared with routine care, after accounting for many potential confounders. The association between BS and the reduction in incident STDR took longer to become apparent compared with the other microvascular complications (Supplementary Fig. 2). In addition, BS was associated with greater reductions in weight and HbA_{1c} compared with routine care during the follow-up, with the greatest reductions observed in the RYGB and DS groups.

Our results are similar to other published findings but add novel aspects. Our group previously showed in single-center matched controlled studies that over 3 years, BS was associated with less eGFR decline (37) and incident maculopathy (38) compared with routine care; but these studies were of a small sample size, from a single center, and with a limited number of patients.

Sheng et al. (39) also showed that BS was associated with lower risk of incident composite microvascular complications in a systematic review, but unlike our study, there were no results based on individual microvascular complications.

The Swedish Obese Subject (SOS) study, a prospective matched controlled intervention study, showed a reduction in the incidence rate of composite microvascular complications in patients who had undergone BS ($n = 343$) compared with control subjects ($n = 260$) (18). However, there were limitations in that the majority surgical procedure performed was vertical gastroplasty, mean (±SD) diabetes duration in surgical group was short (2.9 ± 4.7 years), and there was no assessment of individual microvascular outcomes. In addition, the SOS study started before many of the current type 2 diabetes interventions were established (such as the use of statins and ACE inhibitors/angiotensin receptor blockers).

Another study from the U.S., with a design similar to our study, based on four integrated health systems, found that BS was associated with reduction in incident retinopathy, nephropathy, and neuropathy (40). This study did not examine the impact of BS on STDR, and the impact on nephropathy was measured only using eGFR and not albuminuria.

After BS, patients show a decrease in fat mass as well as a loss of lean mass, including muscle mass (41,42). Therefore, it is difficult to differentiate whether change in creatinine level and creatinine-based eGFR is indicative of true improvement in renal function. However, in our study, the association between surgery and reduction in incident CKD was mainly driven by a reduction in albuminuria, which is not affected by loss of muscle mass.

In another study of similar design from Denmark, RYGB was associated with a reduction in the incidence of microvascular complications (CKD, retinopathy, and neuropathy), similar to what we observed in our study (HR 0.53, 95% CI 0.38–0.73) (43). But in that study, they did not report the outcomes of individual microvascular complications, and our study adjusted for more variables in the Cox regression analysis (such as the Townsend social deprivation index).

The Longitudinal Assessment of Bariatric Surgery (LABS) Study examined the impact of RYGB and GB over a follow-up period of up to 7 years and found beneficial effect on weight loss, diabetes, and hypertension status (44). While this was a study conducted in general population with obesity, our study was specifically focused on people with type 2 diabetes and reported on comprehensive outcomes of multiple vascular complications.

The Teen-LABS study specifically reported the impact of BS on CKD in adolescents with type 2 diabetes with a sample size of 30. No other microvascular complications were analyzed (45). Our study was specific in adults, included multiple bariatric procedures, had a larger sample size, and reported on DFD and STDR.

We recently used the IMRD database to show that BS was associated with a reduction in incident CVD, hypertension, and mortality in patients with and without diabetes (20). Taken together with the findings of this study, this suggests that BS can play an important role in reducing the burden of type 2 diabetes by reducing the incidence of hypertension, CVD, microvascular disease, and mortality as well as resulting in significant improvements in weight and glycemic control. These benefits were observed despite that more patients in the surgical group had insulin treatment at baseline. Furthermore, in addition to reducing the personal burden of type 2 diabetes, the observed potential benefits are likely to have significant savings in health care costs considering the high cost of diabetes-related macro- and microvascular complications (3). Despite these potential benefits in people with type 2 diabetes, access to BS is limited in most Western health care systems, and improving access to BS in patients with type 2 diabetes might therefore have positive implications for diabetes care (46).

