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Research Articles

Short-term Effects of Sleeve Gastrectomy on Type 2 Diabetes Mellitus in Severely Obese Subjects

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Background: Data on the effectiveness of sleeve gastrectomy (SG) in improving or resolving type 2 diabetes mellitus (T2DM) are scarce.

Methods: A 4-month prospective study was conducted on the changes in glucose homeostasis in 35 severely obese T2DM subjects undergoing laparoscopic SG (LSG) and 50 subjects undergoing laparoscopic Roux-en-Y gastric bypass (LRYGBP), matched for DM duration, type of DM treatment, and glycemic control.

Results: At 4-months after surgery, LSG and LRYGBP operated subjects lost a similar amount of weight (respectively, 20.6 ± 0.7% and 21.0 ± 0.6%). T2DM had resolved respectively in 51.4% and 62.0% of the LSG and LRYGBP operated subjects (*P*=0.332). A shorter preoperative DM duration (*P*<0.05), a preoperative DM treatment not including pharmacological agents, and a better pre-surgical fasting plasma glucose (*P*<0.01) or HbA1c (*P*<0.01), were significantly associated with a better type 2 DM outcome in both surgical groups.

Conclusions: Our data show that LSG and LRYGBP result in a similar rate of type 2 DM resolution at 4-months after surgery. Moreover, our data suggest that mechanisms beyond weight loss may be implicated in DM resolution following LSG and LRYGBP.

Key words: Morbid obesity, type 2 diabetes mellitus, sleeve gastrectomy, gastric bypass, insulin sensitivity, weight loss

Introduction

Bariatric surgery is associated with a high rate of resolution of type 2 diabetes mellitus (T2DM) in morbidly obese subjects, with resolution being more common following the predominantly malabsorptive and the mixed malabsorptive-restrictive procedures, compared to the purely restrictive operations.[1] It has been proposed that weight loss accounts for resolution of T2DM following purely restrictive procedures.[2,3] In contrast, it has been hypothesized that changes in gastrointestinal hormonal secretion would favor not only the higher T2DM resolution rate but also an earlier improvement of glucose tolerance in procedures in which the stomach and part of the gut are bypassed.[2]

Sleeve gastrectomy (SG) has recently emerged as a restrictive bariatric procedure.[4] SG was originally conceived as the first stage for achieving weight loss and reducing co-morbidities in patients who were super-obese before performing a Roux-en-Y gastric bypass (RYGBP) or a biliopancreatic diversion with duodenal switch (DS).[5] However, it has recently been proposed that SG could also be considered as a potential single bariatric operation in severely obese subjects.[4-6] Notably, Himpens et al[7] recently showed that weight loss following SG was larger than that following adjustable gastric banding (AGB) at 1 and 3 years follow-up.[7] Moon Han et al[8] concluded that SG without the second-stage operation was associated with an excess weight loss of 71% and a 100% resolution rate of T2DM at 6 months after surgery in Korean subjects. It has been suggested that decreased ghrelin from the resected fundus as in SG may help to explain the better weight loss results relative to AGB.[9] Moreover, it has been found that the SG is associated with an acceleration of gastric emptying despite preservation of the pylorus.[10] Thus, it could be hypothesized

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that the relative superiority of SG over AGB may involve some of the mechanisms that have been postulated to participate in the amelioration of glucose tolerance in T2DM subjects undergoing RYGBP.

The aim of our study was to evaluate the effects of laparoscopic SG on T2DM in morbidly obese subjects. As an approximation to the evaluation of the potential contribution of mechanisms beyond weight loss on T2DM resolution, we compared the changes in glucose tolerance at short-term after surgery in subjects undergoing laparoscopic SG (LSG) relative to subjects undergoing laparoscopic RYGBP (LRYGBP).

