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Association of Gastric Bypass Surgery With Risk of Developing Diabetic Retinopathy Among Patients With Obesity and Type 2 Diabetes in Sweden
An Observational Study

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IMPORTANCE Knowledge of the incidence and progression of diabetic retinopathy (DR) after gastric bypass surgery (GBP) in patients with obesity and diabetes could guide the management of these patients.

OBJECTIVE To investigate the incidence of diabetic ocular complications in patients with type 2 diabetes after GBP compared with the incidence of diabetic ocular complications in a matched cohort of patients with obesity and diabetes who have not undergone GBP.

DESIGN, SETTING, AND PARTICIPANTS Data from 2 nationwide registers in Sweden, the Scandinavian Obesity Surgery Registry and the National Diabetes Register, were used for this cohort study. A total of 5321 patients with diabetes from the Scandinavian Obesity Surgery Registry who had undergone GBP from January 1, 2007, to December 31, 2013, were matched with 5321 patients with diabetes from the National Diabetes Register who had not undergone GBP, based on sex, age, body mass index (BMI), and calendar time (2007-2013). Follow-up data were obtained until December 31, 2015. Statistical analysis was performed from October 5, 2018, to September 30, 2019.

EXPOSURE Gastric bypass surgery.

MAIN OUTCOMES AND MEASURES Incidence of new DR and other diabetic ocular complications.

RESULTS The study population consisted of 5321 patients who had undergone GBP (3223 women [60.6%]; mean [SD] age, 49.0 [9.5] years) and 5321 matched controls (3395 women [63.8%]; mean [SD] age, 47.1 [11.5] years). Mean (SD) follow-up was 4.5 (1.6) years. The mean (SD) BMI and hemoglobin A_{1c} concentration at baseline were 42.0 (5.7) and 7.6% (1.5%), respectively, in the GBP group and 40.9 (7.3) and 7.5% (1.5%), respectively, in the control group. The mean (SD) duration of diabetes was 6.8 (6.3) years in the GBP group and 6.4 (6.4) years in the control group. The risk for new DR was reduced in the patients who underwent GBP (hazard ratio, 0.62 [95% CI, 0.49-0.78]; $P < .001$). The dominant risk factors for development of DR at baseline were diabetes duration, hemoglobin A_{1c} concentration, use of insulin, glomerular filtration rate, and BMI.

CONCLUSIONS AND RELEVANCE This nationwide matched cohort study suggests that there is a reduced risk of developing new DR associated with GBP, and no evidence of an increased risk of developing DR that threatened sight or required treatment.

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Supplemental content

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Bariatric surgery has become a well-established treatment for patients with severe obesity. Positive associations with morbidity and mortality have been demonstrated with bariatric surgery, but several adverse effects, both short term and long term, have also been described.[1-4] Beneficial outcomes after surgery include improved metabolic control and remission of type 2 diabetes.[5,6] In the prospective Swedish Obese Subject study, 72% of patients with diabetes had discontinued treatment of diabetes 2 years after the surgery.[7] Similar findings have been observed 2 years postoperatively in the the Scandinavian Obesity Surgery Registry (SOReg) cohort.[8] Reduced incidence of diabetes-associated macrovascular and microvascular complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, has been found up to 6 years after surgery.[1,9-11]

Divergent results have been reported with regard to the progression of diabetic retinopathy (DR) after gastric bypass surgery (GBP) in patients with diabetes. In most studies, no aggravation of preexisting DR was observed.[12,13] However, there are reports describing sight-threatening postoperative deterioration in DR, suggesting that closer monitoring of these patients is desirable.[14-16] Regression of DR has been described after bariatric surgery but not confirmed.[17,18] The aim of the present study was to investigate the incidence of diabetic ocular complications in patients with obesity and type 2 diabetes after GBP compared with a matched cohort of patients with diabetes who did not undergo GBP.

