

SLEEVE GASTRECTOMY TO CORRECT OBESITY AND ASSOCIATED CO-MORBIDITIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS – EARLY RESULTS –

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Abstract

Obesity has become a serious health problem and it is a major risk factor for the development of insulin resistance and type 2 diabetes mellitus (T2DM). Laparoscopic sleeve gastrectomy (LSG) has revealed to be effective for achieving weight loss and a potential competitor with other operations. The aim of this study is to evaluate weight loss and the reversibility of associated comorbidities in obese T2DM patients, one and three months after LSG. Data collected between January 1st – June 30th 2011 from 23 subjects with obesity and T2DM were analyzed retrospectively. The following parameters recorded before, one and three months after surgery were compared: body mass index (BMI), fasting plasma glucose, lipid profile, arterial blood pressure, hypoglycemic drugs, antihypertensive and hypolipidemic drugs. Mean BMI decreased from $45.17 \pm 8.342\text{kg/m}^2$ to $39 \pm 6.031\text{kg/m}^2$ at one month and to $34.91 \pm 4.435\text{kg/m}^2$ 3 months after surgery. Fasting plasma glucose decreased to $117.87 \pm 35.143\text{mg/dl}$ at one month and to $102.22 \pm 16.605\text{mg/dl}$, 3 months after surgery. Following surgery, a full remission of T2DM was achieved in 39% of patients in the first month and in 65% of patients at 3 months. There was also an important improved in lipid profile, blood pressure control and obstructive sleep apnea (OSA). Our study has shown positive early effects of LSG on obese T2DM patients regarding weight loss and obesity - related comorbidities reduction.

key words: laparoscopic sleeve gastrectomy, obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea.

Introduction

Obesity, a physiological dysfunction in humans, associated with environmental,

genetic and endocrinological causes, has become a serious health problem [1]. The latest World Health Organisation (WHO) data show that worldwide obesity has more than

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doubled since 1980. In 2008, 1.5 billion adults, 20 years and older, were overweight. Of these over 200 million men and nearly 300 million women were obese. 65% of the world's population live in countries where overweight and obesity kills more people than underweight does. Nearly 43 million children under the age of five were overweight in 2010 [2]. Obesity is becoming endemic, particularly because of increased food intake and a decrease in physical exercise [3].

Obesity is a major risk factor for the development of insulin resistance and T2DM [4, 5]. In morbidly obese patients, the relative risk of T2DM is at least 5% in men and 8-20% in women [6-8].

Many methods have emerged for treating morbid obesity, such as diet, exercise, known as lifestyle modification, liposuction, drugs and surgery: among these, there is extensive evidence that bariatric procedures, including bilio pancreatic diversion (BPD), gastric bypass (GBP) and gastric banding, reduce weight and successfully control most of the obesity - related co morbidities, such as T2DM, hypertension, dyslipidemia and OSA [9-13].

LSG, originally conceived as a first stage for achieving weight loss in morbidly obese patients before performing GBP or BPD, has revealed to be effective on its own and also a potential competitor with these operations [9, 14-17].

Few studies have examined the effects of LSG on weight loss and associated comorbidities in obese T2DM patients [18-21].

The positive effect of LSG on diabetes seems to be related not only to the fat mass but also to the extensive resection of the gastric fundus that could be, *per se*, a factor that

induces pathophysiological changes able to improve type 2 diabetes. It has been suggested that changes in ghrelin and PYY after LSG may help to explain the rapid weight-independent glycemic effects of LSG [22-25].

Ghrelin is an orexigenic hormone produced primarily by the stomach. Administration of ghrelin or its analogues stimulates food intake. Ghrelin levels have an inverse relationship with body weight; consequently, obese individuals have lower ghrelin levels. Diet - induced weight loss results in increased ghrelin levels and may be contributing to the resistance to lifestyle interventions for obesity. Recent data from human and animal studies suggest a role for ghrelin in glucose homeostasis beyond its effect on caloric intake. In fact, ghrelin can stimulate insulin counter regulatory hormones, suppress the insulin-sensitizing hormone adiponectin, block hepatic insulin signaling at the level of phosphatidylinositol-3-kinase and inhibit insulin secretion. Ghrelin deletion in diabetic *ob/ob* mice has also been shown to reduce FBG and insulin levels, and improve glucose tolerance [26-32].

