Obesity Surgery (2020) 30:1046–1051
https://doi.org/10.1007/s11695-019-04350-0

ORIGINAL CONTRIBUTIONS

Weight Regain and Diabetes Evolution After Sleeve Gastrectomy: a Cohort Study with over 5 Years of Follow-Up

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Published online: 18 December 2019

Abstract

Background A number of meta-analyses have demonstrated the effectiveness of bariatric surgery in improving morbid obesity and its associated co-morbidities. The aim of the study was to evaluate at long term a cohort of obese patients with type 2 diabetes (T2DM) submitted to laparoscopic sleeve gastrectomy (LSG) analyzing the incidence of weight regain (WR) and the impact of the WR on T2DM evolution.

Methods Seventy-eight morbid obese patients (54 females) with T2DM, aged 49.6 ± 8.7 years, weight 121.1 ± 24.4 kg, BMI 44.1 ± 7.2 kg/m^2, underwent primary LSG. The trend over time of T2DM after LSG was analyzed in the different groups, subdivided on the basis of the absence or presence of WR and of its different degrees: no regain (NR), mild regain (MR), and severe regain (SR) groups.

Results In the NR group, 54% show complete remission, 46% persistence, and no case of diabetes relapse; in the MR group, 59% show complete remission, 36% persistence, and 5% relapse; in the SR group, 61% show complete remission, 22% persistence, and 17% relapse. A statistically significant difference concerns the preoperative values of fasting glucose, glycosylated hemoglobin, and duration of diabetes, major in the group with diabetes relapse (respectively, $p = 0.002$, $p = 0.001$, and $p < 0.0001$).

Conclusions The results of this study showed no significant difference regarding the trend of diabetes remission comparing the "no regain," "mild regain," and "severe regain" groups and confirmed the importance of the duration of the illness and an early intervention towards surgical therapy.

Keywords Type 2 diabetes · Obesity · Sleeve Gastrectomy

Introduction

Morbid obesity is associated with an increased incidence of chronic diseases including hypertension, type 2 diabetes mellitus (T2DM), coronary artery disease, stroke, and dyslipidemia [1]. Furthermore, each 5-point increase in body mass index (BMI) over 25 kg/m^2 is associated with 30% increases in all causes of mortality [2].

A number of meta-analyses have demonstrated the effectiveness of bariatric surgery in improving morbid obesity as well as its associated co-morbidities [3–6].

The efficacy of bariatric/metabolic surgery against T2DM is recognized worldwide, and the international guidelines agree in defining criteria of partial/complete remission of T2DM after surgery [7].

However, it is estimated that approximately 10–20% of patients regain a significant portion of their weight loss at long-term follow-up [8–10]. This weight recidivism has important health consequences including recurrence of obesity-related co-morbidities. Weight regain may occur after all most commonly performed bariatric procedures such as Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB), and sleeve gastrectomy (SG) in different proportion and interval of time [11].

As concerns the advocated causes responsible of the weight recovery, several hypotheses have been postulated. Some authors argue that there is a loss of "nutritional compliance,"

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thus justifying the recovery of body weight, especially in the behavioral "profiles" of "grazing" or "sweet-eating" [12]. Other studies attribute the weight regain to hormonal changes, due to the progressive increase in circulating levels of ghrelin, with consequent reduction of the satiety [13]. Thereafter, the insufficient physical activity may hinder the maintenance of body weight achieved after bariatric surgery [14]. Finally, anatomical modification (dilation of the gastric pouch) may increase the food capacity and reduce the early satiety [15]. In summary, weight regain seems to be multifactorial involving behavioral, psychological, hormonal, and anatomical components; however, it remains unpredictable in the majority of the cases and represents a challenge for the multidisciplinary team. However, the definition of "weight regain" is still controversial and several criteria have been proposed. Some authors define "regain" as increase of body weight, expressed in kilograms, above body weight nadir; others define it by evaluating the change in BMI points [16].

A recent review [10] classified patients after bariatric surgery in 3 different categories:

- Primary responder: patients with excess weight loss (EWL) > 50%
- Primary non-responder: patients with EWL < 50%
- Secondary non-responder weight regain: primary responder patients with any regain of lost weight

The aim of the present retrospective study was to evaluate at long term a cohort of morbid obese patients with T2DM submitted to laparoscopic sleeve gastrectomy analyzing the incidence of weight regain and the impact of the weight recovery on T2DM evolution.

