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Clinical Study

Impact of Sleeve Gastrectomy on Weight Loss, Glucose Homeostasis, and Comorbidities in Severely Obese Type 2 Diabetic Subjects

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This study was undertaken to assess medium-term effects of laparoscopic sleeve gastrectomy (LSG) on body weight and glucose homeostasis in severely obese type 2 diabetic (T2DM) subjects. Twenty-five obese T2DM subjects (10 M/15 F, age 45 ± 9 years, BMI 48 ± 8 kg/m^2, M ± SD) underwent evaluation of anthropometric/clinical parameters and glucose homeostasis before, 3 and 9–15 months after LSG. Mean BMI decreased from 48 ± 8 kg/m^2 to 40 ± 9 kg/m^2 ($P < .001$) at 3 months and 34 ± 6 kg/m^2 ($P < .001$) at 9–15 months after surgery. Remission of T2DM (fasting plasma glucose < 126 mg/dL and HbA1c < 6.5% in the absence of hypoglycemic treatment) occurred in all patients but one. There was a remarkable reduction in the percentage of patients requiring antihypertensive and hypolipidemic drugs. Our study shows that LSG is effective in producing a significant and sustained weight loss and improving glucose homeostasis in severely obese T2DM patients.

1. Introduction

Obesity is one of the most serious and urgent public health problems in western societies because of its metabolic and cardiovascular complications that negatively impact on life expectancy [1]. Equally alarming is the increase of morbid obesity (BMI ≥ 40 kg/m^2) that quadrupled over the last decade, whereas extreme obesity (BMI > 50 kg/m^2) increased fivefold [2].

Bariatric surgery, also known as metabolic surgery, has emerged as a highly effective and long-lasting treatment in patients with morbid obesity and in those with BMI ≥ 35 kg/m^2 in the presence of type 2 diabetes (T2DM) and other comorbidities [3]. There is extensive evidence that bariatric procedures, including biliopancreatic diversion (BPD), gastric bypass (GBP), and gastric banding, can successfully control most of the obesity-related comorbidities, such as hypertension, dyslipidemia, and T2DM [4]. The rate of success is higher with the predominantly malabsorptive and mixed malabsorptive-restrictive procedures than purely restrictive operations [5].

Laparoscopic sleeve gastrectomy (LSG) is emerging as a new promising therapy for the treatment of morbid obesity [6]. This procedure, originally conceived as a first stage for achieving weight loss in superobese patients before performing GBP or BPD, has revealed to be effective on its own and a potential competitor with these operations. In fact, LSG has the advantage to be less invasive than GBP and BDP, and not inferior in terms of sustained weight loss, as demonstrated in some preliminary studies [6]. Few studies have examined the effects of LSG on glucose control and comorbidities in obese T2DM patients, and limited information is available on the long-term efficacy of this procedure [7–9]. Therefore, in the present study we assessed the medium-term (9–15 months) effects of LSG on body weight and glucose homeostasis in severely obese T2DM subjects not adequately controlled with

medical therapy. In addition, we evaluated the impact of LSG on other pathological conditions linked to obesity, that is, hypertension and dyslipidemia.

2. Methods

The study was conducted at the Department of Surgery, S. Giovanni Bosco Hospital, Naples and at the Department of Clinical and Experimental Medicine, Federico II University, Naples.

A total of 25 obese T2DM subjects (10 M/15 F, age 45 ± 9 years, BMI 48 ± 8 kg/m^2, M ± SD) underwent LSG surgery. All patients were examined by a multidisciplinary and integrated medical team consisting of a diabetologist, a bariatric surgeon, a psychiatrist, and a dietician.

The inclusion criteria were as follows: age 35–65 years, BMI ≥ 35 kg/m^2, duration of diabetes >1 year. Exclusion criteria were age <35 years or >65 years, BMI < 35 kg/m^2, fasting C-peptide level <1 ng/mL, endocrine obesity, a history of medical problems such as mental impairment, drug or alcohol addiction, recent major vascular event and excessive surgical risks due to debilitating diseases that considerably impair life expectancy according to perioperative bariatric guidelines [9].