There are several plausible mechanisms for the observed beneficial effects of BS on incident microvascular complications. It is likely that BS exerts its beneficial effects by improving the established risk factors for microvascular complications, including weight, HbA_{1c}, blood pressure, lipids, and CVD (19,47,48). In addition, recent data suggest that BS can result in SGLT2 inhibition (49), and several studies previously showed that BS is associated with increased incretin and GLP-1 responses (50). These could contribute to the improved vascular outcomes after BS considering the latest cardiovascular outcomes trials in type 2 diabetes showing that GLP-1 receptor agonists and SGLT2 inhibitors can reduce CVD and CKD (51–53).

We managed to conduct subgroup analysis by type of procedure, which added novelty to our study. We showed that all types of surgery included in this study were associated with a reduction in the incidence of composite microvascular complications versus the nonsurgical arm. However, there was some variation in the relationship between the type of surgery and individual microvascular outcomes. GB had a favorable impact on DFD and STDR but not CKD, SG had a favorable impact on CKD only, and RYGB had a favorable impact on CKD and DFD but not STDR. These observations are not fully understood as yet and require further evaluation.

We could not find any studies comparing the impact of different bariatric procedures on microvascular diseases as we did in our study. The systematic review by Billeter et al. (21) showed that only three studies included all types of surgery in same study (18,38,54). However, none of these articles reported the outcomes based on type of surgery, and only the Johnson et al. (54) article reported individual microvascular complications, and again, no subgroup analysis by types of surgery was reported.

Limitations and Strengths

The main limitation of our study is its observational nature, and hence, causation cannot be proven. However, we used matching and extensive adjustments to account for confounding. Participants with the outcome of interest at baseline were excluded from the analysis due to methodological considerations. Therefore, any effect of BS in patients who already have microvascular complications requires future research. C-peptide data were not available in our study data set because it is not yet a routine care test in the U.K.; however, we included the information on diabetes duration and baseline insulin use and adjusted our outcomes for these variable. We had a short follow-up period duration.

Our study has several strengths: we used a validated primary care data source (the IMRD database) and used previously by our team (23–27) and other researchers to explore similar outcomes (55,56). Using IMRD allowed us to include a large sample size, matched with a nonsurgical sample, and adjust for several covariates, improving the generalizability of our findings. Furthermore, the outcomes of our study were measured as part of the QOF annually, ensuring consistency in definitions and militating against detection bias.

Conclusion

BS was associated with a reduction in microvascular complications, including DFD, STDR, CKD, and DPN, in patients with type 2 diabetes and obesity. Improving access to BS could reduce the burden of type 2 diabetes, and access to surgery needs to be improved.

Ethics Review and Copyright Statement. Use of IMRD is approved by the U.K. 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) (in January 2019, reference number: 18THIN097). IMRD 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 deidentified data provided by patients as a part of their routine primary care. THIN is a registered trademark of Cegedim SA in the U.K. and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. P.S. designed and performed the analysis. P.S. wrote the first draft of the paper. P.S., A.S., K.N., and A.A.T. contributed to the data analysis and interpretation. P.S., K.N., and A.A.T. had the original idea for the study. P.S., K.N., and A.A.T. designed the study. P.S., K.N., and A.A.T. affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. N.A., A.S., and K.N. reviewed the analysis. N.A., K.G., R.S., K.A.T., S.B., K.N., and A.A.T. revised and edited the first draft of the paper. K.G. undertook data extraction. P.S. and K.N. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the NeuroDiab conference at the 55th Annual Meeting of the European Association for the Study of Diabetes (EASD), Barcelona, Spain, 16–20 September 2019, and at the Virtual EASD Annual Meeting, 22–25 September 2020.