Key Points

Question What is the association of gastric bypass surgery with the risk of developing diabetic retinopathy (DR) among patients in Sweden with type 2 diabetes compared with a matched cohort of patients with obesity and type 2 diabetes who did not undergo gastric bypass surgery?

Findings This cohort study of 5321 patients who had undergone gastric bypass surgery and 5321 matched controls found that gastric bypass surgery was associated with a decreased risk of developing DR, and there was no evidence of increased risk for development of sight-threatening DR.

Meaning The results support previous studies showing a decreased risk of developing DR after gastric bypass surgery and suggest that the DR that develops is not sight-threatening DR.

Methods

We conducted a cohort study using data from 2 nationwide registers in Sweden, the SOReg and the National Diabetes Register (NDR). The SOReg contains clinical information about patients undergoing bariatric surgery, including the type of surgery, the outcome of surgery, and the possible postoperative adverse effects. The NDR comprises clinical information, updated regularly, about almost all of the patients with type 2 diabetes in Sweden. These registers have been validated and described previously.[19,20] The study was made with deidentified register data, and therefore informed consent was waived. The study was approved by the Regional Ethical Review Board in Gothenburg, Sweden.

Patients with diabetes who had undergone GBP and were reported to the SOReg between January 1, 2007, and December 31, 2013, were matched 1:1 with patients from the NDR with diabetes who had not undergone GBP, based on sex, age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and calendar time (2007-2013), as described in previous studies.[1,4] Follow-up data were obtained until December 31, 2015. The data from the NDR and SOReg were linked to nationwide register data in the Swedish Inpatient Register, Statistics Sweden, and the Swedish Cause of Death Register. These registers have been described previously.[21] The diagnoses before and after surgery were obtained from the Swedish Inpatient Register, and the detailed procedures and diagnoses obtained are described in the eMethods and eTable 1 in the Supplement.

Outcomes

The primary outcome measure was time to first occurrence of any retinopathy. Secondary outcome measures were time to first occurrence of any diabetic ocular complications and/or interventions, such as focal or grid laser treatment, panretinal photocoagulation, vitrectomy, or intravitreal injection. All diagnoses used to evaluate these outcomes are listed in eTable 2 and eTable 3 in the Supplement.

Statistical Analysis

Statistical analysis was performed from October 5, 2018, to September 30, 2019. Controls were matched with treated patients by means of a time-updated propensity score using greedy 1-to-1 matching. The propensity scores were estimated using a Cox proportional hazards regression analysis with sex and time-updated observations, age, and BMI as independent variables and with treatment with GBP as the event of interest.[22] Descriptive statistics for the matched cohort are presented in terms of mean (SD) values for continuous variables and numbers (percentages) for categorical variables. Differences between exposed patients and controls are described using the standardized mean difference. The incidence rate is estimated in terms of events per 10 000 person-years, and the associated 95% CIs are based on the Poisson distribution. The time to each event is censored at the end of follow-up or death, whichever comes first, and presented descriptively using Kaplan-Meier curves. Exposed patients are formally compared with controls using Cox proportional hazards regression analysis with age, sex, BMI, geographical region of birth, educational level, marital status, and income as independent variables in addition to the exposure. All P values were from 2-sided tests and results were deemed statistically significant at $P < .05$. The analysis was performed in SAS, version 9.4 (SAS Institute Inc).

Results

The study population consisted of 5321 patients (3223 women [60.6%]; mean [SD] age, 49.0 [9.5] years) from the SOReg who had undergone GBP between 2007 and 2013 and 5321 matched

