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EFFECTS OF SLEEVE GASTRECTOMY VERSUS GASTRIC BYPASS ON TYPE 2 DIABETES MELLITUS REMISSION IN OBESE PATIENTS

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Abstract

Objectives: *To determine and compare the efficacy of two weight-reducing surgical interventions, gastric bypass (GBP) and sleeve gastrectomy (SG), in inducing remission/improvement of type 2 diabetes mellitus (T2DM).* ***Materials and Methods:*** *Data were collected from 162 obese T2DM subjects who underwent SG (96) or GBP (66) between 2009 and 2011. The following parameters were recorded: body mass index, waist-hip-ratio, blood pressure, fasting plasma glucose, HbA1c, lipid profile, hypoglycemic drugs used.* ***Results:*** *Remission of T2DM was achieved in 83% of patients who underwent SG and in 81% of patients who underwent GBP. For both procedures, T2DM remission rate was higher for patients with a shorter duration of T2DM, with better preoperative glycemic control and for those not requiring pharmacological agents before surgery.* ***Conclusions:*** *SG and GBP are effective in inducing T2DM remission in obese patients. The clinical features of T2DM are important predictors for the remission of the disease after bariatric surgery.*

key words: *sleeve gastrectomy, gastric bypass, obesity, type 2 diabetes mellitus.*

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally, particularly in developing countries. The latest World Health Organization (WHO) data show that more than 346 million people worldwide have diabetes. The causes are complex, but mainly due to the rapid increases in overweight and obesity prevalence [1]. Thus, several large prospective studies estimated that overweight and obesity account for about 65–80% of new T2DM cases [2,3].

Both obesity and T2DM are difficult to control by conventional treatment, including diet and exercise (known as lifestyle

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optimization) and drug therapy [4-6]. It has been reported that bariatric surgery, including biliopancreatic diversion (BPD), gastric bypass (GBP), sleeve gastrectomy (SG) and gastric banding, reduce weight and successfully control most of the obesity - related co-morbidities, such as T2DM, hypertension, dyslipidemia, metabolic syndrome and sleep apnea syndrome [6-12]. Furthermore, there are extensive evidence that certain bariatric procedures may improve T2DM control through mechanisms beyond weight loss [13-15].

The underlying mechanism for T2DM remission after GBP is intriguing. Four possible mechanisms have been proposed, including the starvation followed by weight loss hypothesis, the ghrelin hypothesis, the lower intestinal (hindgut) hypothesis, and the upper intestinal (foregut) hypothesis. None of these theories necessarily precludes the others, so any combination may be operational to some degree [16-18].

SG, originally conceived as a first stage for achieving weight loss in morbidly obese patients before performing GBP or BPD, has emerged as a new restrictive bariatric procedure [10-12,19]. The positive effect of SG on T2DM seems to be related not only to the fat mass loss but also to the extensive resection of the gastric fundus that could be, *per se*, a factor that induces patho-physiological changes able to improve T2DM. It has been suggested that changes in ghrelin level after SG may help to explain the rapid weight-independent glycemic effects of this surgical procedure [17,10-24]. In addition to the ghrelin effect, SG was also reported to have a hindgut effect, increasing glucagon-like peptide 1 (GLP-1) and peptide YY (YYP) due to increased transit time after SG [17,21].

The primary objective of our study was to determine and compare the efficacy of two surgical weight-loss interventions, GBP and SG, in inducing remission or improvement of T2DM at 1, 3, 6 and 12 months after surgery.

Secondary end points were changes from baseline in body weight, waist and hip circumference, arterial blood pressure, fasting plasma glucose (FPG) and HbA1c and lipid levels including total cholesterol (CT), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and triglycerides (TG) at 1, 3, 6 and 12 months after surgery.

Material and Methods

An observational prospective study was performed based on the analysis of data obtained from 162 subjects with obesity and T2DM or impaired glucose tolerance (IGT). All patients were submitted to bariatric surgery: 96 subjects to SG and 66 subjects to GBP.