Patients and Methods

This is a single-center retrospective study based on a prospectively maintained database.

In the period between January 2008 and December 2011, seventy-eight morbid obese patients (54 females) with T2DM, aged 49.6 ± 8.7 years, weight 121.1 ± 24.4 kg, BMI 44.1 ± 7.2 kg/m^2, underwent primary laparoscopic sleeve gastrectomy (LSG). In the present study, we report the long-term results of a homogenous cohort of patients (history of T2DM < 10 years, no super-super obese) submitted at single center to primary LSG.

Mean diabetes duration before surgery was 3 years (range 1–10 years). Before surgery, 74% of the diabetic patients were receiving oral hypoglycemic agents and 19% were receiving insulin, while 7% were treated with diet regimen [17].

All the procedures were completed laparoscopically with nil perioperative mortality and no case of re-operation. The technique has been reported extensively in a previous publication [18].

Briefly, LSG was performed by five-trocar technique with pneumoperitoneal pressure of 12–15 mmHg [19]. Ultrasound dissection (Harmonic Scalpel, Ethicon Endo-Surgery, Johnson & Johnson Company, Cincinnati, OH, USA) or Thunderbeat Technology (Olympus Japan) was used randomly.

We started 5–6 cm from the pylorus and proceed to the angle of His. We used a linear stapler (Echelon Flex Endopath, Ethicon Endo-Surgery, Johnson & Johnson Company, Cincinnati, OH, USA) with black, green, and yellow cartridges depending on the thickness of the gastric wall (from the antrum up to the fundus). The last stapler cartridge was typically at 1.5 cm from the angle of His.

Since 2012, absorbable buttressing material was used (Seamguard W.L. Gore & Associates, Inc., Newark, DE, USA) [19].

The sleeve was performed using a 42-Fr calibrating bougie to obtain 80–100 ml of gastric volume and tested with intraoperative methylene blue through an orogastric tube to check for gastric leak and evaluate volume and shape.

All patients were evaluated preoperatively by the multidisciplinary team and then after 30 days, 3 and 6 months up to the fifth year, then annually up to 10 years.

Before surgery, T2DM was diagnosed according to American Diabetes Association criteria [20]. After surgery, patients were followed up by monitoring glycemic status according to the ADA [21] and the American Society for Metabolic and Bariatric Surgery (ASMBS) [22] recommendations, with the assessment of glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and diabetes medication use.

At each scheduled visit, all the subjects were assessed by anthropometric measurements (weight, BMI) and routine laboratory tests (including fasting glycaemia and glycated hemoglobin), and information on patient medical treatment regimens for diabetes, hypertension, and dyslipidemia were recorded. Body weight loss nadir was achieved at 18–24 months.

Based on the review published last year by Bonouvrie et al. [10], the patients were divided into 2 groups:

"Primary responders" or "weight loss success": subjects who at the follow-up period are still in weight loss or maintain the minimum weight achieved
"Secondary non-responder" or "weight regain group": subjects who at the follow-up period have a weight regain

The patients of the second group were subdivided into:

"Mild regain": subjects with an increase in body weight from 5 to 10 kg, from the nadir

"Severe regain": subjects with an increase in body weight of more than 10 kg from the nadir

In order to evaluate the impact of the weight regain on the evolution ofT2DM, four different scenarios were considered:

Complete remission: defined according to international guidelines such as baseline blood glucose < 100 mg/dl and HbA1c < 6% maintained for at least 1 year, in the absence of hypoglycemic therapy
Partial remission: defined according baseline blood glucose 100–125 mg/dl or HbA1c 6–6.5% in the absence of therapy or who have not discontinued hypoglycemic therapy
Relapse: patients who maintained the criteria to define complete remission for more than a year and who, in different times, underwent recurrence of diabetes, diagnosed with fasting glycaemia > 126 mg/dl or with frankly diabetic OGTT (glycaemia) ≥ 200 mg/dl at 120
Persistence: patients who do not maintain the characteristics necessary to define complete remission for a duration of more than 1 year.

Follow-up periods were indicated as short (until 2 years), medium (between 2 and 5 years), and long (until 10 years).

