Factors associated with resolution of type-2 diabetes mellitus after sleeve gastrectomy in obese adults

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Many bariatric procedures are more effective for improving type-2 diabetes mellitus (T2DM) than conventional pharmacotherapy. The current research evaluated factors linked to complete and partial remission or improvement of T2DM after laparoscopic sleeve gastrectomy (LSG). The current prospective study included all diabetic patients who were submitted LSG between January 2015 and June 2018 and completed a 2-year follow-up period. Patients were assessed at baseline and 2 years after LSG. This work comprised of 226 diabetic cases. Two years after LSG, 86 patients (38.1%) achieved complete remission of DM, and 24 (10.6%) reached partial remission. Only 14 patients (6.2%) showed no change in their diabetic status. On univariate analysis, age ≤ 45 years, duration of diabetes ≤ 5 years, use of a single oral antidiabetic, HbA1c ≤ 6.5%, HOMA-IR ≤ 4.6, C-peptide > 2.72 ng/mL, and BMI ≤ 40 kg/m² predicted complete remission. The independent predictors of complete remission were age ≤ 45 years, duration of diabetes ≤ 5 years, use of a single oral antidiabetic, HOMA-IR ≤ 4.6, and C-peptide > 2.72 ng/mL. A combined marker of young age, short duration of DM, and low HOMA-IR predicted complete remission with sensitivity 93% and specificity 82%. Independent predictors of complete remission of T2DM after LSG were younger age, shorter duration, single oral antidiabetic, lower HOMA-IR, and higher C-peptide.

In 1997, obesity was declared an epidemic by the World Health Organization1; however, its prevalence is increasing worldwide. It is estimated that over 2 billion adults, i.e., about 39% of human beings, were overweight or obese in 20162. The burden of obesity is aggravated by its associated comorbidities as type 2-diabetes mellitus (T2DM) and cardiovascular diseases (CVD), among others3. The increase in obesity rates seems to be the main factor for the recent surge in the prevalence of T2DM4. About 44% of the burden of T2DM is attributable to overweight and obesity5, and 9.5% of all body mass index-related deaths were due to diabetes in obese patients5.

Despite efforts through lifestyle interventions to treat obesity and T2DM, only a minority of patients achieved long-term weight loss and glycemic targets6. There is a reasonable body of evidence to confirm that many bariatric procedures are more effective than conventional pharmacotherapy for improvement or even inducing complete remission of T2DM6–10. These procedures include Roux-en-Y gastric bypass11, sleeve gastrectomy12, and duodenal switch/biliopancreatic diversion13.

Recently, laparoscopic sleeve gastrectomy (LSG) turned into the most popular bariatric operation in many parts of the world14. The current analysis aimed to assess the possible factors linked to complete and partial remission or improvement of T2DM after laparoscopic sleeve gastrectomy (LSG).

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**Patients and methods**

This prospective work included patients who were submitted LSG between January 2015 and June 2018. The ethics committee approved the study at the Cairo University Hospitals. All methods were performed in accordance with the relevant guidelines and regulations. Besides, written informed consent was obtained from all subjects. Inclusion criteria were subjects with T2DM, aged 18–65 years, with BMI ≥ 35. Exclusion criteria were subjects who had revisional LSG and those with type-1 diabetes mellitus.

Patients were reviewed at baseline and 2 years after LSG. Data registered were demographic and anthropometric (age, sex, weight), laboratory (fasting blood glucose, HbA1c, C-peptide, insulin level), and clinical (insulin and/or oral medications, diabetes duration, the existence of elevated blood pressure, hyperlipidemia) characteristics. Percent weight loss and BMI change were obtained using the previously reported methods. Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR).

The current analysis adopted the standardized American Society of Bariatric and Metabolic Surgery definitions of evolution of T2D post-bariatric procedures (Table 1).

The operation began with the division of gastroplenic ligament along the greater curvature 4 cm from the pylorus up to the left diaphragmatic crus with ultrasonic shears. The stomach was then mobilized and divided along the lesser curvature from antrum (4 cm from pylorus) till reaching the angle of His using buttressed (SeamGuard, Gore, Inc., Flagstaff, Arizona, USA) linear 60-mm stapler (Covidien Tristapler, Medtronic, Minneapolis, Minnesota, USA) over the calibration tube (Midsleeve 36 Fr) introduced into the gastric lumen. The specimen was extracted through the umbilical port. The operation was ended with a methylene blue leak testing.