The study was conducted at the Centre of Excellence for Bariatric and Metabolic Surgery of Delta Hospital, Bucharest, between January 2009 and December 2011. Choice of surgical technique was made in accordance with the patient and after consultation of a multidisciplinary team comprising a general physician, surgeon, anesthesiologist, psychia-trist and endocrinologist/diabetologist. All patients provided written informed consent to participate in the study.

The main criteria for inclusion in the study were represented by obese patients (BMI $\geq$ 30 kg/m^2) with T2DM or Impaired Glucose Tolerance (IGT) who were submitted to sleeve gastrectomy or gastric bypass.

Exclusion criteria were represented by any condition that would be a contraindication to bariatric surgery, medical conditions that alter glucose metabolism (other than T2DM) or weight, use of drugs that alter glucose metabolism (other than antidiabetic) or weight.

All patients underwent complete evaluation before and at 1, 3, 6, 12 and 24 months after surgery including anthropometric/clinical parameters and laboratory tests. Body weight and height were determined and BMI was calculated as weight in kilograms divided by height in square meter. Weight changes were expressed as the percentage of weight excess loss relative to baseline (EWL). The waist circumference was measured at the level midway between the lateral lower rib margin and the superior anterior iliac crest. Hip circumference was measured at the maximum protuberance of the buttocks, and the waist-to-hip ratio (WHR) was calculated. Blood pressure was measured 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. A venous blood sample was used in order to determine FPG, HbA1c, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides.

The presence/absence of a diagnosis of T2DM or IGT was noted. For the diagnosis of the metabolic syndrome we used the criteria from the statement of IDF, NHLBI, AHA, World Heart Federation; International Atherosclerosis Society and International Association for the Study of Obesity editorialized in 2009. By these criteria the presence of any 3 of following 5 risk factors constituted a diagnosis of metabolic syndrome: waist circumference ≥ 94 cm for men and ≥ 80 cm for women, serum triglycerides ≥ 150 mg/dl (1.70 mmol/l), serum levels of HDL cholesterol < 40 mg/dl (1.03 mmol/l) for men and < 50 mg/dl (1.30 mmol/l) for women, blood pressure ≥ 130/85 mmHg, and serum glucose level ≥ 100 mg/dl (5.6 mmol/l) [25]. The hypoglycemic medication and T2DM duration for each patient were also recorded.

According to the recommendations from an expert consensus meeting organized in 2009 by the American Diabetes Association [26] and in agreement to the new (2011) American Diabetes Association cut points for T2DM and IGT diagnosis [27], complete remission of T2DM was defined as a FPG level of less than 100 mg/dl and HbA1c level of less than 5.7% for at least 1 year duration without active pharmacologic therapy. Partial remission of T2DM was defined as a FPG level of 100 to 125 mg/dl and a HbA1c level of 5.7 to 6.4% and a value of glucose level at 2 hours after the glucose load test between 140-199 mg/dl without active pharmacologic therapy for at least 1 year duration. 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 ± 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 of patients who underwent SG was 46 ± 9 years, and the female gender was predominant (41 M/55 F). The baseline characteristics of the studied patients are shown in Table 1.

For patients who underwent GBP the mean age was 46 ± 7.5 years, and the female gender was also predominant (31M/35F). The baseline characteristics of this group are shown in Table 2.

At 12 months after surgery, both groups had a marked reduction in body weight, waist and hip circumference and improvement of other associated metabolic traits, including reduction of FPG, HbA1c, blood lipid and blood pressure levels (Table 1 and 2).

