Factors affecting relapse of type 2 diabetes after bariatric surgery in Sweden 2007–2015: a registry-based cohort study

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Received 30 April 2021; accepted 1 December 2021

Abstract

Background: Although a large proportion of patients with type 2 diabetes (T2DM) who have undergone metabolic surgery experience initial remission some patients later suffer from relapse. While several factors associated with T2D remission are known, less is known about factors that may influence relapse.

Objectives: To identify possible risk factors for T2D relapse in patients who initially experienced remission.

Setting: Nationwide, registry-based study.

Methods: We conducted a nationwide registry-based retrospective cohort study including all adult patients with T2D and body mass index ≥35 kg/m² who received primary metabolic surgery with Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) in Sweden between 2007 and 2015. Patients who achieved complete diabetes remission 2 years after surgery was identified and analyzed. Main outcome measure was postoperative relapse of T2D, defined as reintroduction of diabetes medication.

Results: In total, 2090 patients in complete remission at 2 years after surgery were followed for a median of 5.9 years (interquartile range [IQR] 4.3–7.2 years) after surgery. The cumulative T2D relapse rate was 20.1%. Duration of diabetes (hazard ratio [HR], 1.09; 95% confidence interval [CI], 1.05–1.14; P < .001), preoperative glycosylated hemoglobin A1C (HbA1C) level (HR, 1.01; 95% CI, 1.00–1.02; P = .013), and preoperative insulin treatment (HR, 2.67; 95% CI, 1.84–3.90; P < .001) were associated with higher rates for relapse, while postoperative weight loss (HR, .93; 95% CI, .91–.96; P < .001), and male sex (HR, .65; 95% CI, .46–.91; P = .012) were associated with lower rates.

Conclusion: Longer duration of T2D, higher preoperative HbA1C level, less postoperative weight loss, female sex, and insulin treatment prior to surgery are risk factors for T2D relapse after initial remission. (Surg Obes Relat Dis 2021;:1–8.) © 2021 American Society for Bariatric Surgery. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: Bariatric surgery; Metabolic surgery; Gastric bypass; Sleeve gastrectomy; Obesity; Type 2 diabetes; Diabetes; Relapse

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https://doi.org/10.1016/j.soard.2021.12.005
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Obesity is a strong risk factor for developing type 2 diabetes (T2D) [1,2]. Bariatric surgery is currently the most effective way to achieve long-term weight loss as well as reduced mortality in individuals with severe obesity [3,4]. Individuals with obesity and concomitant T2D have a good chance, through metabolic surgery, to reduce the symptoms and signs of T2D without active treatment (i.e., remission) [5]. Unfortunately, some of the patients who initially achieve postoperative T2D remission later relapses [5,6]. Previous studies have suggested that approximately 31%–35% of patients with initial remission later suffer from relapse and that the number of pre-operative diabetes medications and pre-operative T2D duration are risk factors [6,7]. While several factors associated with T2D remission are known, less is known about factors that may influence relapse [8,9].

Patients who experience relapse of disease still show significantly better glycemic control and improved cardiovascular risk factors than preoperatively [7]. However, knowledge of risk factors associated with T2D relapse could be used in a preoperative risk-benefit evaluation in patients with diabetes and severe obesity. The information could also be used to design postoperative follow-up programs to identify patients with diabetes who relapse.

The aim of the present study was to identify factors associated with T2D relapse in patients with severe obesity and T2D who have undergone metabolic surgery in Sweden.

**Methods**

This study was a retrospective cohort study on prospectively collected data from the Scandinavian Obesity Surgery Registry (SOREg). The registry was launched in 2007 as a national quality and research register reporting preoperative, intraoperative, and follow-up data at 30 days and 1, 2, 5, and 10 years after surgery. At present, the registry covers virtually all metabolic surgical procedures in Sweden, with very high acquisition rate and internal validity [10]. All patients who underwent a primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) surgery between January 1, 2007, and December 31, 2015, and registered in the SOReg were considered for inclusion in the study. Only patients with T2D as defined by the American Diabetes Association prior to surgery and included in the study. Only patients with T2D as defined by the American Diabetes Association prior to surgery and later achieved complete remission at 2 years after surgery were included [1].