Table. Descriptive Statistics by Treatment Group

Characteristic	Gastric bypass (n = 5321)	Control (n = 5321)	Standardized difference, %
Sex, No. (%)			
Male	2098 (39.4)	1926 (36.2)	4.7
Female	3223 (60.6)	3395 (63.8)	4.7
Age, mean (SD), y	49.0 (9.5)	47.1 (11.5)	12.2
Duration of diabetes, mean (SD), y	6.8 (6.3)	6.4 (6.4)	4.5
BMI, mean (SD)	42.0 (5.7)	40.9 (7.3)	11.7
Hemoglobin A_{1c} concentration, mean (SD)			
Millimoles per mole	60.0 (16.8)	58.5 (16.9)	6.3
% of Total hemoglobin	7.6 (1.5)	7.5 (1.5)	6.3
Blood pressure, mm Hg, mean (SD)			
Diastolic	80.3 (9.6)	80.0 (9.9)	2.2
Systolic	132.8 (14.5)	132.5 (15.6)	1.2
Cholesterol, mean (SD), mg/dL			
LDL	107.8 (35.1)	109.4 (35.4)	3.2
HDL	42.4 (11.6)	43.6 (12.2)	7.1
Total	187.8 (40.9)	189.8 (41.7)	3.3
Triglycerides, mean (SD), mg/dL	201.9 (133.1)	193.9 (132.2)	4.2
Creatinine, mean (SD), mg/dL	0.8 (0.3)	0.8 (0.3)	1.3
eGFR, mean (SD), mL/min/1.73 m^2	97.4 (25.2)	98.5 (27.5)	2.8
Smoking, No. (%)[a]	573 (15.8)	965 (19.8)	7.5
Mean income per year, median (interquartile range)			
Swedish krona	199 638 (139 136-261 558)	168 380 (121 840-239 368)	15.6
US dollars	23 137 (16 125-30 313)	19 514 (14 121-27 741)	15.6
Marital status, single, No. (%)	1602 (30.1)	2064 (38.8)	13.0
Educational level, elementary school, No. (%)[a]	1069 (20.2)	1431 (27.5)	12.2

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors: To convert total, HDL, and LDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and creatinine to micromoles per liter, multiply by 88.4.

[a] Calculated based on nonmissing observations.

controls (3395 women [63.8%]; mean [SD] age, 47.1 [11.5] years) from the NDR. The mean (SD) follow-up time was 4.5 (1.6) years. Baseline characteristics are shown in the **Table**. Groups were similar in terms of sex, duration of diabetes, hemoglobin A_{1c} (HbA_{1c}) concentration, blood pressure, blood lipid levels, and renal function (standardized differences <10%). Patients who had undergone GBP were somewhat older and had a slightly higher BMI than the controls. There were also differences with regard to income, marital status, and educational level between the groups (standardized differences >10% for all).

One year after GBP, there were significant differences in the change from baseline between the groups regarding BMI (7.5 [95% CI, 7.3-7.7]; $P < .001$) and HbA_{1c} concentration (14.82 mmol/mol [95% CI, 14.24-15.41 mmol/mol]; 1.36% [95% CI, 1.14%-1.30%]; $P < .001$). Kaplan-Meier probability curves for the cumulative incidence of new DR during the follow-up period are shown in **Figure 1**. In total, 188 patients in the GBP group and 317 patients in the control group developed new DR. The risk for DR was reduced in the GBP group (hazard ratio [HR], 0.62 [95% CI, 0.49-0.78]; $P < .001$). The most important risk factors for the development of DR at baseline were diabetes duration, HbA_{1c} concentration, use of insulin, glomerular filtration rate, and BMI (**Figure 2**).

The cumulative incidence of the development of sight-threatening diabetic macular edema was not different between the GBP group and controls (0.8% [95% CI, 0.6%-1.1%] vs 0.6% [95% CI, 0.4%-0.9%]) (**Figure 3**A). In total, 42 patients in the GBP group and 45 patients in the control group received a new diagnosis of diabetic macular edema. Likewise, there was no evidence of increased risk of the development of other sight-threatening or treatment-requiring diabetic ocular complications,

Figure 1. Cumulative Incidence of New Diabetic Retinopathy After Gastric Bypass Surgery and in Patients Who Have Not Undergone Surgery