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). The power of the test used for primary outcome measure was estimated using the G Power software (Institutfür Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, Germany) version 3.1.9.2. Numerical variables were calculated as mean and standard deviation or median and range as appropriate. Qualitative variables were calculated as frequency and percentage. Chi-square test (Fisher’s exact test) was used to examine the relation between qualitative variables. For quantitative variables, comparison between two arms was made using independent sample t-test or Mann–Whitney test. Multivariate analysis was performed using logistic regression method for the significant factors found on univariate analysis. Odds ratio (OR) with its 95% confidence interval (CI) were used for risk estimation. A p-value < 0.05 was considered significant.

**Consent to participate.** Consents were done for all enrolled cases.

**Results**

At the start of the study, 254 patients were included, however, only 226 completed the follow-up. Only those who completed the follow-up were included in the analysis.

Table 2 shows the baseline data of the 226 patients of the studied group. Hypertension and dyslipidemia were common comorbidities. Near 40% of the studied group received insulin for glycemic control.

Two years after LSG, 86 patients (38.1%) achieved complete remission of DM, and 24 (10.6%) reached partial remission. Besides, improvement of diabetes occurred in 102 patients (45.1%). Only 14 patients (6.2%) showed no change in their diabetic status. More than half of those with hypertension and dyslipidemia got resolution of the disease (Table 3).

Table 4 shows a significant difference between patients who developed complete remission of T2DM and those who did not, in all pre-and postoperative characteristics except sex, hypertension, dyslipidemia, insulin therapy, and preoperative weight.

On univariate analysis, predictive factors for complete remission were age ≤ 45 years, duration of diabetes ≤ 5 years, use of a single oral antidiabetic, HbA1c ≤ 6.5%, HOMA-IR ≤ 4.6, C-peptide > 2.72 ng/mL, and BMI ≤ 40 kg/m² (Table 5). Using logistic regression, the independent predictors of complete remission were age ≤ 45 years, duration of diabetes ≤ 5 years, use of a single oral antidiabetic, low HOMA-IR ≤ 4.6, and C-peptide > 2.72 ng/mL (Table 6). A combined marker of young age, short duration of DM, and low HOMA-IR provide a very good prediction of complete remission with sensitivity 93% and specificity 82%.

**Discussion**

Several reports have confirmed bariatric surgery’s effectiveness in resolving type-2 diabetes with a diverse remission rate and/or improvement rate. Many studies have proposed predictors of remission of diabetes after weight-loss operations. Others introduced scores for such predictors. The majority of these studies included different types of bariatric procedures, particularly RYGB. Previous studies investigating SG cases involved a

| Status               | Description and criteria                                      |
|----------------------|--------------------------------------------------------------|
| Complete remission   | Normal levels of glucose parameters (HbA1c < 6% and FBG < 100 mg/dL) without the use of hypoglycemic medications |
| Partial remission    | Defined as HbA1c 6%–6.4% and FBG 100–125 mg/dL without the use of hypoglycemic medications |
| Improvement          | Decrease in HbA1c and FBG not fulfilling criteria for remission, or reduction in antidiabetic drug use |
| Unchanged            | Neither remission nor improvement                            |

Table 1. Determination of the status of type 2 diabetes. HbA1c Glycated hemoglobin; FBG fasting blood glucose.
small sample size or omitted many important factors like age, HbA1c, and C-peptide. Almost all studies followed up their patients for 1 year. The current research probably presents the largest series of patients treated with LSG who were followed up for 2 years.

The study demonstrated that predictive factors for T2DM complete remission at 2 years were age ≤ 45 years, duration of diabetes ≤ 5 years, use of a single oral antidiabetic, HbA1c ≤ 6.5%, HOMA-IR ≤ 4.6, C-peptide > 2.72 ng/mL, and BMI ≤ 40 kg/m². On multivariate analysis, independent predictors of complete remission were younger age, shorter duration, single oral antidiabetic, lower HOMA-IR, and higher C-peptide. A combined marker of young age, short duration of DM, and low HOMA-IR provide a very good prediction of complete remission with 93% sensitivity and 82% specificity.