In the SG group, mean BMI decreased from the baseline value of 44 ± 7.9 kg/m² to 29.9 ± 5.7 kg/m² (p<0.001) with a mean EWL of 78 ± 17.7% at 12 months after surgery. Mean waist circumference decreased from 130 ± 18.7 cm to 95 ± 12 cm (p<0.001) and mean hip circumference from 132 ± 12.9 cm to 105 ± 11.1 cm (p<0.001) with a reduction of WHR from 0.98 ± 0.09 to 0.90 ± 0.07 (p<0.05). Blood pressure was significantly reduced one year after SG: average SBP decreased from 138 ± 19.6 mmHg to 121 ± 9.6 mmHg (<0.001) and average DBP decreased from 83 ± 9.6 to 74 ± 6.9 mmHg (<0.001). Mean FPG and mean HbA1c decreased significantly from 142 ± 31.7 mg/dl to 93 ± 9.8 mg/dl (p<0.001), respectively from 7.2 ± 0.6% to 5.9 ± 0.6% (p<0.001) at 12 months after surgery. Total cholesterol, LDL-cholesterol and triglycerides showed significant improvement at 12 months after surgery (p<0.05). HDL-cholesterol increased from the baseline value of 52 ± 7.6 mg/dl to 56 ± 7.3 mg/dl at 12 months after surgery (p<0.05) (Table 1).

Table 1. Evolution of clinical and paraclinical parameters after sleeve gastrectomy in obese patients with T2DM or IGT.

Clinical/Paraclinical parameters	Baseline	Month 1	P value	Month 3	P value	Month 6	P value	Month 12	P value
BMI(kg/m²)	44 ± 7.9	39 ± 7	<0.05	35.5 ± 6.7	<0.001	32 ± 6	<0.001	29.9 ± 5.7	<0.001
EWL (%)		27 ± 8.4		47 ± 12.7		63 ± 14.8		78 ± 17.7	
Waist (cm)	130 ±18.7	119 ± 18	<0.05	112 ± 16.4	<0.001	104 ± 15.4	<0.001	95 ± 12	<0.001
Hip (cm)	132 ± 12.9	124 ± 13.8	<0.05	118 ± 13.1	<0.001	111 ± 12.2	<0.001	105 ± 11.1	<0.001
WHR	0,98 ± 0.09	0,96 ± 0.09	>0.05	0.94 ± 0.08	<0.05	0,93 ± 0.09	<0.05	0.90 ± 0.07	<0.05
BPs (mmHg)	138 ± 19.6	129 ± 12.9	<0.05	127 ± 13.1	<0.05	124 ± 22.6	<0.001	121 ± 9.6	<0.001
BPd (mmHg)	83 ± 9.6	78 ± 8.3	<0.001	76 ±7.5	<0.001	75 ± 7	<0.001	74 ± 6.9	<0.001
FPG (mg/dl)	142 ± 31.7	119 ± 21.4	<0.001	101 ± 16.2	<0.001	96 ± 13.4	<0.001	93 ± 9.8	<0.001
HbA1c (%)	7,2 ± 0.6	7 ± 0.6	>0.05	6.6 ± 0.5	<0.001	6,3 ± 0.5	<0.001	5.9 ± 0.6	<0.001
CT (mg/dl)	219 ± 46.1			186 ± 32.7	<0.05	169 ± 38.2	<0.001	160 ± 32	<0.001
LDL-C (mg/dl)	136 ± 33.4			115 ± 27.1	<0.05	107 ± 26.7	<0.001	99 ± 19.7	<0.001
HDL-C (mg/dl)	52 ± 7.6			54 ± 8.4	>0.05	56 ± 9.6	<0.05	56 ± 7.3	<0.05
TG (mg/dl)	155 ± 89.3			119 ±36.2	<0.05	103 ± 34.2	<0.001	111 ± 32.1	<0.001

In the GBP group, there was also a significant decrease of mean BMI from 44 ± 6.4 kg/m² to 29 ± 5.4 kg/m² (p<0.001) at 12 months after surgery. There was no difference in types of surgery and weight loss between the two groups: EWL = 78% (post LSG) and EWL = 78% (post GBP). Mean waist circumference, hip circumference and WHR were significantly reduced one year after GBP: from 133 ± 17 cm to 96 ± 11.9 cm (p<0.001), from 134 ± 15.4 cm to 105 ± 11.2 cm (p<0.001) and from 0.98 ± 0.07 to 0.91 ±

0.05 (p<0.05) respectively. BP was also significantly reduced at 12 months after GBP: average SBP decreased from 143 ± 17.8 mmHg to 120 ± 7.6 mmHg (p<0.001) and average DBP decreased from 87 ± 9.9 mmHg to 74 ± 7.2 mmHg (p<0.001). FPG and HbA1c decreased significantly at 1 year after GBP from 150 ± 37.6 mg/dl to 91 ± 12.9 mg/dl (p<0.001), respectively from 7.7 ± 0.9 % to 5.6 ± 0.5% (p<0.001). These patients presented also statistically significant changes of lipid profile (Table 2).