In the diabetic groups with weight regain, gender, age, weight, BMI, fasting glycaemia, glycosylated hemoglobin, and duration of diabetes before the sleeve gastrectomy were then analyzed, in order to observe how they could affect the different evolutions of T2DM (Table 1).

Quantitative variables are expressed as mean ± SD for parametric values, with normal distribution, and as median (minimum value-maximum value) for non-parametric values, with non-normal distribution.

For the statistical analysis of the data, the software SPSS 22.0, Italian version, was used. In particular, the following tests were applied to compare the averages or percentages: the Wilcoxon test and *t* test for 2 samples paired with non-parametric and parametric variables, respectively; the Student *t* test for 2 groups of parametric variables; the binary logistic regression between categorical variables, with a dichotomous dependent variable, for the calculation of the consumable ratio.

Results

The cohort of 78 diabetic obese patients presented a median follow-up of 6 years and 7 months. For each year, the follow-up rate was calculated. It was 100% in the first year, 89% in the second year, 79% in the second year, 76% from the third to sixth year, 64% in the last 5 years.

As shown in Fig. 1, mean BMI significantly decreased in all patients until the short-term follow-up and then slowly increased in the following years, without mean BMI < 35 up to the eighth year and never reaching preoperative levels.

Parallel to the progressive reduction of basal blood glucose and glycated hemoglobin (HbA1c) values following surgery (Fig. 2), it was then observed that 86% of patients with T2DM before intervention completely stopped the drug therapy since the first month after surgery and the subjects still in therapy enjoy the reduction in the dosage of oral hypoglycemic drugs and/or the number of insulin units a day. The levels of glycated hemoglobin are significantly reduced during follow-up showing a slight increase at 10 years but always remaining within the range of good glycemic control.

In the long-term follow-up, the use of diabetes medications was markedly reduced vs baseline (p 0.003), and among the subgroup of patients who did not achieve diabetes remission (36%), half of the patients were treated by only diet or metformin.

Particularly, there was a significant reduction in the proportion of patients taking oral hypoglycemic agents (2.4% vs 23%). Most patients (84%) treated with insulin before surgery continued to use insulin also after surgery, but there was a significant reduction of daily insulin requirement (from 30 units of insulin before surgery to 12 units of insulin after surgery, p 0.002).

However, all patients with diabetes relapse had a good glycemic control, as shown by the HbA1c values that never exceeded the 7% limit after surgery.

In accordance with diabetes remission criteria, we can establish that, in our population of diabetic patients, 55% (43 out of 78) are in complete remission and 17% (13 of 78) in partial remission at a mean follow-up of 6.7 years (Table 2).

As regards the evolution of body weight, 24 subjects were "primary responders" or "weight loss success"; otherwise, 54 subjects were "secondary non-responders" or "weight regain group."

Patients with regain showed different degrees of regain: "mild regain," 32 (60%) subjects with an increase in body weight of more than 5 kg from the nadir; "severe regain," 22 (40%) subjects with an increase in body weight of more than 10 kg from the nadir.

The trend over time of T2DM after LSG was analyzed separately in the different groups of diabetic patients, subdivided on the basis of the absence or presence of weight regain, and in the latter considering further the division in degree of entity, highlighting the following:

"No regain group," 54% show complete remission, 46% persistence, and no case of diabetes relapse
"Mild regain group," 59% of these individuals have complete remission, 36% persistence, and 5% relapse

Table 1 Baseline characteristics in patients with diabetes remission, persistence, and relapse

	T2DM remission	T2DM persistence	T2DM relapse	*p*
Gender M	29.2%	16.7%	25%	–
Gender F	70.8%	83.3%	75%	–
Age (mean ± SD) (years)	47.2 ± 7.9	53.2 ± 6.8	53.2 ± 6.1	–
BMI (mean ± SD) (kg/m^2)	45.8 ± 9.4	43.0 ± 7.1	43.3 ± 2.6	–
Blood glucose (mean ± SD) (mg/dl)	127 ± 92.4	176 ± 37.4	118 ± 6.3	0.002
HbA1c (mean ± SD) (%)	6.6 ± 2.4	9.3 ± 3.2	6.2 ± 1.6	0.001
T2DM duration (mean) (years)	1	7	4	< 0.0001

"Severe regain group," 61% of these individuals have complete remission, 22% persistence, and 17% relapse (Table 3)

In the group of patients with diabetes relapse, preoperative values of fasting blood glucose and glycated hemoglobin as well as the duration of diabetes were significantly higher when compared with the group of patients with diabetes remission (respectively, $p = 0.002$, $p = 0.001$, and $p < 0.0001$).