Research Design and Methods

Study Subjects

From January 2005 to November 2006, a total of 35 severely obese T2DM Caucasian subjects underwent LSG at our Institution. LSG in these individuals was performed based on their large BMIs, the estimated operative risk, or the presence of an enlarged liver.[11] LSG-operated subjects were compared to a group of 50 T2DM subjects that had undergone LRYGBP at our Institution in the same time period. LRYGBP-operated subjects were selected to match the LSG group for the age at diagnosis of DM, the type of treatment of DM prior to surgery, preoperative fasting plasma glucose (FPG), and HbA1c, because these variables have been shown to influence resolution of T2DM following LRYGBP.[12] The study was approved by the Hospital Ethics Committee and written informed consent was obtained from all participants.

Study Protocol

All subjects were prospectively evaluated within 8 weeks before and at ~4 months after surgery. Before surgery, diagnosis of T2DM was based on a positive history of T2DM, FPG, or on an oral glucose tolerance test according to criteria established by the American Diabetes Association.[13] Duration and type of treatment for T2DM were recorded from participants preoperatively. On the post-surgical evaluation, T2DM resolution was defined as a FPG <126 mg/dl, and an HbA1c in the normal range (3.4-5.5%) in the absence of any hypoglycemic medication. Moreover, based on FPG, patients were classified postoperatively as normal glucose tolerant (NGT, FPG<100 mg/dl), impaired fasting glucose (IFG, FPG 100-125 mg/dl), or T2DM.[13] As for the pre-surgical evaluation, at 4 months after surgery subjects on hypoglycemic medication were classified as having T2DM despite normal values for FPG or HbA1c.

Anthropometric and blood pressure measurements were performed as previously described.[14] Weight changes were expressed as the percentage of weight loss relative to baseline, and as the percent excess BMI loss (%EBL). The metabolic syndrome (MS) was diagnosed according to the revised ATP III criteria,[15] and the MS score was calculated as the sum of the components of the MS present in each individual.[16]

Surgical Procedures

Laparoscopic RYGBP was performed as previously described.[16] For the LSG, in short, the greater curvature including the complete fundus was resected from the distal antrum (5 cm proximal to the pylorus) to the angle of His. A laparoscopic stapler, EndoGIA (Autosuture, Norwalk, CT, USA) with a 60-mm cartridge (3.5-mm staple height, blue load), was used to divide the stomach parallel to and alongside a 46-50 French bougie (placed against the lesser curvature of the stomach). The resected portion of the stomach was extracted from the right upper abdominal 15-mm port site. A running non-absorbable suture (Prolene) was applied to the staple-line to prevent hemorrage. Postoperatively, LSG patients were managed similar to our LRYGBP patients.

Analytical Methods

Venous blood was collected after an overnight fast. Plasma glucose, total cholesterol, HDL cholesterol, triglycerides, HbA1c, and insulin were determined as previously described.[14] From fasting plasma glucose and fasting insulin levels, the HOMA-IR insulin sensitivity index was calculated.[14]

Statistical Analysis

All data are expressed as means ± SEM. Statistical analyses were carried out using SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). Comparisons between groups were performed using Chi-squared and parametric or non-parametric test (Student *t* and Mann-Whitney *U*) when appropriate. Statistical significance was set at a *P* value <0.05.

Results

The clinical and biochemical characteristics of the study subjects are shown in Table 1. As per study design, the two surgical groups were matched preoperatively for DM duration, DM treatment, and glycemic control. Because of the criteria used to select the type of surgery (see Research Design and Methods), subjects who underwent LSG were significantly more obese and presented a larger waist circumference compared to those in the LRYGBP group. However, the two groups were well balanced for the rest of evaluated variables. In most study participants, T2DM was accompanied by at least two additional components defining the MS.