Peptide YY (PYY) is an anorexigenic hormone co-secreted with GLP-1 from intestinal L cells in response to food intake. PYY3-36 has been shown to decrease food intake in humans when injected. Experimental studies in rodents suggest that PYY may directly ameliorate insulin resistance [26, 33].

The aim of this study is to evaluate weight loss and the reversibility of associated co morbidities in obese T2DM patients, at one and three months after LSG.

Material and Methods

An observational retrospective study was performed based on the analysis of data

obtained from 23 subjects with obesity and T2DM.

The study was conducted at the Centre of Excellence for Bariatric and Metabolic Surgery of Delta Hospital, Bucharest. Between January 2011 and June 2011, all patients were submitted to LSG (a gastric tube is created using repeated firing with linear staplers from the distal antrum to the Hiss angle, with complete removal of the greater curvature and fundus. A 100 ml gastric pouch is finally obtained).

All patients underwent complete evaluation before and at one and three months after surgery including anthropometric/clinical parameters and laboratory tests. Body weight and height were determined and BMI was calculated. Venous blood sample was used in order to determine fasting plasma glucose (FPG), total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides. Blood pressure was noted with patient in the supine position after 10 minutes of rest. The Korotkoff method was used and the mean of two measurements for systolic (SBP) and diastolic (DBP) blood pressure was recorded. Antidiabetic medication, antihypertensive drugs and hypolipidemic drugs were noted. The sleep polysomnography findings were used to determine the presence of obstructive sleep apnea syndrome. A positive test for OSA was established using the apnea-hypopnea index (AHI). Respiratory disturbance as measured by AHI was considered mild for AHI 5-15, moderate for AHI 16-30 and severe for AHI > 30. Also the gas exchange as measured by oxygen saturation were noted (minimum and mean oxygen saturation) in order to determine the severity of OSA. All patients with OSA required continuous positive airway pressure when sleeping.

Remission of T2DM was defined as sustained FPG less than 110mg/dl in the absence of antidiabetic treatment (several successive results below 110mg/dl were obtained). Remission of hypertension was defined as blood pressure below 140/90mmHg in the absence of antihypertensive treatment. Remission of dyslipidemia was defined as fasting plasma LDL-cholesterol below 130 mg/dl and/or fasting plasma triglycerides below 150mg/dl in the absence of pharmacological therapy. Remission of OSA was defined as a apnea-hypopnea index <5 in the absence of a continuous positive airway pressure therapy. Improvement was defined as either improved control of the mentioned parameters while on the same dose of medication or continued adequate control of parameters while on a reduced amount of medication.

The statistical analysis was performed using SPSS 17.0 software for Windows. Results are shown as mean \pm standard deviation (SD). The variables were tested for normal distribution. ANOVA and t-test were used to compare the parameters of the subjects before and after surgery. $P < 0.05$ was considered significant.

Results

The mean age was 50.6 ± 8.8 years and the female gender was predominant (8 Male/15 Female). The main characteristics of the studied patients are shown in Table 1.

Before surgery obesity - related comorbidities rates were: 100% (n=23) for T2DM, 83% (n=19) for hypertension, 83% (n=19) for dyslipidemia and 39% (n=9) for OSA. 48% (n=11) patients took oral antidiabetic agents and 13% (n=3) were on combined therapy (oral antidiabetic agents

plus insulin). 71% (n=17) patients were on antihypertensive therapy and 35% (n=8) patients received hypolipidemic drugs. The

changes in anthropometric and biochemical variables following LSG are reported in Table 1.

Table 1. Changes in main clinical and paraclinical parameters following LSG.