By using the Swedish personal identification number, unique to each citizen, the SOReg data file was linked to the Swedish National Patient Register, the Swedish Population Register (for mortality data), the Swedish Prescribed Drug Register, and Statistics Sweden. Information on baseline characteristics, surgery, and follow-up were based on data from SOReg. Since cardiovascular comorbidity and previous pulmonary embolus/deep venous thrombosis are not obligatory variables in SOReg, data on these conditions were based on combined data from the Swedish National Patient Register and SOReg. Preoperative duration of diabetes was based on a combination of data from SOReg, the National Patient Register, and the Swedish Prescribed Drug Register. Data on specific pharmacologic treatments for diabetes were based on data from SOReg and the Swedish Prescribed Drug Register. Information on the educational level was based on patient-specific data from Statistics Sweden.

**Procedures**

The surgical method for gastric bypass is highly standardized in Sweden, with 99% being an antecolic/antegastric gastric bypass procedure with a small gastric pouch [11]. The sleeve gastrectomy is less standardized, but routinely performed using a 32–36 Fr bougie with the gastric division starting 5 cm from the pylorus and ending 1 cm from the angle of His. Perioperative care closely follows the Enhanced Recovery After Surgery guidelines, with early mobilization, routine thromboprophylaxis, and start of oral fluids on the day of surgery [12].

**Outcomes and definitions**

The main outcome measure was T2D relapse in those patients who had T2D prior to surgery and were in complete remission 2 years after surgery.

Complete remission of diabetes was defined as a glycated hemoglobin A1C (HbA1C) <42 mmol/mol (6%) without medical treatment, in accordance with the recommendations of the American Society for Metabolic and Bariatric Surgery [13]. Relapse of diabetes was defined as reintroduction of diabetes medications. Insulin treatment pre-operatively was defined by the presence of insulin treatment pre-operatively regardless of the duration of insulin treatment.

Comorbidity was defined as a medical condition requiring pharmacologic treatment, or continuous positive airway pressure treatment in the case of sleep apnea. Cardiovascular comorbidity was defined as a history of ischemic heart disease, angina pectoris, cardiomyopathy, cardiac failure, or arrhythmic heart disease.

Postoperative complications were classified according to the Clavien-Dindo classification, and having a postoperative complication was defined as Clavien-Dindo ≥1. Postoperative complications graded ≥3b (intervention under general anesthesia or need for care in the intensive care unit) were considered as serious complications [14]. Since more specific classification of postoperative complications was made obligatory in SOReg starting January 1, 2010, only patients operated on from this date onwards were included in the analysis of serious postoperative complications.
Statistics

Baseline data (before surgery) and follow-up data are presented as numbers of individuals (n) with percentages of patients for categorical values, mean ± standard deviation (SD) for continuous variables assuming normal distribution, and median ± interquartile range (IQR) for continuous variables not assuming normal distribution. Time to relapse was estimated and visualized using the Kaplan-Meier method and presented as cumulative relapse rate (1-Kaplan-Meier estimate). All patients were followed until reintroduction of diabetes medication, and censored in case of emigration, death, or on December 31, 2018, whichever came first. Cox regression analyses were considered appropriate since the duration between operation and prescription of diabetes medications was known in cases where diabetes relapse had occurred. Univariable Cox regression analyses were conducted to evaluate risks related to the major endpoint of the study. Based on previous studies and plausible impact of preoperatively available factors, diabetes duration, insulin treatment, body mass index (BMI), age, sex, HbA1C, education, postoperative weight loss, and surgical method were incorporated in the multivariable Cox regression analyses [7,15,16]. The model was also tested for multicollinearity using linear regression. A variance inflation factor (VIF) >2 was considered to indicate an issue with multicollinearity. Since no multicollinearity issues were detected, the original analysis plan was retained. Due to potential of over-adjustment of weight effects on surgical method, a further supplementary multivariable Cox regression analysis was conducted where postoperative weight loss was omitted. In response to differences in relapse depending on sex, a supplementary post hoc analysis stratified by sex was conducted. Missing data were handled by listwise exclusion. \( P < .05 \) was considered to represent statistical significance.

SPSS Statistics version 25 (IBM, Armonk, New York) was used for all statistical analyses.

Ethics

The study was approved by the Swedish Ethical Review Authority (Dnr 2020–03005) and conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. No written consent was obtained from the study participants. However, in accordance with Swedish legislation, all participants were informed of the research and quality registry and that the data would be used in clinical research, giving the patients the right to decline participation.

Results

During the inclusion period, 8546 patients with T2D according to the definition of the American Diabetes Association were identified in SOReg. Two years after surgery, 58 patients had died, and 3256 patients were lost to follow-up. A HbA1C value was available at 2 years for 3595 patients, and of these, 2090 patients achieved complete T2D remission (Fig. 1). During the study period, 10 patients (.5%) underwent revisional surgery. These were kept in the study in accordance with the intention-to-treat. Patients with complete remission at 2 years were defined as the study group. Follow-up for T2D relapse as defined by prescription of diabetes drugs was 100%.