Table 2. Evolution of clinical and paraclinical parameters after gastric bypass in obese patients with T2DM or IGT.

Clinical/Paraclinical parameters	Baseline	Month 1	P value	Month 3	P value	Month 6	P value	Month 12	P value
BMI(kg/m²)	44 ± 6.4	39 ± 5.7	<0.05	35 ±5.6	<0.001	31.9 ± 5.2	<0.001	29 ± 5.4	<0.001
EWL (%)		26 ± 7.5		45 ± 11.3		62 ± 14.1		78 ± 13	
Waist (cm)	133 ± 17	122 ± 16.1	<0.05	113 ± 15.5	<0.001	105 ± 14.2	<0.001	96 ± 11.9	<0.001
Hip (cm)	134 ± 15.4	126 ± 14.5	<0.05	119 ± 14.5	<0.001	113 ± 13.8	<0.001	105 ± 11.2	<0.001
WHR	0.98 ± 0.07	0.97 ± 0.7	>0.05	0.94 ± 0.06	<0.05	0.93 ± 0.06	<0.05	0.91 ± 0.05	<0.05
BPs (mmHg)	143 ± 17.8	133 ± 11.4	<0.05	128 ± 10.4	<0.05	123 ± 8.3	<0.001	120 ± 7.6	<0.001
BPd (mmHg)	87 ± 9.9	81 ± 7.6	<0.05	78 ± 6.9	<0.05	76 ± 6.3	<0.001	74 ± 7.2	<0.001
FPG (mg/dl)	150 ± 37.6	122 ± 20.3	<0.001	105 ± 18.2	<0.001	97 ± 15.8	<0.001	91 ± 12.9	<0.001
HbA1c (%)	7.7 ± 0.9	7.1 ± 0.8	<0.05	6.5 ± 0.7	<0.001	6 ± 0.6	<0.001	5.6 ± 0.5	<0.001
CT (mg/dl)	214 ± 39.6			179 ± 32.2	<0.001	154 ± 38.5	<0.001	138 ± 33.2	<0.001
LDL-C (mg/dl)	134 ± 25.1			115 ± 22.7	<0.001	100 ± 20.6	<0.001	92 ± 18.6	<0.001
HDL-C (mg/dl)	50 ± 7			52 ± 6.8	>0.05	58 ± 7.6	<0.05	59 ± 6	<0.05
TG (mg/dl)	160 ± 73.5			113 ± 23.2	<0.001	93 ± 17.7	<0.001	89 ± 20.7	<0.001