	Baseline (N=23)	1 month (N=23)	p value	3 months (N=23)	p value
BMI (kg/m ²)	45.17 ± 8.342	39.71 ± 6.031	0.017	34.91 ± 4.435	<0.001
FPG (mg/dl)	158.78 ± 55.834	117.87 ± 35.143	0.002	102.22 ± 16.605	<0.001
Total cholesterol (mg/dl)	206.22 ± 43.9780			182.43 ± 25.993	0.001
LDL-cholesterol (mg/dl)	122.43 ± 42.037			111.91 ± 27.759	0.099
HDL-cholesterol (mg/dl)	48.83 ± 9.442			51.26 ± 9.237	0.051
Triglycerides (mg/dl)	212.87 ± 104.960			120.96 ± 25.195	<0.001
Antidiabetic agents (n)	14	11		8	
Antihypertensive drugs (n)	17	12		12	
Hypolipidemic drugs (n)	8			1	

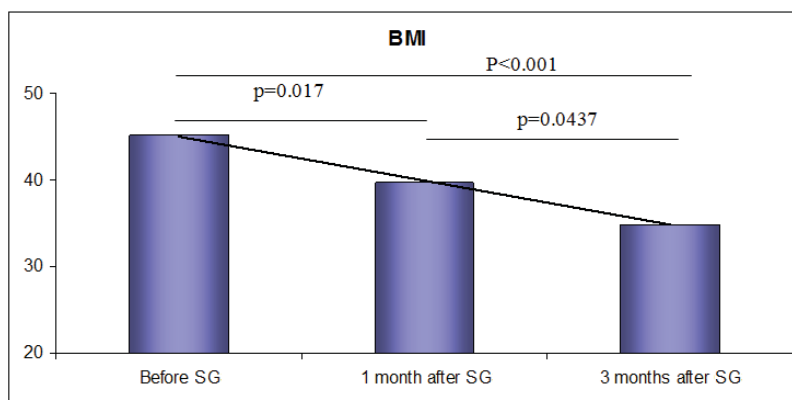


Figure 1. Evolution of body mass index after sleeve gastrectomy (SG).

Mean BMI decreased from the baseline value of 45.17 ± 8.342kg/m² to 39.71 ± 6.031kg/m² (p=0.017) at month one and to 34.91 ± 4.435kg/m² (p<0.001) three months after surgery (Figure 1). Fasting plasma glucose decreased from 158.78 ± 55.834mg/dl to 117.87 ± 35.143mg/dl (p=0.002) at one month and to 102.22 ± 16.605mg/dl (p<0.001) three months after surgery (Figure 2). Total cholesterol and triglycerides showed significant improvement at three months after surgery (p<0.001) (Figures 3 and 4). HDL-cholesterol increased from the baseline value

of 48.83 ± 9.442mg/dl to 51.26 ± 9.235mg/dl three months after LSG, but the result is not significant (p=0.051) (Figure 5).

There was post surgery resolution or improvement in obesity associated comorbidities: diabetes was considered remitted in 65% (n=15) and improved in 35% (n=8), hypertension resolved in 37% (n=7) and improved in 12% (n=63) and dyslipidemia resolved in 74% (n=14) and improved in 26% (n=5), OSA resolved in 56% (n=5) and improved in 33% (n=3) (Table 2).

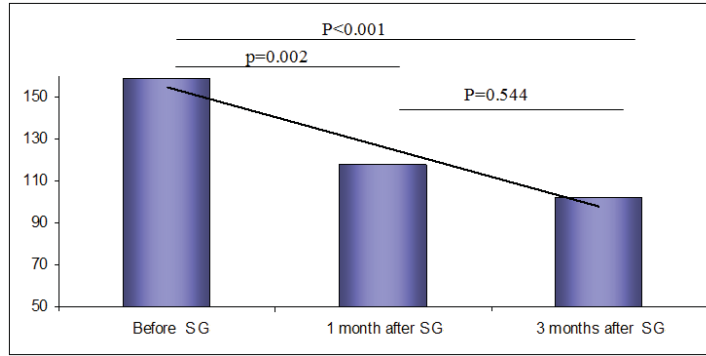


Figure 2. Evolution of fasting plasma glucose after sleeve gastrectomy.