Data on baseline characteristics for the study group are presented in Table 1.

Surgical data

Among the 2090 patients who achieved total T2D remission at 2 years after surgery, 2013 (96.3%) underwent a gastric bypass procedure, and 77 (3.7%) a SG. A laparoscopic procedure was completed in 1963 operations (93.9%), 89 (4.3%) were primary open procedures, and 38 (1.8%) were converted to open surgery. A postoperative
Table 1
Baseline characteristics

| Characteristic                                      | Missing data |
|-----------------------------------------------------|--------------|
| Preoperative BMI, mean ± SD, kg/m²                  | 0 (%), 42.7 ± 5.83 |
| Age, mean ± SD, yr                                  | 0 (%), 46.6 ± 10.10 |
| Percentage total weight loss 1 yr after surgery, % ± SD | 87 (4.2%), 29.9 ± 7.24 |
| Procedure                                           | 0 (%), 2013 (96.3) |
| Gastric bypass, n (%)                               | 77 (3.7) |
| Sleeve gastrectomy, n (%)                           | 1350 (64.6%), 740 (35.4%) |
| Sex                                                 | 0 (0.0%) |
| Female, n (%)                                       | 0.0% |
| Male, n (%)                                         | 0.0% |
| Comorbidity                                         | 0.0% |
| Sleep apnoea, n (%)                                 | 380 (18.2%) |
| Cardiovascular comorbidity, n (%)                   | 194 (9.3%) |
| Hypertension, n (%)                                 | 1078 (51.6%) |
| Dyslipidaemia, n (%)                                | 485 (23.2%) |
| Dyspepsia / Gastroesophageal reflux disease, n (%)  | 192 (9.2%) |
| Depression, n (%)                                   | 277 (13.3%) |
| Previous pulmonary embolus / Deep venous thrombosis, n (%) | 55 (2.6%) |
| Glycosylated hemoglobin A1C, mmol/mol ± SD          | 203 (9.7%), 54.8 ± 16.0 |
| Preoperative diabetes duration, median (IQR), yr    | 0.0%, 1 (0–4) |
| Insulin treatment prior to surgery, n (%)           | 0.0%, 286 (13.7) |
| Education                                           | 17 (8%) |
| Primary education ≤9 yr, n (%)                      | 350 (16.7%) |
| Secondary education 10–12 yr, n (%)                 | 1260 (60.3%) |
| Higher education ≤3 yr, n (%)                       | 228 (10.9%) |
| Higher education >3yr, n (%)                        | 235 (11.2%) |

BMI = body mass index; SD = standard deviation; IQR = interquartile range.

Fig. 2. Kaplan-Meier plot. Proportion of patients free from diabetes medication. Only patients with complete remission at 2 years after surgery.
complication (Clavien-Dindo ≥1) occurred within 30 days after 201 (9.7%) operations. For patients operated after 2010, a serious postoperative complication (Clavien-Dindo ≥3b) occurred after 41 operations (2.5%). Mean BMI loss at 2 years was 12.8 ± 4.6 kg/m², total weight loss 29.8 ± 8.6%, and excess BMI loss 75.3 ± 23.1%.

**Diabetes relapse**

In this study, patients were followed up to 9 years after surgery (median, 5.9 years; IQR, 4.3–7.2 years). During the follow-up period, relapse occurred in 199 cases (9.5%) with a cumulative relapse rate 20.1%. Disease-free survival is visualized in Fig. 2.

Longer duration of diabetes (hazard ratio [HR], 1.09; 95% CI, 1.05–1.14; *P* < .001), higher preoperative HbA1C level (HR, 1.01; 95% CI, 1.00–1.02; *P* = .013) and insulin treatment prior to surgery (HR, 2.67; 95% CI, 1.84–3.90; *P* < .001) were all associated with diabetes relapse in multivariable Cox regression, while higher postoperative weight loss (HR, .93; 95% CI, .91–.96; *P* < .001), and male sex (HR, .65; 95% CI, .46–.91; *P* = .012) were associated with lower risk. No significant correlation with age, preoperative BMI, level of education, or surgical method was found (Table 2).

In the supplementary analysis, where postoperative weight loss was omitted in multivariable Cox analysis (Supplementary Table 1), sleeve gastrectomy (HR, 3.14; 95% CI, 1.14–8.68), and preoperative BMI (HR, .97; 95% CI, .94–.99) also emerged as significant factors for T2D relapse. When stratified by sex, sleeve gastrectomy was significantly associated with higher risk for T2D relapse for men (HR, 5.95; 95% CI, 1.36–25.95), but not for women (HR, 1.67; 95% CI, .40–7.08) (Supplementary Table 2 and 3).