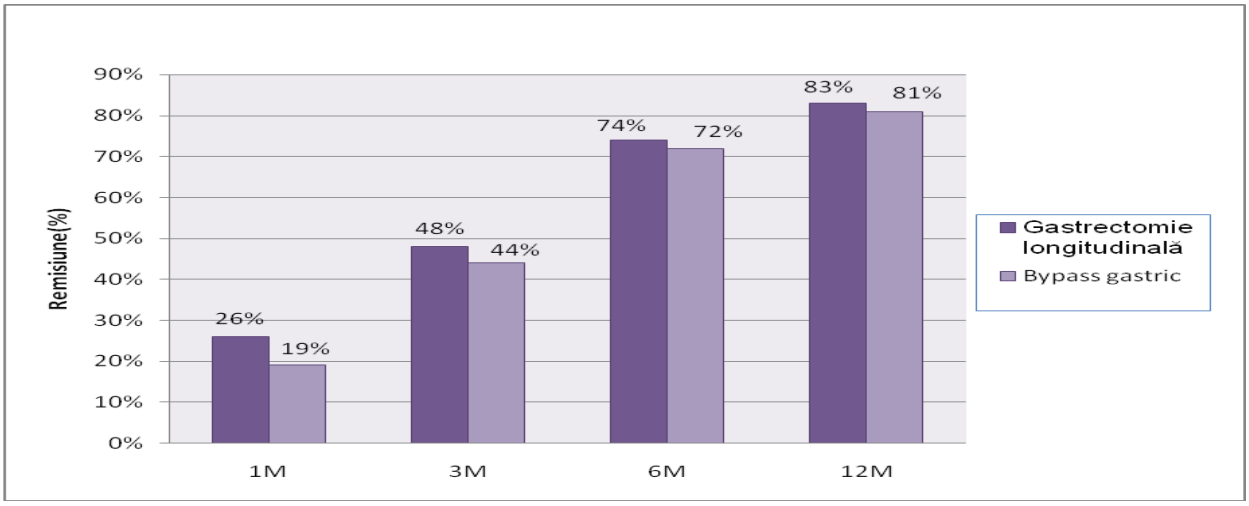

Figure 1. The rate of remission of T2DM in obese patients following sleeve gastrectomy versus gastric bypass.

At baseline, 42 patients from the SG group were diagnosed with IGT. At 12 months after surgery, all patients presented the normalization of the blood glucose parameters. The other 54 patients from this group were diagnosed with T2DM before surgery: 19 were treated with diet, 27 were treated with oral antidiabetics (OAD) and 8 were treated with insulin. T2DM remission occurred in 26% of patients at one month after surgery and in 48%, 74%, and 83% of patients at 3, 6 and, respectively, 12 months after SG. Complete remission of T2DM in this group was achieved by 26% of patients at 6 months and by 54% of patients at 12 months (Figure 1 and 2).

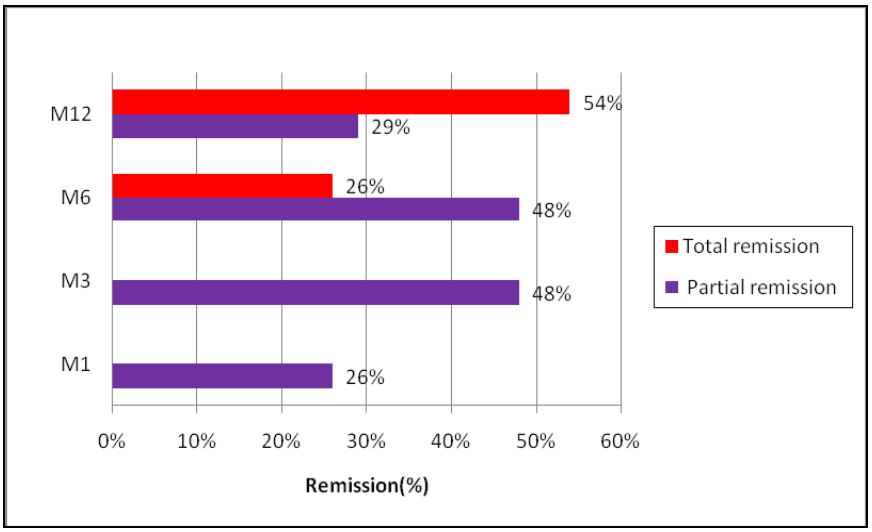

Figure 2. Partial/total remission of T2DM in obese patients following sleeve gastrectomy.