As shown in Table 2, at 4 months after surgery the two surgical procedures were associated with a similar weight loss, either considering the weight loss relative to baseline or the %EBL. On that post-surgical evaluation, T2DM had resolved respectively in 51.4% and 62.0% of the LSG and LRYGBP operated subjects (P=0.332). Based on fasting plasma glucose, NGT and IFG were present at similar rates in the two cohorts (P=0.990; NGT: LSG 42.9%, LRYGBP 44.0%; IFG: LSG 25.7%, LRYGBP 26.0%). The proportion of subjects requiring oral hypoglycemic agents and/or insulin for DM control declined significantly in both groups (LSG: 28.6%, P<0.05; LRYGBP: 34%, P<0.05). An HbA1c

Table 1. Clinical and biochemical characteristics of the study subjects

	Sleeve gastrectomy N=35	**Gastric bypass** N=50
Age (years)	49.4 ± 1.5	49.4 ± 1.3
Gender (female) (%)	57.1	66.0
BMI (kg/m^2)	52.0 ± 1.2	47.6 ± 0.7*
Waist circumference (cm)	145.5 ± 2.2	135.3 ± 2.0*
Age at diagnosis of DM (years)	48.3 ± 1.6	46.6 ± 0.6
DM treatment (D/OHA/Ins) (%)	37.1 / 54.3 / 8.6	40.0 / 52.0 / 8.0
Current smoker (yes) (%)	28.6	18.0
Hypertension (yes) (%)	65.7	72.0
Dyslipidemia (yes) (%)	34.0	48.0
Fasting plasma glucose (mg/dl)	166.9 ± 10.6	161.0 ± 7.6
HbA1c (%)	7.26 ± 0.35	7.00 ± 0.23
HDL-cholesterol (mg/dl)	45.4 ± 1.6	47.3 ± 1.6
Triglycerides (mg/dl)	172.8 ± 11.3	202.7 ± 25.6
Systolic blood pressure (mmHg)	139.0 ± 2.4	137.6 ± 2.1
Diastolic blood pressure (mmHg)	83.2 ± 1.6	80.7 ± 1.8
Metabolic Syndrome (yes) (%)	91.4	94.0
Metabolic Syndrome Score	3.9 ± 0.2	3.9 ± 0.1
HOMA-IR	14.1 ± 2.0	10.2 ± 0.8

Data are expressed as mean ± standard error of the mean (SEM). *P<0.01

Table 2. Change in clinical and metabolic variables in morbidly obese operated subjects according to the type of surgery

	Sleeve gastrectomy N=35	**Gastric bypass** N=50
Weight loss (% from baseline)	20.6 ± 0.7	21.0 ± 0.6
Excess BMI loss (%)	41.4 ± 1.8	45.3 ± 1.3
Δ Waist circumference (%)	- 13.8 ± 1.3	- 13.5 ± 1.1
Δ Fasting plasma glucose (%)	- 32.9 ± 3.1	- 32.3 ± 2.6
Δ HbA1c (%)	- 22.9 ± 2.5	-23.5 ± 1.8
Δ HDL-cholesterol (%)	-16.7 ± 2.8	-12.5 ± 2.8
Δ Triglycerides (%)	-19.8 ± 5.4	-22.3 ± 4.2
Δ Systolic blood pressure (%)	- 9.4 ± 1.6	- 5.3 ± 1.7
Δ Diastolic blood pressure (%)	- 7.9 ± 3.8	- 4.2 ± 2.3
Δ Metabolic Syndrome Score (%)	-12.8 ± 4.8	-11.6 ± 3.9
Δ HOMA-IR (%)	- 51.6 ± 7.3	- 60.8 ± 3.2
Δ C-reactive protein (%)	- 11.1 ± 9.5	- 17.9 ± 6.3

Data are expressed as mean ± standard error of the mean (SEM).

<6.5% was present respectively in 85.7% and 94.0% of the LSG and LRYGBP operated subjects (P=0.181). Likewise, the two surgical procedures were associated with a similar descent in the MS components and insulin sensitivity (Table 2).

Finally, we evaluated the factors associated with T2DM resolution. As shown in Table 3, the pre-surgical features associated with T2DM resolution at 4 months after surgery were similar between the two surgical groups. A shorter preoperative DM duration, a DM treatment not including pharmacological agents, and a better glycemic control as assessed either from FPG or HbA1c, were significantly associated with a better T2DM outcome in LSG and LRYGBP operated subjects. As shown in Table 4, neither the attained BMI nor the weight loss was significantly associated with T2DM outcome in the two surgical groups. Likewise, neither the degree of decrease in the waist circumference nor the improvements in the insulin sensitivity were associated with T2DM resolution following LSG or LRYGBP.