Discussion

Sleeve gastrectomy is the most commonly performed bariatric operation nowadays. Weight regain after bariatric surgery, when significant, may be associated with recurrence of diabetes and deterioration in quality of life. Yet the understanding of the significance of weight regain is hampered by poor reporting and no consensus statements or guidelines.

In the last years, several authors have reported new criteria in order to classify post-bariatric surgery outcomes [23–26]. However, none of the proposed criteria has been extensively used.

In this study, in accordance with the recent systematic review [10], weight regain was defined as the recovery of body weight after the maximum weight loss achieved (nadir). In addition, weight regain data were distinguished as mild (> 5 kg from the nadir) and severe (> 10 kg from the nadir). Based on the daily practice and clinical experience, we focused on the severe regain.

To study the impact of severe weight regain on diabetes, we consider four possible evolutions:

(*Complete remission, partial remission, relapse, and persistence)*. These four possible scenarios were evaluated based on the presence or absence of weight regain.

We expected that patients who are no longer diabetic after the operation can more easily return to it after an important increase in body weight.

In the present study, we report the long-term results of a homogenous cohort of patients (history of T2DM < 10 years, no super-super obese) submitted at single center to primary LSG.

We observed that 55% of diabetic patients are in complete remission and 17% in partial remission at a mean follow-up of 6.7 years after surgery. This data confirms the close link