All patients underwent complete evaluation before and at 3 and 9–15 months after surgery including anthropometric/clinical parameters and laboratory tests. Insulin-resistance was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) index using a standard formula: fasting insulin (U/L) × fasting glucose (mmol/L) divided by 22.5.

All patients provided written informed consent before undergoing surgery.

2.1. Operative Technique. All operative procedures were performed laparoscopically. The first step consists in opening the gastrocolic ligament attached to the stomach, usually starting 10–12 cm from the pylorus toward the lower pole of the spleen. Then the gastric greater curvature is freed up to the cardiooesophageal junction close to stomach sparing the gastroepiploic vessels. Meticulous dissection is performed at the angle of His with full mobilization of the gastric fundus. The mobilization of the stomach continues dissecting the greater gastric curve toward the antrum up to 3–5 cm from the pylorus. At this time a 40-Fr orogastric tube is inserted direct toward the pylorus, proximal to the lesser curvature of the stomach. Then, the stomach is resected with linear staplers parallel to orogastric tube along the lesser curve starting 3–5 cm far from pylorus. The orogastric bougie is replaced by a nasogastric tube that is positioned in the distal stomach to perform a methylene blue test. The transection line is inspected to search blue positivity. In case of negative test, the resected stomach is removed by left midabdominal trocar usually without prolonging incision. The gastric residual volume ranged from 60 to 80 mL.

2.1.1. Remission of Comorbidities. Remission of T2DM was defined as fasting plasma glucose below 126 mg/dL and HbA1c below 6.5% in the absence of hypoglycemic treatment. Remission of hypertension was defined as blood pressure below 140/90 mmHg in the absence of antihypertensive treatment; remission of dyslipidemia was defined as fasting plasma LDL-cholesterol below 100 mg/dL and/or fasting plasma triglycerides below 190 mg/dL in the absence of pharmacological therapy.

2.2. Statistical Analysis. Results are expressed as mean ± standard deviation or number. ANOVA with repeated measures was used to detect changes over time of the anthropometric and biochemical variables. Paired Student's *t*-tests were used to compare data before and after surgery. A P value of .05 was considered statistically significant. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL).

3. Results

The main characteristics of the patients studied are shown in Table 1. All patients had a duration of T2DM > 1 year (3 ± 2 years), and most of them (68%) were in poor glycaemic control, as evidenced by HbA1c > 7%. Two patients were on diet, twenty-one patients took oral hypoglycemic agents, and two were on combined therapy (oral agents plus insulin). Twenty-one (84%) patients were on antihypertensive therapy, and fourteen (56%) patients received hypolipidemic drugs.

The changes in clinical and biochemical variables following LSG are reported in Table 1. Mean BMI decreased from the basal value of 48 ± 8 kg/m^2 to 39 ± 8 kg/m^2 ($P < .001$) at 3 months and to 34 ± 6 kg/m^2 ($P < .001$) 9–15 months after surgery. Percent excess weight was 81 ± 42% at 3 months and 61 ± 33%) at 9–15 months compared to basal value (122 ± 39%; $P < .001$ for both). Fasting plasma glucose significantly decreased to 87 ± 19 mg/dL 3 months after LSG and remained within the normal range at 9–15 months in all patients but one. Mean HbA1c reached 5.9 ± 0.6% at 3 months and remained unchanged at 9–15 months (5.8 ± 0.7%) ($P < .03$). Fasting plasma insulin declined significantly by 68–87% following the intervention ($P < .005$). As a consequence HOMA-IR dramatically decreased by 86% ($P < .008$) 3 months after surgery and remained stable thereafter (91%, $P < .04$).

Following surgery, all patients discontinued their hypoglycemic medications, and a full remission of T2DM was achieved in 24 out of 25 patients. Eighteen patients discontinued antihypertensive drugs, and 12 patients discontinued hypolipidemic drugs at 3 months. A major perioperative complication occurred in one patient who was admitted to intensive care unit for acute renal failure due to severe dehydration. This complication went to complete resolution in few days.

4. Discussion

Our study shows that LSG is effective in producing a significant and sustained weight loss and improving glucose

Table 1: Changes in body weight, arterial blood pressure, and main biochemical parameters following LSG.