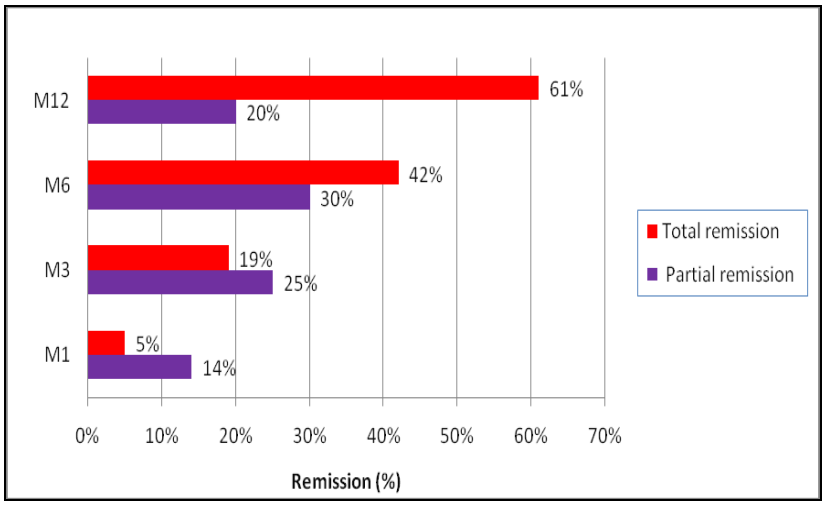

Figure 3. Partial/total remission of T2DM in obese patients following gastric bypass.

In the GBP group, 30 patients were diagnosed with IGT before surgery. At 12 months after GBP, all patients presented the normalization of glycemic parameters. In this group, 36 patients had T2DM before surgery: 9 patients were treated with diet, 23 patients with OAD and 4 with insulin. One month after surgery 19% of subjects presented the remission of T2DM; at 3, 6 and 12 months after GBP the rate of remission was 44%, 72% and, respectively, 81%. The complete remission of T2DM was noted at 5%, 19%, 42% and 61% of subjects at 1, 3, 6 and, respectively, 12 months after GBP (Figure 1 and 3).

T2DM remission rate was higher in patients with younger age ($p<0.001$), with a shorter T2DM duration ($p<0.05$) and with a better glycemic control before surgery (lower levels of fasting plasma glucose and HbA1c) ($p<0.05$) as shown in Table 3. Antidiabetic treatment used preoperatively has proved also to be a predictor factor for T2DM remission: patients requiring insulin therapy to control their T2DM prior to surgery presented a lower remission rate of T2DM ($p<0.05$); the best

results were obtained for patients whose T2DM was controlled with diet only, followed by those with OAD therapy prior to surgery (Figure 4,5). The absence of metabolic syndrome prior to surgery was associated with a higher rate of T2DM remission ($p<0.05$). The rate of remission of T2DM either after sleeve gastrectomy or gastric bypass has proven to be independent of excess weight loss ($p>0.05$) as shown in Table 3.