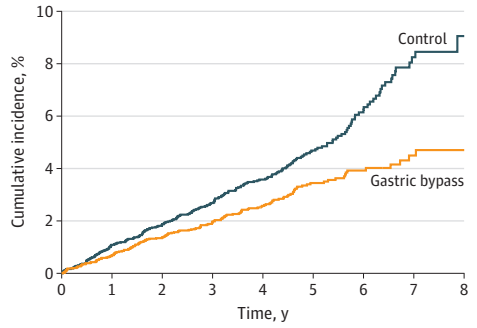
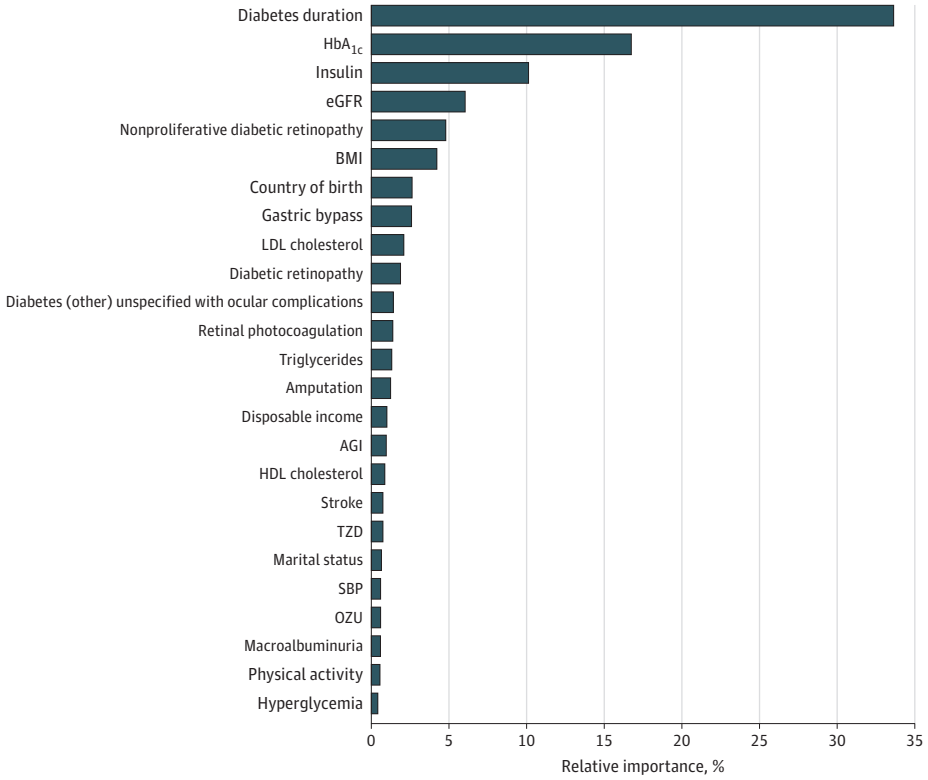


Figure 2. Relative Importance of Risk Factors at Baseline for the Development of New Diabetic Retinopathy in Patients With Type 2 Diabetes Who Have Had Gastric Bypass Surgery



AGI indicates α-glucosidase inhibitors; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OZU, ozurdex; SBP, systolic blood pressure; TZD, glitazones.

such as proliferative DR and the need for intravitreal drug administration (GBP group, 0.9% [95% CI, 0.6%-1.2%]; controls, 0.6% [95% CI, 0.4%-0.9%]) (Figure 3B) or panretinal photocoagulation (GBP group, 1.6% [95% CI, 1.3%-2.1%]; controls, 2.3% [95% CI, 1.9%-2.8%]) (Figure 3C).

Discussion

In this large nationwide matched cohort study of patients with diabetes, GBP was associated with a decreased risk of developing new DR. Furthermore, there were no indications of increased occurrence of sight-threatening or treatment-requiring DR in patients with no DR at baseline.