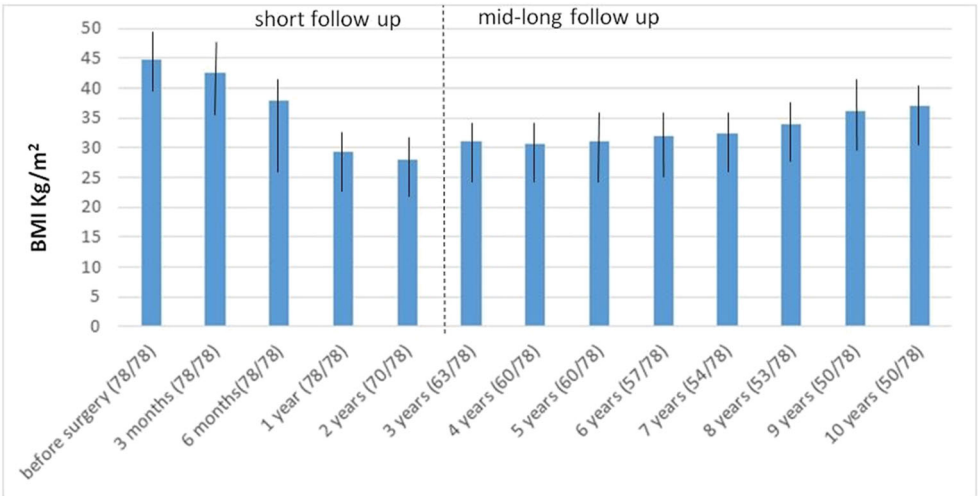

Fig. 1 BMI trend in the short and mid-long follow-up

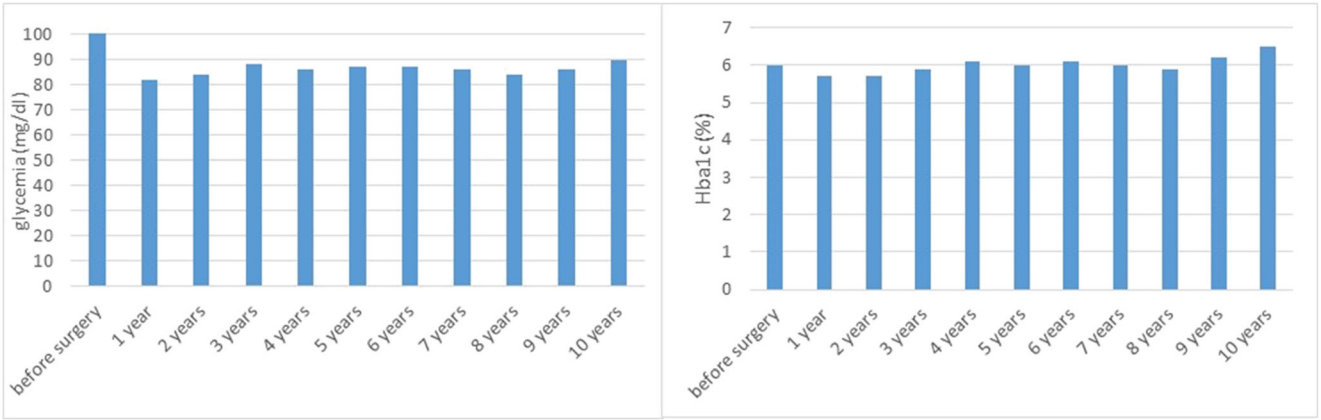

Fig. 2 Medium glycaemia and HbA1c for each year of follow-up of the entire cohort

between obesity and diabetes, confirming the importance of treating diabetes by sustained body weight loss.

The results of the present study showed no statistically significant difference regarding the trend of diabetes remission comparing "no regain" (54%), "mild regain" (59%), and "severe regain" (61%). As concerns the main outcome, no case of relapse in the "no regain" group vs 17% of the "severe regain" group. These data suggest that at long term the severe regain carries a substantial relapse of T2DM. On the contrary, when the weight regain is inferior to 5 kg, the relapse rate is very low (5%).

The data of the study confirm the overall therapeutic role of sleeve gastrectomy in morbid obesity, even in cases where there is a recovery of body weight during a long-term follow-up period.

The most relevant clinical data arising from this study, however, is the favorable evolution of diabetes mellitus after LSG confirming the reports of previous publications [27, 28].

In any case, even patients with relapse or persistence of diabetes were more easily controlled after SG, and this impact on daily practices of diabetologists improves the management of the patients. The amount of insulin and oral diabetes medication was markedly reduced compared with the baseline, and the levels of glycated hemoglobin in these patients are lower than those before surgery.

Half of the patients who did not achieve diabetes remission were treated by only diet or metformin with a significant reduction of oral hypoglycemic agents (2.4% vs 23%). Eighty-four percent of patients treated with insulin before surgery continued to use insulin after surgery, but there was a significant reduction of daily insulin requirement (30 units of insulin before surgery vs 12 units of insulin after surgery).

In addition to weight regain, further prognostic factors were identified on the relapse of diabetes after bariatric surgery. These include advanced age, longer duration of diabetes, insulin-dependent therapy and/or assumption of 2 or more medications, and worse glycemic control before surgery [27–30].

In our cohort, the patients with relapse of diabetes had a longer history of disease, higher levels of glycate, and insulin therapy before surgery.

This data confirms the importance of the duration of the illness and therefore an early intervention for the diabetic patient towards surgical therapy.

Relapse of diabetes is under study in patients with weight regain 10 years after sleeve at our bariatric center. Currently, of "secondary non-responder" patients, 6 required a revisional surgery and are under evaluation for bypass re-do surgery.

This study has several weaknesses: the small sample of patients, retrospective design of the study, single center, and limited series. However, it presents highlights: high percentage of follow-up over 5 years, selected group of diabetic

Table 2 Short-medium and long-term diabetes remission rates and relapse rate after initial post-surgical remission

	Follow-up rate (%)	Patients with complete remission (%)	Patients with partial remission (%)	Patients with relapse (%)	Patients with persistent diabetes (%)
Short term	94	56.5	9.7	3.2	30.6
Medium term	78	48.1	9.3	9.5	29.6
Long term	65	45.2	7.1	9.9	35.7

Table 3 Trend over time of T2DM in the different groups of diabetic patients, subdivided on the basis of the absence or presence of weight regain

	No regain	Mild regain	Severe regain	*p*
Complete remission (%)	54	59	61	0.12
Persistence (%)	46	36	22	0.03
Relapse (%)	0	5	17	0.05

patients (no super-super obese, no history of diabetes > 10 years), scheduled follow-up by the multidisciplinary team, standard primary LSG, and no complications related to the procedure which required re-operations.

Long-term data on diabetic evolution are needed to inform morbid obese diabetic patients before surgery and may help to select the patient candidates to LSG on the basis of favorable prognostic factors.

An intensive follow-up schedule is mandatory to prevent "severe regain" in diabetic patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed Consent Informed consent was obtained from all patients for being included in the study.

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