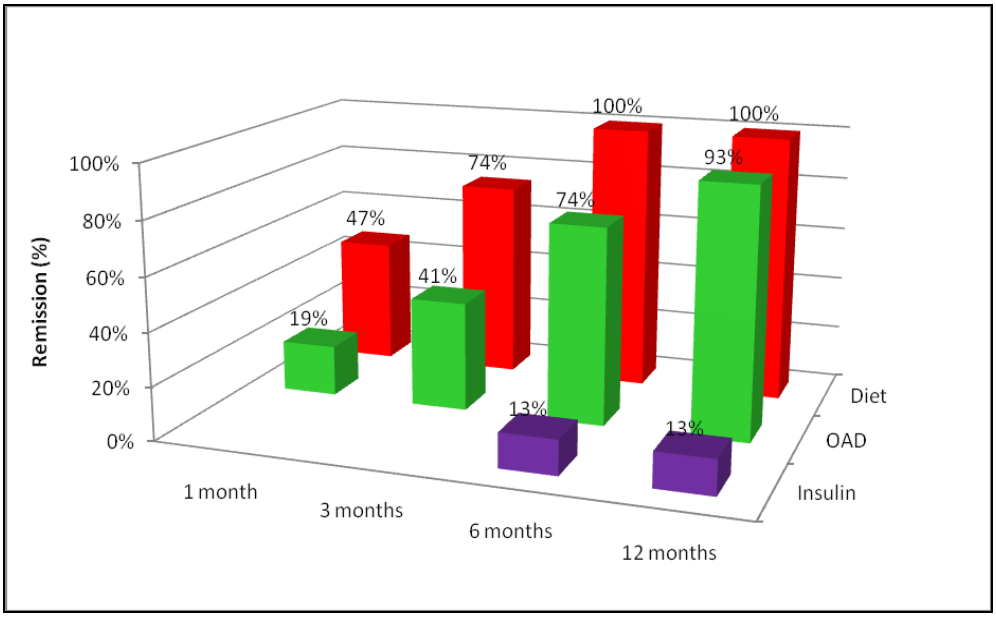

Figure 4. Remission of T2DM in obese patients after sleeve gastrectomy according to the treatment used before surgery.

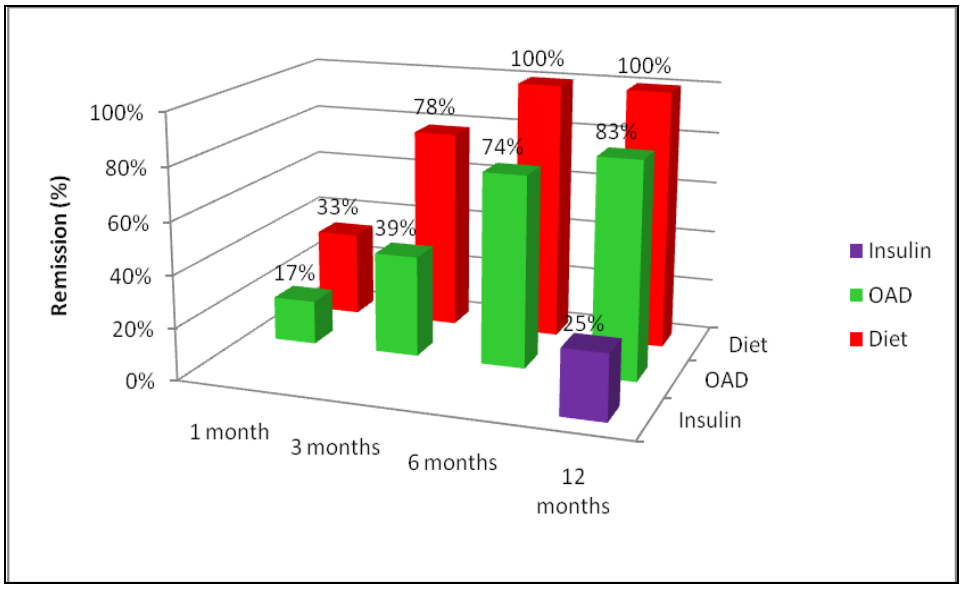

Figure 5. Remission of T2DM in obese patients after gastric bypass according to the treatment used before surgery.

Table 3. Clinical and paraclinical parameters as predictor factors for T2DM remission in obese patients according with the surgical procedure.

Type 2 diabetes mellitus		Remission	Non-responders	P value*
	SG	n=45	n=9	
	GBP	n=29	n=7	
Before surgery				
Age (years)	SG	47.2 ± 8.9	60 ± 4	<0.001
	GBP	48.1 ± 7.6	54.4 ± 2.1	<0.001
T2DM duration (years)	SG	2.8 ± 3	8.9 ± 1.9	<0.001
	GBP	3 ± 2	6 ± 2	0.004
Treatment (Diet/OAD/Insulin)	SG	100%vs93%vs13%	- vs7%vs87%	<0.001, <0.001
	GBP	100%vs83%vs25%	-vs17%vs75%	<0.001, <0.001
FPG (mg/dl)	SG	152.6 ± 28.7	198.2 ± 20.3	<0.001
	GBP	167 ± 31.5	202.6 ± 39.8	0.004
HbA1c (%)	SG	7 ± 0.4	8.2 ± 0.3	<0.001
	GBP	7.4 ± 0.7	8.7 ± 0.7	0.002
Metabolic Syndrome (present/absent)	SG	79%vs100%	21%vs-	<0.001
	GBP	78%vs89%	22%vs11%	<0.001
After surgery				
EWL (%)	SG	72.8 ± 14.05	74.8 ± 19.4	0.776
	GBP	72.9 ± 13.94	80.7 ± 8.7	0.083

*P values reflect comparisons between clinical and paraclinical parameters of patients who presented remission versus those who presented only an amelioration of the disease, for each of the two surgical procedures.