| Value                         |   |
|-------------------------------|---|
| Age (years)                   | 41.6 ± 8.8 |
| Sex (male/female)             | 128/98        |
| Weight (kg)                   | 128.7 ± 13.2 |
| Body mass index (kg/m²)       | 43.1 ± 4.6    |
| Duration of diabetes mellitus | 6 (1–15)      |
| Hypertension                  | 114 (50.4%)   |
| Dyslipidemia                  | 98 (43.4%)    |
| **Treatment of diabetes mellitus** |   |
| Insulin therapy               | 86 (38.1%)    |
| Number of oral hypoglycemic agents | 2 (1–4)    |
| Sulphonylurea                 | 158 (69.9%)   |
| Metformin                     | 190 (84.1%)   |
| Incretin mimics               | 92 (40.7%)    |
| SGLT2-inhibitor               | 40 (17.7%)    |
| Pioglitazone                  | 16 (7.1%)     |
| **Laboratory findings**       |   |
| C-peptide (ng/dL)             | 3.8 ± 1.7     |
| Fasting blood glucose (mg/dL) | 172.6 ± 63.5  |
| Glycated hemoglobin (%)       | 7.7 ± 1.2     |
| Homeostatic Model Assessment of Insulin Resistance | 4.6 (1.3–12.4) |

Table 2. Baseline clinical and laboratory data of the enrolled group. Data are expressed as mean ± SD, median (range), or number (%).

| Value                         |   |
|-------------------------------|---|
| Weight (kg)                   | 102.7 ± 10.5 |
| Body mass index (kg/m²)       | 29.8 ± 5.1    |
| Weight loss (kg)              | 26.0 ± 8.9    |
| Percent weight loss           | 20.0 ± 5.8    |
| Body mass index loss (kg/m²)  | 13.3 ± 2.0    |
| Percent body mass index loss  | 31.1 ± 5.8    |
| **Outcome of diabetes mellitus** |   |
| Complete remission            | 86 (38.1%)    |
| Partial remission             | 24 (10.6%)    |
| Improvement                   | 102 (45.1%)   |
| No change                     | 14 (6.2%)     |
| Hypertension resolution       | 64 (56.1%)    |
| Dyslipidemia resolution       | 52 (53.1%)    |
| **Laboratory findings**       |   |
| Fasting blood glucose (mg/dL) | 132.4 ± 52.7  |
| Glycated hemoglobin (%)       | 6.5 ± 1.3     |
| Homeostatic Model Assessment of Insulin Resistance | 3.2 (1.0–10.4) |

Table 3. Outcome of sleeve gastrectomy after 2 years of follow up. Data are expressed as mean ± SD, median (range), or number (%).
In the current study, complete remission occurred in 38% of patients in addition to 10.6% partial remission. Metabolic failure is observed in only 6.2% of cases. A recent meta-analysis in the United Kingdom reported a rate of diabetes remissions of 94.5 per 1,000 person-years, an 18-fold increased chance for remission than matched controls. The authors found a larger effect size in patients undergoing gastric bypass compared to SG. Malabsorptive procedures tend to have a better antidiabetic impact compared to restrictive procedures as SG. It has been reported that RYGB results in 50–80% remission rate of T2DM.

The explanation for resolution or improvement remains unclear, but decreased energy intake and weight loss probably significantly contribute to this process. However, early resolution of diabetes within 1 week of surgery indicates that weight loss per se cannot explain the entire mechanism. The effect of restrictive procedures as SG may be attributed to the immediate and severe caloric restriction that forces the human body to use internal energy sources. A reduction in liver fat content normalizes hepatic insulin sensitivity by improving fasting plasma glucose. These findings are supported by observing liver volume and liver fat content reduction after a low-calorie diet before bariatric surgery. Moreover, after 1 week of restricted energy intake, normalization of β-cell function has been demonstrated. Therefore, food restriction can sensibly explain the rapid postoperative metabolic improvement.

However, SG can be viewed as more than a restrictive procedure. It has been followed by decreased ghrelin secretion and increased GLP-1 synthesis, changes similar to those reported after RYGB. It was suggested that the balance between ghrelin and GLP-1 might be the key to improved glucose homeostasis. Numerous studies have verified increased levels of bile acids after SG that could lead to ameliorations in insulin sensitivity, incretin secretion, and postprandial glycemia.

The predictive factors found in the current study go in accordance with the shared denominators of diabetes remission in previous studies. Many studies proposed younger age, shorter duration of DM, no preoperative insulin use, lower HbA1c, and no preoperative C-peptide levels as linked to poor control of diabetes after bariatric surgery.