References

1. Fowler MJ. Microvascular and macrovascular complications of diabetes. Clin Diabetes 2008;26:77–82
2. International Diabetes Federation. IDF Diabetes Atlas, 9th edition, 2019. Accessed 16 July 2020. Available from https://www.diabetesatlas.org/en/resources/
3. Diabetes UK. The Cost of Diabetes, 2014. Accessed 19 March 2020. Available from https://www.diabetes.org.uk/resources-s3/2017-11/diabetes%20uk%20cost%20of%20diabetes%20report.pdf
4. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014;370:1514–1523
5. Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719–1724
6. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–136
7. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016;316:602–610
8. Wild SH, Byrne CD. Risk factors for diabetes and coronary heart disease. *BMJ* 2006;333:1009–1011
9. Hsu C-y, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006;144:21–28
10. Hozumi J, Sumitani M, Matsubayashi Y, et al. Relationship between neuropathic pain and obesity. Pain Res Manag 2016;2016:2487924
11. Miscio G, Guastamacchia G, Brunani A, Priano L, Baudo S, Mauro A. Obesity and peripheral neuropathy risk: a dangerous liaison. J Peripher Nerv Syst 2005;10:354–358
12. Tesfaye S, Selvarajah D. The Eurodiab study: what has this taught us about diabetic peripheral neuropathy? Curr Diab Rep 2009;9:432–434
13. Poirier P, Giles TD, Bray GA, et al.; American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898–918
14. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med 2017;5:161
15. Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. Curr Obes Rep 2017;6:187–194
16. Wing RR, Espeland MA, Clark JM, et al.; Action for Health in Diabetes (Look AHEAD) Study Group. Association of weight loss maintenance and weight regain on 4-year changes in CVD risk factors: the Action for Health in Diabetes (Look AHEAD) clinical trial. Diabetes Care 2016;39:1345–1355
17. Schauer PR, Mingrone G, Ikramuddin S, Wolfe B. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. Diabetes Care 2016;39:902–911
18. Sjöstrom L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014;311:2297–2304
19. Ricci C, Gaeta M, Rausa E, Asti E, Bandera F, Bonavina L. Long-term effects of bariatric surgery on type II diabetes, hypertension and hyperlipidemia: a meta-analysis and meta-regression study with 5-year follow-up. Obes Surg 2015;25:397–405
20. Singh P, Subramanian A, Adderley N, et al. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population-based cohort study. Br J Surg 2020;107:432–442
21. Billeter AT, Scheurlen KM, Probst P, et al. Meta-analysis of metabolic surgery versus medical treatment for microvascular complications in patients with type 2 diabetes mellitus. Br J Surg 2018;105:168–181
22. IQVIA Medical Research Data. Accessed 19 March 2020. Available from https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/the-health-improvement-network-thin-database/
23. Hall GC, McMahon AD, Carroll D, Home PD. Observational study of the association of first insulin type in uncontrolled type 2 diabetes with macrovascular and microvascular disease. PLoS One 2012;7:e49908
24. Subramanian A, Adderley NJ, Tracy A, et al. Risk of incident obstructive sleep apnea among patients with type 2 diabetes. Diabetes Care 2019;42:954–963
25. Toulis KA, Willis BH, Marshall T, et al. All-cause mortality in patients with diabetes under treatment with dapagliflozin: a population-based, open-cohort study in The Health Improvement Network Database. J Clin Endocrinol Metab 2017;102:1719–1725
26. Daly B, Toulis KA, Thomas N, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: a population-based cohort study [published correction appears in PLoS Med 2019;16:e1002881]. PLoS Med 2018;15:e1002488
27. Toulis KA, Hanif W, Saravanan P, et al. All-cause mortality in patients with diabetes under glucagon-like peptide-1 agonists: a population-based, open cohort study. Diabetes Metab 2017;43:211–216
28. Alkharaiji M, Anyanwagu U, Donnelly R, Idris I. Effect of bariatric surgery on cardiovascular events and metabolic outcomes in obese patients with insulin-treated type 2 diabetes: a retrospective cohort study. Obes Surg 2019;29:3154–3164
29. 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;18:76–83
30. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2008;167:492–499
31. NHS Digital. Read Codes - NHS Digital, Retirement of Read Version 2 and Clinical Terms Version 3, 2018. Accessed 19 March 2020. Available from https://digital.nhs.uk/services/terminology-and-classifications/read-codes
32. Internal Clinical Guidelines Team. *Diabetic Foot Problems: Prevention and Management*. London, U.K., National Institute for Health and Care Excellence, 2015
33. Leese G, Schofield C, McMurray B, et al. Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. Diabetes Care 2007;30:2064–2069
34. National Institute for Health and Care Excellence (NICE). Chronic kidney disease - NICE CKS 2019. Accessed 9 February 2020. Available from