Discussion

Our results indicated that both SG and GBP were effective in the treatment of obese patients with T2DM. At 12 months after surgery, T2DM remission (partial or total) occurred in 83% of patients undergoing SG and in 81% of patients undergoing GBP. The rate of remission was comparable for both procedures (p=0.277).

T2DM remission in 81% of patients at 1 year after gastric bypass is consistent with results of previous studies [28,29]. It is interesting to note that early remission occurs in 19% of patients at one month after gastric bypass and in 44% of subjects at 3 months. This supports the two theories developed by Rubino et al: "Hindgut theory" and "Exclusion foregut theory" according to which early remission of T2DM seems to be due to changes in secretion of gut hormones after the modification of the anatomy of the digestive tract [18].

Also, for sleeve gastrectomy we noted an early T2DM remission of 26% at one month after surgery and of 48% at three months. This *result reinforces the idea of hormonal*

mechanisms involved in regulating blood glucose levels after sleeve gastrectomy: reducing serum levels of ghrelin and the rise in serum levels of GLP-1 and YYP [21,30-32].

There was no correlation between T2DM remission and percentage of weight loss after sleeve gastrectomy or gastric bypass. These findings support the hypothesis that the two bariatric procedures may exert effects on T2DM that are independent of weight loss.

All patients with IGT (30 underwent GBP and 42 SG) showed normalization of blood glucose levels at one month after surgery and the result was maintained for the entire follow-up period. These data confirm previous reports [28,33-35] and support the role of bariatric surgery in preventing progression to T2DM.

In terms of predictive factors for T2DM remission after surgery, our study showed that for both procedures the T2DM remission rate was higher for patients with a shorter duration of disease and with better preoperative glycemic control. Cases with T2DM requiring insulin were associated with lower rate of remission compared with cases on diet or OAD therapy. These observations are in agreement with previous reports [35-37] and suggest that the remaining functional pancreatic β cell mass is an important predictor factor for T2DM after surgery and should be considered preoperatively.

Besides T2DM remission, the two groups also achieved important weight loss, lower waist circumference, hip circumference, blood pressure values, fasting plasma glucose, HbA1c and blood lipid levels. These results suggest that the two surgical procedures represent a successful strategy in the management of various cardiovascular risk factors, components of the metabolic syndrome.

The strength of our study is represented by the complete evaluation of the the clinical and paraclinical parameters of T2DM for the both groups of patients (SG group and GBP group) and assessing how these parameters affect T2DM remission in our series of subjects. Identifying predictors of T2DM response to bariatric surgery allows establishing a clinical/biological profile for "responder" and "non-responder" patients to this type of treatment, creating premises for an individualized treatment.

Our study limitations include the small number of patients with T2DM, as well as the medium duration of the study. Larger multicenter studies will be required to confirm our findings and to provide the expected duration of T2DM remission.

Conclusion

Our findings indicate that SG and GBP are effective in inducing T2DM remission in obese patients. The clinical features of T2DM (preoperative glycemic control, duration of the disease and the type of T2DM therapy used) are important factors in the prognosis of remission of the disease for patients who underwent either GBP or SG. Remission of T2DM early after surgery, before significant weight loss, supports the involvement of hormonal mechanisms of the digestive tract responsible for the antidiabetic effect of the two surgical procedures, independent of weight loss. Studying the mechanisms by which bariatric surgery improves blood glycemic parameters should help us better understand the pathophysiology of the disease.

Although larger studies and longer follow-up are needed, the results of this study strongly recommend that SG and GBP should be included in the armamentarium of T2DM treatment in obese patients.

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