Bariatric surgery has been found to reduce all-cause mortality and the incidence of macrovascular morbidity among patients with diabetes for more than 3 to 5 years.[1,23] In the present cohort, BMI and HbA_{1c} concentration were reduced in the GBP group 1 year postoperatively compared with the controls, in accordance with published 5-year results on approximately 25 000 patients from the SOReg who underwent GBP.[8] The rapid improvement in metabolic control after bariatric surgery may entail a risk for paradoxical deterioration in preexisting DR.[24,25]

In the Diabetes Control and Complications Trial, 13.1% of 711 patients with type 1 diabetes in the intensive treatment group had early worsening of DR compared with 7.6% of 728 patients in the conventional treatment group.[26] More recently, in the clinical trial evaluating semaglutide (SUSTAIN [Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes]), a glucagon-like peptide-1 receptor agonist for the treatment of diabetes, a significant increase in the risk for DR complications was observed compared with placebo.[27] There was also a numerical but not statistically significant increase in a recent randomized clinical trial with another glucagon-like peptide-1 receptor agonist, dulaglutide, vs placebo.[28] Whether bariatric surgery entails a risk of early worsening and development of sight-threatening DR (owing to its association with metabolic control in patients with diabetes) has been discussed.[16] Case reports of severe worsening of DR after bariatric surgery have been published.[14]

In contrast, the present study demonstrated a reduced incidence of new DR, indicating an association of GBP with microvascular diabetic complications. Similar findings were observed in a recently published matched cohort study on various surgical weight-reducing procedures.[11] The findings in the present study are also in line with results from a case-control study of 45 patients, although interpretation of those study results was impeded by significant heterogeneity between the groups.[29] The incidence of advanced end-stage microvascular diabetic ocular complications, measured as blindness in at least 1 eye or the performance of ocular surgery, was reduced in a population-based controlled cohort study.[23] This supported the finding of a reduced risk for microvascular diabetic complications after GBP in patients with diabetes.

The most important risk factors for the development of DR at baseline were diabetes duration, HbA_{1c} concentration, use of insulin, estimated glomerular filtration rate, and BMI, in line with findings from other studies.[30,31] We found no indications, such as diabetic macular edema, proliferative DR, need for intravitreal drug administration, panretinal photocoagulation, or vitrectomy after GBP, of increased incidence of DR that threatened sight or required treatment. Retrospective reviews of ophthalmologic data on patients who had undergone bariatric surgery indicate that the degree of preexisting DR remains stable in most patients.[13,15] Similar results were obtained in a prospective study of 56 patients followed up for 12 months after bariatric surgery.[12] In addition, a reduced rate of progression in DR was observed in a smaller study of 96 patients with diabetes undergoing surgery compared with 48 controls who did not undergo surgery.[32] Nevertheless, small proportions of patients have been found to exhibit improvement in, as well as worsening of, the degree of DR after surgery.[13,15] In a study by Amin et al,[33] the overall incidence of DR was reduced in patients who underwent bariatric surgery compared with controls who did not undergo surgery during a 3-year follow-up period. However, the incidence of potentially sight-threatening DR in that study was 12% in patients with preoperative DR compared with 6% in patients without retinopathy before they underwent bariatric surgery.