Discussion

Our study shows that LSG is associated with a high resolution rate of T2DM at short-term after surgery and, importantly, this resolution rate is comparable to that in subjects undergoing LRYGBP. The effectiveness of SG in improving or resolving T2DM has seldom been reported. Moon Han[8] and Silecchia,[17] reported higher resolution rates than ours in shorter series of T2DM patients undergoing LSG. However, in these studies, post-surgical evaluation was performed at 6 or more months of follow-up, information on the clinical features of T2DM was not provided, and a direct comparison with another surgical procedure was not attempted. Likewise, RYGBP surgery has been associated with a rate of resolution of T2DM in the 80 to 98% range.[1,18] Direct comparison of these figures with ours is also problematic because (1) the distribution of glucose tolerance categories and description of the clinical characteristics

Table 3. Baseline clinical and biochemical characteristics of morbidly obese operated subjects according to type 2 diabetes resolution

		Not resolved	Resolved
	Sleeve gastrectomy	n = 17	n = 18
	Gastric bypass	n = 19	n = 31
Age (years)	Sleeve gastrectomy	51.3 ± 2.0	47.6 ± 2.2
	Gastric bypass	52.3 ± 1.9	47.6 ± 1.8
Gender (female) (%)	Sleeve gastrectomy	50.0	50.0
	Gastric bypass	39.4	60.6
Diabetes duration (years)	Sleeve gastrectomy	4.8 ± 1.3	1.7 ± 0.5 #
	Gastric bypass	5.6 ± 1.0	2.3 ± 0.5 *
DM treatment (%, diet / OHA / insulin)	Sleeve gastrectomy	3 / 11 / 3	10 / 8 / 0 P=0.065
	Gastric bypass	1 / 14 / 4	19 / 12 / 0 *
Metabolic Syndrome (%)	Sleeve gastrectomy	88.2	94.4
	Gastric bypass	94.7	93.5
Metabolic Syndrome score	Sleeve gastrectomy	3.8 ± 0.2	3.9 ± 0.2
	Gastric bypass	3.9 ± 0.2	3.8 ± 0.2
BMI (kg/m^2)	Sleeve gastrectomy	52.5 ± 1.8	47.2 ± 1.3
	Gastric bypass	51.6 ± 1.7	47.8 ± 0.9
Waist circumference (cm)	Sleeve gastrectomy	145.2 ± 2.5	145.8 ± 3.7
	Gastric bypass	132.9 ± 2.9	136.6 ± 2.6
HbA1c (%)	Sleeve gastrectomy	8.4 ± 0.6	6.2 ± 0.2 *
	Gastric bypass	8.3 ± 0.4	6.2 ± 0.2 *
Fasting plasma glucose (mg/dl)	Sleeve gastrectomy	196.4 ± 15.5	139.7 ± 7.3 *
	Gastric bypass	195.9 ± 12.6	139.7 ± 7.3 *
HOMA-IR	Sleeve gastrectomy	13.7 ± 3.0	14.4 ± 2.7
	Gastric bypass	12.6 ± 1.6	8.7 ± 0.8 #

Data are expressed as mean ± standard error of the mean (SEM). # P<0.05; *P<0.01

Table 4. Post-surgical clinical and biochemical characteristics of morbidly obese operated subjects according to type 2 diabetes resolution