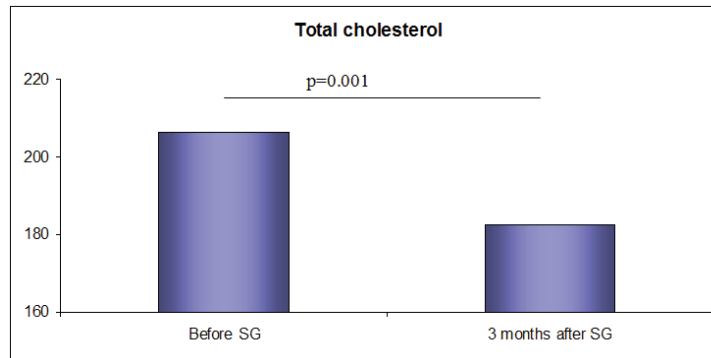


Figure 3. Evolution of total cholesterol after sleeve gastrectomy.

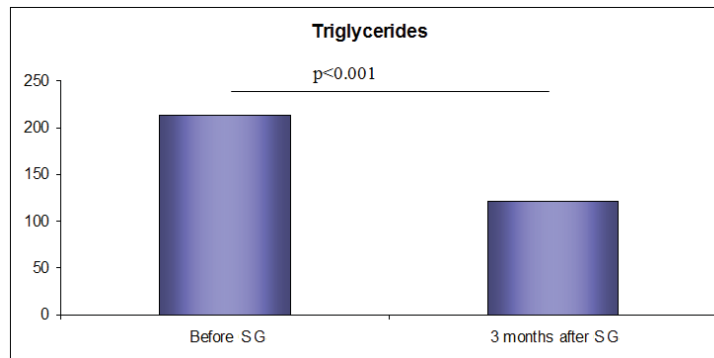


Figure 4. Evolution of blood triglycerides after sleeve gastrectomy.

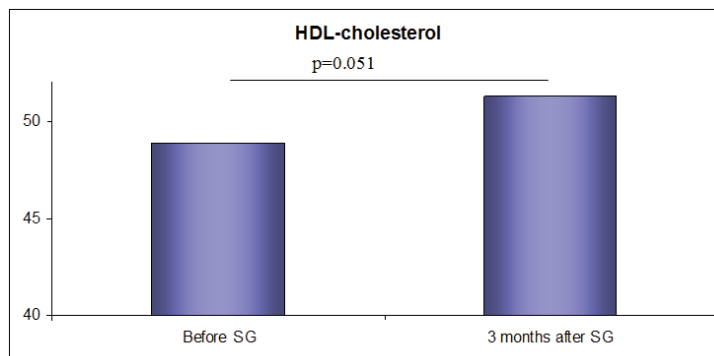


Figure 5. Evolution of HDL-cholesterol after sleeve gastrectomy.

Table 2. Pre- and post surgery obesity-related comorbidities changes among patients who underwent LSG.

Comorbidity	Preoperative	1 month			3 months		
		Resolved	Improved	Unchanged	Resolved	Improved	Unchanged
Type 2 diabetes mellitus	23	9	12	2	15	8	0
Insulin treatment	3	0	3	0	0	3	0
Dyslipidemia	19				14	5	0
Hypertension	19	5	5	9	7	12	0
Obstructive sleep apnea	9	0	7	2	5	3	1

In the studied group, 19 subjects were diagnosed with high blood pressure before the surgery and received treatment. One month after surgery, five of the subjects (26.31%) presented normal blood pressure without any medication and other five subjects (26.31%) requested the reduction of the treatment.

Three months after surgery, 7 subjects (36.84%) did not need any treatment for lowering blood pressure and the other 12 subjects (63.15%) reduced their treatment (Figure 6).

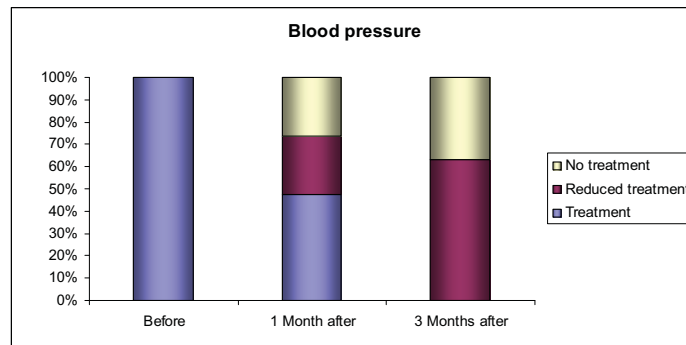


Figure 6. Improvement of blood pressure after sleeve gastrectomy.