**Discussion**

Longer T2D duration, less controlled disease with higher preoperative HbA1C and insulin treatment, as well as less significant postoperative weight loss and female sex were all associated with higher risk for relapse after initial diabetes remission.

The factors of relevance for relapse are to large extent similar to those influencing diabetes remission, mainly representing longer duration and higher severity of disease [6,9]. After metabolic surgery, improved insulin sensitivity and beta cell function is achieved [17–19]. It has been suggested that after metabolic surgery there may also be regeneration or hyperplasia of beta-cells which can then protect against T2D relapse [17]. In a previous porcine model, an increase in beta-cell mass was seen after RYGB compared with control pigs on the same diet [20]. However, long T2D duration, insulin therapy, and low C-peptide levels are likely markers of irreversible beta-cell death [17]. Even effective antidiabetic treatment, such as metabolic surgery, cannot reverse an end-stage beta-cell failure [17]. Consequently, after metabolic surgery, beta-cell function, measured as disposition index, does not recover as well in patients with T2D compared with patients without T2D [19].

Weight loss in itself seems to increase insulin sensitivity and improve beta-cell function without being dependent on either surgical method or whether weight loss occurs surgically or non-surgically [18,21]. Thus, it seems reasonable

| Characteristic                                | Unadjusted HR (95% CI) | Adjusted HR (95% CI)* | Adjusted *P value† |
|-----------------------------------------------|------------------------|-----------------------|-------------------|
| Diabetes duration (years prior to surgery)    | 1.11 (1.07–1.14)       | 1.09 (1.05–1.14)      | <.001             |
| Glycosylated hemoglobin A1C (HbA1C) prior to surgery | 1.02 (1.01–1.02)       | 1.01 (1.00–1.02)      | .013              |
| Insulin treatment prior to surgery            | 3.53 (2.63–4.73)       | 2.67 (1.84–3.90)      | <.001             |
| Percentage total weight loss 1 yr after surgery| .94 (.92–.96)          | .93 (.91–.96)         | <.001             |
| Age                                           | .99 (.98–1.00)         | .98 (.97–1.00)        | .050              |
| BMI                                           | .96 (.94–.99)          | .98 (.95–1.01)        | .219              |
| Sex                                           |                        |                       |                   |
| Female                                        | Reference              | Reference             | Reference         |
| Male                                          | .96 (.72–1.29)         | .65 (.46–.91)         | .012              |
| Education                                     |                        |                       |                   |
| Primary education <9 yr                       | .91 (.62–1.35)         | .83 (.54–1.27)        | .388              |
| Secondary education 10–12 yr                  | Reference              | Reference             | Reference         |
| Higher education ≤3 yr                        | 1.16 (.75–1.78)        | 1.33 (84–2.10)        | .226              |
| Higher education >3yr                         | .85 (.53–1.38)         | .96 (.57–1.60)        | .870              |
| Surgical method                               |                        |                       |                   |
| Roux-en-Y gastric bypass                      | Reference              | Reference             | Reference         |
| Sleeve gastrectomy                            | 2.42 (.89–6.61)        | 2.67 (.96–7.43)       | .061              |

HR = hazard ratio; CI = confidence interval; BMI = body mass index.
* Multivariable Cox regression including all factors listed in the table.
† Reference
that patients with poor initial weight loss or late weight regain have a greater risk of T2D relapse [7]. In the current study, there was no significant difference between SG compared with RYGB in achieving relapse \( (P = .061) \). However, the lack of statistical significance could be a result of an insufficient number of patients in the SG group \( (n = 77, 3.7\%) \). The association between surgical method and weight loss has been shown in some previous studies where the weight loss was generally greater after RYGB than SG [22,23]. Omitting the initial weight loss in the multivariable Cox regression analysis resulted in a significant difference in HR between the surgical techniques with more relapses after SG (Supplementary Table 1). In this study, only RYGB and SG were analyzed, and the results can therefore not be readily extrapolated to other metabolic surgical techniques. However, RYGB and SG account for >95% of all metabolic surgical procedures worldwide [24]. Given the small numbers of SG in relation to RYGB in the present study, the comparison between the surgical methods should be interpreted with caution.