Table 4. Pre- and postoperative characteristics in cases who developed complete remission of T2DM 2 years after LSG and those who did not. CR complete remission, BMI body mass index, HOMA-IR homeostatic model assessment of insulin resistance.

| CR n=86 | No CR n=140 | p value |
|---------|-------------|---------|
| Age (years) | 36.4 ± 6.7 | 44.8 ± 8.4 | <0.001 |
| Sex (male/female) | Male 50 (39.1%) | 78 (60.9%) | 0.721 |
| | Female 36 (36.7%) | 62 (63.3%) | |
| Duration of diabetes mellitus | 4 (1–8) | 7 (1–15) | <0.001 |
| Hypertension | Yes 46 (40.4%) | 68 (59.6%) | 0.473 |
| | No 40 (35.7%) | 72 (64.3%) | |
| Dyslipidemia | Yes 38 (38.8%) | 60 (61.2%) | 0.845 |
| | No 48 (37.5%) | 80 (62.5%) | |

| Treatment of diabetes mellitus | | |
|-----------------------------|--------------------------|
| Insulin therapy | Yes 26 (30.2%) | 60 (69.8%) | 0.058 |
| | No 60 (42.9%) | 80 (57.1%) | |
| No. of oral hypoglycemics | Single 36 (69.2%) | 16 (30.8%) | <0.001 |
| | Multiple 50 (28.7%) | 124 (71.3%) | |

| Preoperative findings | | |
|----------------------|-----------------------------|
| Weight (kg) | 130.8 ± 13.3 | 127.4 ± 13 | 0.058 |
| BMI (kg/m²) | 42.2 ± 4.5 | 43.6 ± 4.7 | 0.025 |
| C-peptide (ng/mL) | 5.3 ± 1.5 | 2.9 ± 1.1 | <0.001 |
| Fasting blood glucose (mg/dL) | 135.5 ± 40.6 | 195.4 ± 64.4 | <0.001 |
| Glycated hemoglobin (%) | 7.1 ± 1.0 | 8.1 ± 1.2 | <0.001 |
| HOMA-IR | 3.39 ± 1.23 | 6.18 ± 2.21 | <0.001 |

| Postoperative findings | | |
|-----------------------|-----------------------------|
| Weight (kg) | 97.2 ± 8.5 | 106.0 ± 10.2 | <0.001 |
| BMI (kg/m²) | 27.4 ± 4.3 | 31.3 ± 5.0 | <0.001 |
| % Weight loss | 25.5 ± 4.0 | 16.7 ± 3.8 | <0.001 |
| % BMI loss | 35.3 ± 4.4 | 28.5 ± 4.9 | <0.001 |
| Fasting blood glucose (mg/dL) | 84.4 ± 7.2 | 161.9 ± 46.5 | <0.001 |
| Glycated hemoglobin (%) | 5.3 ± 0.4 | 7.2 ± 1.2 | <0.001 |
| HOMA-IR | 2.2 ± 0.9 | 4.3 ± 1.5 | <0.001 |
In obesity-associated T2DM, decreased insulin sensitivity is the first lesion, ensued by elevated insulin levels. Hyperglycemia arises because of β-cell failure to synthesize sufficient insulin. T2DM develops when pancreatic β-cell dysfunction follows in the face of decreased insulin sensitivity. Hepatic insulin resistance is mainly implicated in elevated blood glucose levels and overt diabetes. Insulin resistance with caloric overload leads to hepatic steatosis causing hepatic insulin resistance. Consequently, insulin fails to suppress liver glucose production leading to hyperglycemia, and the process is self-exacerbating. Higher HOMA-IR levels indicating greater insulin resistance can be markers of less chance of diabetic remission after bariatric surgery.

It sounds logical that less preoperative β-cell dysfunction is a determinant of diabetes remission following surgery. This is because the steady deterioration of β-cell function is an aspect of the natural history of diabetes. The current study found that a C-peptide level < 2.7 ng/mL is an independent factor predicting complete remission of DM. C-peptide is considered a more accurate evaluation of pancreatic β-cell function than insulin. A large percentage of insulin synthesized by the pancreas is degraded during the first pass hepatic metabolism compared to a negligible C-peptide amount. Older age and longer duration of diabetes are consequently associated with lower residual β cell mass.

Prediction models of diabetes remission were previously suggested for more practical implementation in clinical practice. For example, the DiaRem score included four variables for accurate remission prediction.