		Not resolved	Resolved
	Sleeve gastrectomy	n = 17	n = 18
	Gastric bypass	n = 19	n = 31
BMI (kg/m^2)	Sleeve gastrectomy	42.2 ± 1.7	40.5 ± 1.4
	Gastric bypass	36.4 ± 0.8	38.0 ± 0.8
Weight loss (% from baseline)	Sleeve gastrectomy	19.7 ± 1.0	21.6 ± 0.8
	Gastric bypass	21.4 ± 1.1	20.8 ± 0.7
Excess BMI loss (%)	Sleeve gastrectomy	39.4 ± 2.9	43.4 ± 2.1
	Gastric bypass	47.0 ± 2.2	44.3 ± 1.6
Waist circumference (cm)	Sleeve gastrectomy	125.8 ± 4.2	123.9 ± 3.1
	Gastric bypass	114.6 ± 2.3	117.5 ± 2.7
Δ Waist circumference (%)	Sleeve gastrectomy	- 13.3 ± 2.3	- 14.1 ± 1.4
	Gastric bypass	-13.0 ± 1.6	-14.1 ± 1.2
Δ HOMA-IR (%)	Sleeve gastrectomy	- 51.9 ± 9.6	- 51.3 ± 11.3
	Gastric bypass	- 65.5 ± 4.4	-57.9 ± 4.3

Data are expressed as mean ± standard error of the mean (SEM). *P<0.01

of T2DM participants varies among RYGBP series, and (2) resolution rates of T2DM at short-term after RYGBP are not well documented. Schauer[12] and Torquati[18] reported on the glucose tolerance outcomes following LRYGBP in large series of T2DM subjects [respectively, 191 subjects (93% T2DM), and 112 subjects (100% T2DM)]. After a mean follow up of ≥12 months, the resolution rates of T2DM were respectively 83% and 74%. Unfortunately, the rate of T2DM resolution at shorter follow-up was not reported in these two studies.

In agreement with previous reports on the evolution of T2DM following bariatric surgery, we have shown that the clinical features of preoperative diabetes are important determinants of the likelihood of biochemical remission. Schauer et al[12] found that following LRYGBP, the odds of T2DM remission were higher with a shorter duration and a milder disease. Similar results were reported by Torquati et al.[18] Our study lends further support to these data, and adds that the duration of DM, the type of DM therapy, and the degree of glucose control are important pre-surgical predictors of T2DM outcome following LSG as well. Overall, these findings would suggest that the remaining pancreatic β-cell function may be an important determinant of the likelihood of T2DM resolution following any type of bariatric surgery.[19]

The primary focus of our study was not to evaluate the potential mechanisms explaining the resolution of T2DM following LSG. However, we would like to contextualize our findings with respect of the various mechanisms proposed for T2DM resolution following bariatric surgery. Notably, weight loss was not significantly different when subjects in whom DM resolved or did not resolve were compared within the LSG- and LRYGBP-operated groups. Moreover, we failed to find a significant association between the changes in waist girth and insulin sensitivity and T2DM resolution. Thus, it could be speculated that at variance to what has been proposed following other types of restrictive bariatric procedures,[3] net weight loss may not be the dominant mechanism driving T2DM following LSG. Circulating plasma ghrelin levels have been shown to be differentially affected by LSG compared to AGB.[9] Moreover, it has been shown that the time required for half of a solid meal to leave the stomach and the percentage of a meal emptied into the small intestine are shortened following LSG.[10] These counter-intuitive data indicate that following LSG the stomach emptying of solid foods into the duodenum is accelerated despite preservation of the pylorus. Thus, it could be speculated that changes in gut hormone secretion may play a role in T2DM resolution following LSG. Against this background, future studies are needed to address the potential participation of GLP-1 or GIP in DM resolution following LSG.[2]

Our study has some limitations and strengths. We acknowledge that the two groups of patients were not matched for the pre-surgical BMI. However, our study was intended as an exploratory evaluation of the relative efficacy of LSG on T2DM resolution, based on accepted criteria for LSG surgery.[11] Moreover, our analysis was based on the comparison of T2DM outcomes between a new and well-established surgical procedure. Moreover, T2DM subjects who underwent LSG in our study were well-matched for variables relevant to glucose homeostasis outcome following LRYGBP.[12,18]

In summary, we have shown that at 4 months after surgery, LSG is as effective as LRYGBP in inducing T2DM remission. Further confirmation of these data in studies with a longer follow-up would strengthen the case for the consideration of LSG as a single bariatric surgery procedure in selected subjects.

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