Strengths and Limitations

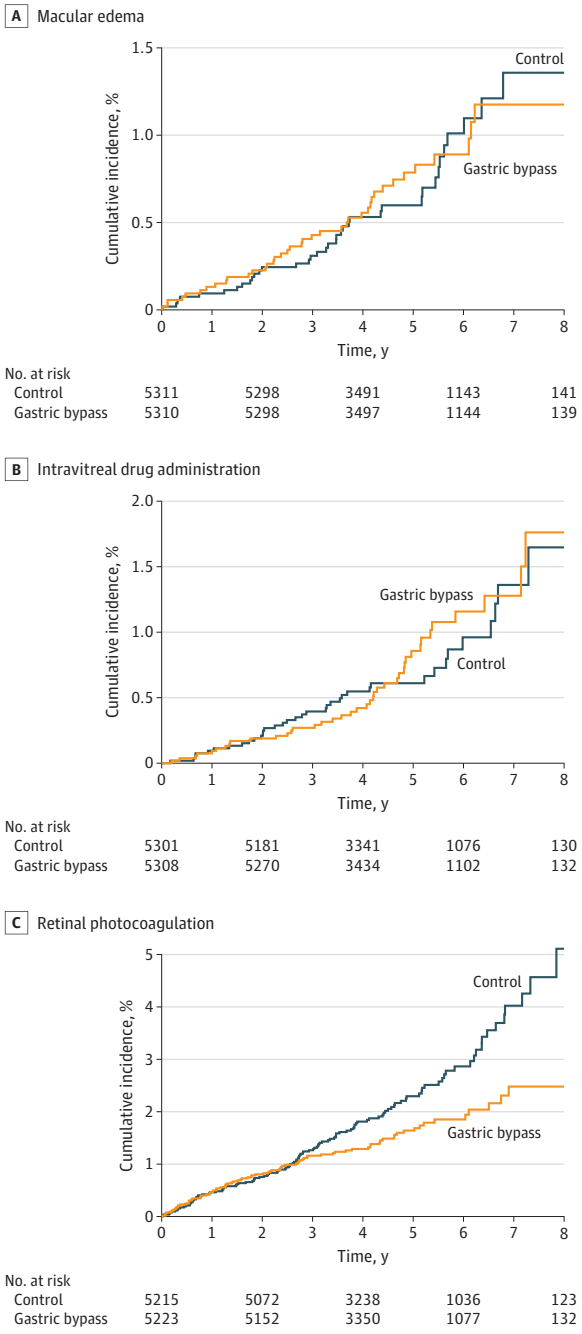
This study has some strengths, including the large matched patient cohort of more than 10 000 individuals with long-term follow-up. Furthermore, using validated data from nationwide quality and other registers minimizes the risk of bias and subjectivity in evaluating ophthalmologic findings.

This study also has some limitations. The development of diabetic macular edema outside the center of the macula, and thus not associated with vision loss or requiring treatment, could not be determined in this study but would be an interesting outcome. Similarly, development of severe nonproliferative DR could not be determined with certainty. Severe nonproliferative DR might portend a greater risk of vision loss in the future if the incidence were greater in one of the cohorts. Furthermore, in our analysis of the incidence of sight-threatening diabetic ocular complications or need for ophthalmic treatment, we found that only a few events occurred. Although reassuring, the results must nevertheless be interpreted with some caution.

Conclusions

This nationwide cohort study of patients with diabetes demonstrated that GBP is associated with a decreased risk of developing new DR. Furthermore, there were no indications of increased occurrence of DR that threatened sight or required treatment. These data support the view that, besides standard screening for DR, there is no need for extended ophthalmologic surveillance of patients with diabetes undergoing GBP surgery if there is no DR at baseline.

Figure 3. Cumulative Incidence of Outcomes in Patients After Gastric Bypass Surgery and in Patients Who Have Not Undergone Surgery



A, New diabetic macular edema. B, Intravitreal drug administration. C, Photocoagulation.

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Author Contributions: Drs Franzén and Svensson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Franzén, Morén, Ottosson, Sundbom, Svensson, Granstam.
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Conflict of Interest Disclosures: Dr Åkerblom reported serving as a member of the advisory board for Novartis, unrelated to the submitted work. Dr Eliasson reported receiving personal fees from AMGEN, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Navamedic, NovoNordisk, and RLS Global; and grants and personal fees from Sanofi, outside the submitted work. Dr Granstam reported serving as a member of advisory boards for Novartis, Bayer, and Allergan, unrelated to the submitted work. No other disclosures were reported.

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