https://cks.nice.org.uk/topics/chronic-kidney-disease/
35. CKD-EPI Adults (Conventional Units). National Institute of Diabetes and Digestive and Kidney Diseases, 2019. Accessed 9 February 2020. Available from https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units
36. National Institute for Health and Care Excellence. Quality and Outcomes Framework Indicators: Standards and Indicators, 2019. Accessed 19 March 2020. Available from https://www.nice.org.uk/standards-and-indicators/qofindicators?categories=&page=2
37. Mirajkar N, Bellary S, Ahmed M, Singhal R, Daskalakis M, Tahrani AA. The impact of bariatric surgery on estimated glomerular filtration rate in patients with type 2 diabetes: a retrospective cohort study. Surg Obes Relat Dis 2016;12:1883–1889
38. Amin AM, Wharton H, Clarke M, Syed A, Dodson P, Tahrani AA. The impact of bariatric surgery on retinopathy in patients with type 2 diabetes: a retrospective cohort study. Surg Obes Relat Dis 2016;12:606–612
39. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The long-term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta-analysis. Obes Surg 2017;27:2724–2732
40. O'Brien R, Johnson E, Haneuse S, et al. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. Ann Intern Med 2018;169:300–310
41. Zalesin KC, Franklin BA, Lillystone MA, et al. Differential loss of fat and lean mass in the morbidly obese after bariatric surgery. Metab Syndr Relat Disord 2010;8:15–20
42. Carey DG, Pliego GJ, Raymond RL. Body composition and metabolic changes following bariatric surgery: effects on fat mass, lean mass and basal metabolic rate: six months to one-year follow-up. Obes Surg 2006;16:1602–1608
43. Madsen LR, Baggesen LM, Richelsen B, Thomsen RW. Effect of Roux-en-Y gastric bypass surgery on diabetes remission and complications in individuals with type 2 diabetes: a Danish population-based matched cohort study. Diabetologia 2019;62:611–620
44. Courcoulas AP, King WC, Belle SH, et al. Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study. JAMA Surg 2018;153:427–434
45. Bjornstad P, Hughan K, Kelsey MM, et al. Effect of surgical versus medical therapy on diabetic kidney disease over 5 years in severely obese adolescents with type 2 diabetes. Diabetes Care 2020;43:187–195
46. Borisenko O, Colpan Z, Dillemans B, Funch-Jensen P, Hedenbro J, Ahmed AR. Clinical indications, utilization, and funding of bariatric surgery in Europe. Obes Surg 2015;25:1408–1416
47. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis [published correction appears 2in JAMA 2005;293:1728]. JAMA 2004;292:1724–1737
48. Brix JM, Herz CT, Kopp HP, et al. Albuminuria in patients with morbid obesity and the effect of weight loss following bariatric surgery. Obes Surg 2019;29:3581–3588
49. Akalestou E, Noriega LL, Chabosseau PL, Leclerc I, Rutter GA. 161-LB: Inhibition of kidney SGLT2 expression following bariatric surgery in mice (Abstract). Diabetes 2019;68(Suppl. 1)
50. Cummings DE, Overduin J, Shannon MH, Foster-Schubert KE; 2004 ABS Consensus Conference. Hormonal mechanisms of weight loss and diabetes resolution after bariatric surgery. Surg Obes Relat Dis 2005;1:358–368
51. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
52. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
53. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
54. Johnson BL, Blackhurst DW, Latham BB, et al. Bariatric surgery is associated with a reduction in major macrovascular and microvascular complications in moderately to severely obese patients with type 2 diabetes mellitus. J Am Coll Surg 2013;216:545–556; discussion 556–558
55. Guest JF, Fuller GW, Vowden P. Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J 2018;15:43–52
56. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study [published correction appears in BMJ Open 2016;6:e010210corr1]. BMJ Open 2016;6:e010210