Sex did not appear as a significant factor for T2D relapse when analyzed by itself but emerged as a significant factor after adjustment for multiple potentially obscuring factors. Male obesity is characterized by a larger proportion of visceral fat than in women, and the visceral fat is likely to have a greater negative metabolic effect [25]. Weight loss in men may therefore have a greater positive metabolic effect and thus probably reduce the risk of T2D relapse. Although the prevalence of obesity in Sweden is approximately equally distributed between men and women, there is a significantly larger proportion of women than men among the individuals with T2D who undergo bariatric surgery [9,26]. It is a possibility that the subgroup of men undergoing bariatric surgery may differ from the corresponding female subgroup also in terms of factors that have not been addressed in this study. In an animal study with a rodent model, different effects on lipid metabolism between males and females could be seen after SG [27]. Although no sex-related differences in T2D remission after metabolic surgery was reported in a matched-pair baseline. Despite the high rates of diabetes remission after bariatric surgery, high rates of relapse have been reported [6,7]. Although the cumulative T2D relapse rate of 20.1% up to 9 years postoperatively in the present study was lower than that reported in the North American context, this still represents a significant rate of relapse. The differences in relapse rates are likely to be attributed to differences in patient populations as well as differences in definitions of remission and relapse. In our study, the time 2 years postoperatively was used in the definition of complete remission, while other time frames were used in other studies. A major reason why the risk of relapse in our study is slightly lower than in other studies could be that relapse is only identified based on represcription of diabetes drugs and not HbA1C value. In Sweden, patients are usually followed up at least annually after metabolic surgery (initially at the surgical clinic, but later taken over by primary care facilities). According to Nordic guidelines, analysis of HbA1C or fasting plasma glucose is recommended at the annual follow-ups [30]. Consequently, the possibility of detecting a T2D relapse should be high. Compared with some other studies, a significantly smaller proportion of patients had insulin treatment preoperatively (13.7%), which indicates a generally better metabolic control and therefore also contribute to the lower risk of T2D relapse.

However, it is likely that despite a late T2D relapse, surgery still has a beneficial metabolic effect even in the long term [7]. The presence of risk factors for relapse may thus be used for clinical guidance, to identify patients for whom long-term close follow-up is particularly important. However, a higher risk for relapse should not be considered a reason to disqualify patients from surgery. Furthermore, metabolic surgery early after T2D diagnosis has previously been shown to have a positive effect on T2D remission [9], but as the present study suggests, surgery early in the course of disease also reduces the risk of T2D relapse after initial remission. Consequently, patients with obesity and T2D should be prioritized for metabolic surgery at an early stage.

**Strengths and limitations**

Despite the strengths of the study—large number of patients, nationwide data, and the high quality of the registers used—there are also limitations that must be acknowledged. The main limitations of the study lie in its retrospective nature and the low availability of HbA1C values and data on body weight at long-term follow-up. To minimize the loss of data in the Cox regression analyses, we therefore chose to use weight loss during the first postoperative year instead of the first 2 years as a marker for weight loss. However, it has been previously shown that the degree of initial weight loss can be used to predict long-term weight trajectory [31]. Combining diabetes medications and HbA1C in the definition of T2D would have been optimal. Due to limited access...
to HbA1C data after the 2-year follow-up, the relapse assessment could only be based on drug prescription.

With access to all prescriptions of diabetes medications via the Swedish Prescribed Drug Register without any loss of data, all cases where a drug was introduced due to a T2D relapse was assessable. For patients with low adherence to follow-up, there is a risk that a possible T2D relapse could become delayed and not be documented as a relapse in this study. However, we believe that the vast majority of patients treated preoperatively for T2D are likely to be followed up with vigilance in healthcare, not least due to a general distrust of definitive cure of chronic disease [32]. Finally, including patients who underwent revision surgery may risk overestimating treatment effects, however these patients were few (5%), and we find it unlikely that they would have any strong influence on the main results.

**Conclusion**

The risk of T2D relapse in patients who have achieved initial complete T2D remission after bariatric surgery is increased by longer duration of pre-operative T2D, higher preoperative HbA1C level, less postoperative weight loss, female sex, and insulin treatment prior to surgery.

**Acknowledgments**

This work was supported by grants from Region Örebro County, the Bengt Ihre Foundation, Stockholm County Council, and SRP Diabetes.

**Disclosures**

I.N. has received consultant fees from Baricol Bariatrics AB and Johnson & Johnson Medical and lecturing fees from AstraZeneca. J.O. has received consultant fees from Johnson & Johnson Medical and Vifor Pharma. E.S. has received lecturing fees from Johnson & Johnson Medical. None of the mentioned disclosures were related to the contents of this work. None of the remaining authors declares any conflict of interest.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2021.12.005.

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