	Baseline $N = 25$	3 months $N = 25$	Change %	P value	9–15 months $N = 15$	Change %	P value
Body weight (Kg)	136 ± 30	112 ± 30	18	.001	98 ± 25	28	.001
BMI (Kg/m^2)	48 ± 8	39 ± 8	19	.001	34 ± 6	30	.001
FPG (mg/dL)	131 ± 42	87 ± 19	33	.008	91 ± 20	31	.01
FPI (mU/L)	20 ± 13	6.5 ± 5	68	.005	2.5 ± 0.7	87	.001
HbA1c (%)	7.5 ± 1.9	5.9 ± 0.6	21	.03	5.8 ± 0.7	23	.03
HOMA-IR	6.4 ± 3.9	0.7 ± 0.35	86	.008	0.54 ± 0.2	91	.04
Total cholesterol (mg/dL)	201 ± 42	199 ± 46	1	ns	228 ± 51	12	ns
LDL-cholesterol (mg/dL)	121 ± 29	120 ± 37	1	ns	146 ± 40	17	ns
Triglycerides (mg/dL)	198 ± 123	119 ± 42	40	.04	104 ± 17	47	ns
SBP (mmHg)	124 ± 8	118 ± 11	5	ns	126 ± 12	2	ns
DBP (mmHg)	77 ± 9	68 ± 11	12	ns	79 ± 9	3	ns
Hypoglicemic drugs (n)	23	0			0		
Anti-hypertensive drugs (n)	21	3			2		
Hypolipidemic drugs (n)	14	2			2		

homeostasis in severely obese T2DM patients. In fact, after 9–15 months from surgery all patients but one achieved a good glycemic control with discontinuation of hypoglycaemic treatment. This finding is in line with previous studies demonstrating that diabetes resolution occurs in 66–80% of patients undergoing LSG [7–11].

Although the mechanisms underlying T2DM remission following LSG has yet to be fully determined, some human studies have reported favourable changes in insulin sensitivity [12, 13]. In our patients, insulin resistance evaluated by HOMA index decreased by 80% thus confirming previous data by Abbatini et al. who demonstrated a near-normalization of insulin resistance measured by euglycemic clamp in patients treated with LSG [12]. The improvement in insulin sensitivity is primarily due to weight loss, reduction in inflammatory mediators, and decreased calorie intake although the contribution of weight independent mechanisms seems very likely. Potential mechanisms include enhanced stimulation of gastrointestinal hormones secondary to rearrangement of gastrointestinal anatomy. For malabsorptive/mixed procedures (RYGB and BDP) relevant and rapid changes in the enterohormonal axis have been demonstrated, consisting of complete recovery of meal-stimulated response of GLP-1 and GIP [14]. These modifications, evident already a few days after surgery, may explain the rapid improvement of glucose homeostasis before substantial weight loss has occurred [14, 15]. The long-term evaluation of these patients has also shown that the recovery of incretin response is maintained over time, probably contributing to the recovery of beta-cell function [16]. Regarding LSG, recent studies have shown that this procedure is associated with a marked reduction of ghrelin secretion, an orexigenic peptide produced by the gastric fundus involved in mealtime hunger regulation [17]. Ghrelin is also known to exert several diabetogenic effects (increase in growth hormone, cortisol, and epinephrine); therefore its suppression could contribute to improved glucose homeostasis. Interestingly, we observed an increased meal-stimulated GLP-1 and GIP response in our patients at 3 weeks postoperatively, which may have concurred to amelioration of glucose metabolism (unpublished observations).

None of the patients studied presented any sign of nutritional deficiencies at 9–15-month follow-up, confirming that LSG is a safe procedure in terms of nutritional status at odds with malabsorptive or mixed surgical procedures which often lead to multiple nutritional consequences due to the bypass of duodenum and jejunum [18].

In conclusion, LSG induces stable weight loss and resolution of T2DM diabetes and other obesity-associated comorbidities in a large majority of patients. Controlled long-term comparisons between different bariatric interventions are needed to establish the optimal procedure in relation to patients' characteristics.

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