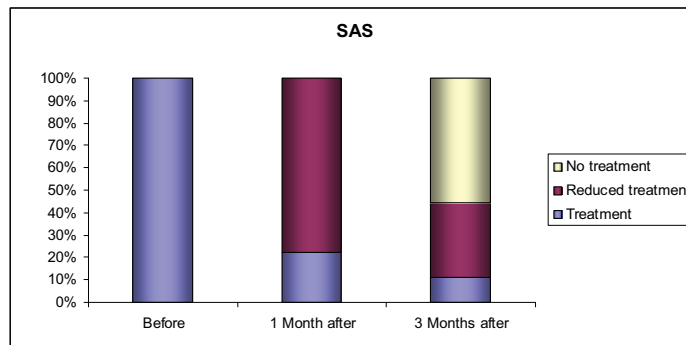


Figure 7. Improvement of obstructive sleep apnea syndrome after SG.

Nine subjects presented obstructive sleep apnea syndrome. One month after surgery, 7 subjects requested reduction of treatment (77.77%), three months after surgery 5

subjects (55.55%) did not need any treatment and 3 subjects (33.33%) reduced their treatment (Figure 7).

Discussions

Our study shows that LSG is effective in achieving a significant weight loss. In addition to weight loss, reduction in obesity - related comorbidities is another important outcome in bariatric surgery. The resolution of T2DM was noticed in 65% of the subjects. This finding is in line with previous studies demonstrating that diabetes resolution occurs in 66-80% of patients undergoing LSG [18-21,34,35]. Resolution of T2DM occurs in 39% of our patients at one month following LSG. The early changes in T2DM status observed in our group show the independence of T2DM resolution from weight loss as reported in the literature [18]. The rapid resolution of T2DM seems to be due to many changes of gastrointestinal hormones regulation after gastrointestinal anatomy rearrangement.

Karamanakos et al. showed, in experimental studies, a significant increase both in fasting and postprandial PYY levels and a marked reduction in fasting ghrelin levels after SG [34]. These changes may be of great importance in the control of T2DM consequent to SG. Yada et al. suggested that the lack of ghrelin and its insulinostatic activity increase the maximal capacity of glucose-induced insulin release and enable islets to secrete more insulin to meet an increased demand associated with obesity, thereby achieving normoglycemia [36]. Moreover recent studies reported that low circulating levels of PYY are linked to both insulin resistance and insulin hyper secretion and demonstrated that lack of PYY alters the intrinsic properties of the islet of Langerhans such as they hypersecrete insulin in response to maximal stimulatory glucose concentrations [37].

Peterli et al. showed an increase in fasting and stimulated PYY and also in GLP-1 levels after SG [38]. In the literature, a relationship between GLP-1 and a “gastric factor” is reported [39].

The three patients requiring insulin therapy for T2DM control before LSG have presented an improvement in their diabetes status, demonstrated by the reduction of total insulin dose, but not a complete remission. This is consistent observations in the literature sustaining that the insulin treatment prior to surgery was associated with a lower rate of T2DM resolution [18, 40].

Hypertension was resolved in only 36.84% of our patients and dyslipidemia in 55.55%. The lower rate of resolution than in other studies may be explained by the short follow-up period. This is consistent with the results from the literature indicating that components of the metabolic syndrome, others than T2DM are dependent on weight loss [18, 41].

The 55.55% resolution rate of OSA in our patient population was also consistent with the results reported in the literature [42].

Conclusions

Our study has shown positive early effects of LSG on obese T2DM patients regarding weight loss and obesity - related comorbidities reduction. The hormonal changes induced by SG may have significance in early effect of this procedure on glucose metabolism. Our results and data from SG literature support our expectation for continuing improvement in health and quality of life for T2DM obese patients. Larger studies and longer follow-up terms are needed to validate short-term results and determine the long-term ones. Our hopes are to report the data at 6, 12 and 24 months of follow-up in order to have a better understanding of the process.

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