| CR (n=86) | No CR (n=140) | p value | OR (95% CI) |
|-----------|--------------|---------|-------------|
| Age (years) |
| ≤ 45 | 76 (53.5%) | 66 (46.5%) | <0.001 | 8.52 (4.07–17.83) |
| > 45 | 10 (11.9%) | 74 (88.1%) | 1 |
| Duration of DM |
| ≤ 5 years | 70 (64.8%) | 38 (35.2%) | <0.001 | 11.74 (6.08–22.69) |
| > 5 years | 16 (13.6%) | 102 (86.4%) | 1 |
| Insulin therapy |
| No | 60 (42.9%) | 80 (57.1%) | 0.058 | 1.73 (0.98–3.06) |
| Yes | 26 (30.2%) | 60 (69.8%) | 1 |
| No. of oral hypoglycemics |
| Single | 36 (69.2%) | 16 (30.8%) | <0.001 | 5.58 (2.84–10.95) |
| Multiple | 50 (28.7%) | 124 (71.3%) | 1 |
| Preoperative BMI |
| ≤ 40 kg/m² | 33 (47.8%) | 36 (52.2%) | 0.045 | 1.80 (1.01–3.20) |
| > 40 kg/m² | 53 (33.8%) | 104 (66.2%) | 1 |
| C-peptide (ng/mL) |
| > 2.72 | 84 (56.8%) | 64 (43.2%) | <0.001 | 49.88 (11.80–210.76) |
| ≤ 2.72 | 2 (2.6%) | 76 (97.4%) | 1 |
| Glycated hemoglobin (%) |
| ≤ 6.5 | 22 (78.6%) | 6 (21.4%) | <0.001 | 7.68 (2.97–19.86) |
| > 6.5 | 64 (32.3%) | 134 (67.7%) | 1 |
| HOMA-IR |
| ≤ 4.6 | 76 (67.9%) | 36 (32.1%) | <0.001 | 21.96 (10.26–45.97) |
| > 4.6 | 10 (8.8%) | 104 (91.2%) | 1 |

Table 5. Factors linked to complete remission of T2DM 2 years after LSG. OR odds ratio, CI confidence interval, CR complete remission, BMI body mass index, HOMA-IR homeostatic model assessment of insulin resistance.

| B | p value | OR (95% CI) |
|---|---------|-------------|
| Age ≤ 45 vs. > 45 | 1.929 | 0.001 | 6.9 (2.1–22.2) |
| Duration of DM ≤ 5 vs. > 5 years | 2.808 | <0.001 | 16.6 (4.8–57.9) |
| Oral hypoglycemics Single vs. Multiple | 2.079 | 0.006 | 8.0 (1.8–35.4) |
| C-peptide > 2.72 vs. ≤ 2.72 ng/mL | 5.643 | <0.001 | 282.2 (23.6–3377.5) |
| HOMA-IR ≤ 4.6 vs. > 4.6 | 3.579 | <0.001 | 35.8 (9.6–134.0) |

Table 6. Independent factors linked to complete remission of T2DM 2 years after LSG using logistic regression. B regression coefficient, OR odds ratio, CI confidence interval, HOMA-IR homeostatic model assessment of insulin resistance.
namely the use of insulin, age, HbA1c, and type of antidiabetic medication. The need for insulin therapy was the strongest indicator in this scoring system. Later studies ensured external validation of this score in independent populations. ABCD score determined four factors; age at surgery (A), baseline BMI (B), C-peptide level (C), and diabetes duration (D) to construct a 0 to 10 scoring system.

Almost all studies and predicting scores share common factors that can be categorized into two groups, disease status and preoperative management characteristics. Collectively, a longer duration and more progressive disease requiring more aggressive treatment allocate the patient fewer odds of diabetic remission. Careful preoperative assessment of these factors may guide a better selection of bariatric surgery candidates who will benefit from resolving the serious comorbidity T2DM alongside weight reduction.

Although the literature reported much data regarding the improvement of T2DM after LSG, to our knowledge, only a few studies addressed the factors linked to complete and partial remission, improvement, or unchanged status of T2DM after LSG. Besides, the reasonable number of cases with an acceptable follow-up period is a strength point of this study. The limitations of our study are mainly its nature as a single-center study. This raises the possibility of selection bias and difficulty of generalization to the entire bariatric population.

It should be noted that patient who did respond to sleeve may proceed malabsorptive procedures such as single anastomosis gastric bypass or Roux-en-Y gastric bypass. Duodenal switch as well as (Single anastomosis duodeno–ileal bypass) SADI are not commonly practiced in our center.

In conclusion, we found that independent predictors of complete remission of T2DM after LSG were younger age, shorter duration, single oral antidiabetic, lower HOMA-IR, and higher C-peptide. A combined marker of young age, short duration of DM, and low HOMA-IR provide a perfect prediction of complete remission with 93% sensitivity and 82% specificity. It is sensible to say that this work can help recognize cases that are most likely to avail from SG regarding the extent of T2DM remission.

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Competing interests
The authors declare no competing interests.
Additional information

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