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ORIGINAL CONTRIBUTIONS

A Prospective Randomized Controlled Trial of the Metabolic Effects of Sleeve Gastrectomy with Transit Bipartition

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Abstract

Purpose To compare the effects of the sleeve gastrectomy with transit bipartition (SG + TB) procedure with standard medical therapy (SMT) in mildly obese patients with type II diabetes (T2D).

Methods This is a prospective, randomized, controlled trial. Twenty male adults, ≤ 65 years old, with T2D, body mass index (BMI) > 28 kg/m^2 and < 35 kg/m^2, and HbA1c level > 8% were randomized to SG + TB or to SMT. Outcomes were the remission in the metabolic and cardiovascular risk variables up to 24 months.

Results At 24 months, SG + TB group showed a significant decrease in HbaA1c values (9.3 ± 2.1 versus 5.5 ± 1.1%, $P = < 0.05$) whereas SMT group maintained similar levels from baseline (8.0 ± 1.5 versus 8.3 ± 1.1%, P = NS). BMI values were lower in the SG + TB group (25.3 ± 2.8 kg/m^2 versus 30.9 ± 2.5 kg/m^2; $P = < 0.001$). At 24 months, none patient in SG + TB group needed medications for hyperlipidemia/hypertension. HDL-cholesterol levels increased in the SG + TB group (33 ± 8 to 45 ± 15 mg/dL, $P < 0.001$). After 24 months, the area under the curve (AUC) of GLP1 increased and in the SG + TB group and the AUC of the GIP concentrations was lower in the SG + TB group than in the SMT. At 3 months, SG + TB group showed a marked increase in FGF19 levels (74.1 ± 45.8 to 237.3 ± 234 pg/mL; $P = 0.001$).

Conclusions SG + TB is superior to SMT and was associated with a better metabolic and cardiovascular profile.

Keywords Cardiovascular risk · Atherosclerosis · Transit bipartition · Sleeve gastrectomy · Bariatric surgery · Type 2 diabetes

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Introduction

Type 2 diabetes mellitus (T2D) is associated with the development of atherosclerosis, the underlying mechanism of cardiovascular disease. Recently, some types of bariatric surgeries (BSs) have emerged as promising treatments for obese patients with T2D.

Indeed, previous studies have demonstrated that after patients undergo BS, T2D remission occurs, and the rate of cardiovascular events are decreased. Interestingly, the metabolic effects and reduction in cardiovascular risk factors occur very early, even before significant weight loss has been achieved [1].

Several players contribute to the sequential events following BS. Incretins, such as glucagon-like peptide-1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP), induce metabolic effects and are associated with the BS outcomes [2, 3]. Additional metabolically active proteins that are modulated by BS, such as fibroblast growth factor 19 (FGF19), are linked to glycemic control and atherosclerosis progression [4, 5].

Classic BS techniques were proposed to be restrictive and/or promote malabsorption, differently affecting metabolic variables. Sleeve gastrectomy with transit bipartition (SG + TB) procedure was designed to minimize mechanical restriction and malabsorption, aiming to essentially induce metabolic changes [6, 7]. The objective of this study was to prospectively compare the effects on the metabolic variables of overweight and obese T2D patients induced by the SG + TB treatment with those of standard medical therapy.

Methods

Study Design and Participants

This was a 24-month, prospective, randomized, controlled, parallel-group study involving 20 T2D patients. Patients' selection and clinical treatment were conducted at InCor, Universidade de Sao Paulo. Surgical procedures were performed at Hospital Israelita Albert Einstein in São Paulo, Brazil. The study was approved by the Institutional Ethics Committee (CAPPesq 0355/11) and registered with ClinicalTrials.gov (NCT01581099). Because of the small sample size and to mitigate heterogeneity effects, we included only male individuals.

Inclusion criteria were ≤ 65 years old, T2D for > 2 and < 10 years, body mass index (BMI) > 28 and < 35 kg/m^2, waist circumference > 102 cm, and glycated hemoglobin (HbA1c) level > 8% despite standard therapy provided by Brazilian health system (lifestyle management [dietary support and exercise advice] plus metformin, sulfonylurea, and/or insulin). The exclusion criteria were as follows: C-peptide levels < 1.5 ng/mL, positivity for the autoantibodies anti-GAD or ICA, active cancer, relevant acute or chronic infections, alcohol or drug abuse, or current smoking. In addition, 10 healthy participants were included as the control group for FGF19 measurements (BMI > 18.5 and < 25 kg/m^2, fasting blood glucose < 95 mg/dL, and HbA1c level < 5.5%).

After a 12-week run-in period during which all patients were evaluated every 2 weeks, patients were randomly assigned in a 1:1 ratio to either the standard medical therapy (SMT group) ($n = 10$) or the SG + TB treatment plus SMT (SG + TB group) ($n = 10$). Patients were evaluated every 3 months, and data were collected at baseline and at 3 (planned interim analysis) and 24 months after the treatment groups had been assigned (Fig. 1).

The main outcome measure was an HbA1c level ≤ 6.0%. Other evaluated variables included the presence of obesity (BMI ≥ 30 kg/m^2), systemic arterial hypertension and dyslipidemia requiring medication, and major signs of undernutrition (anemia, hypoalbuminemia, BMI < 20 kg/m^2) from baseline to 24 months.

Data Collection

BMI, waist circumference, and blood pressure were measured, and fasting blood samples were obtained for glucose, HbA1c, and blood lipids. FGF19 and proinsulin levels were measured at baseline and 3 months, approximately 8:00 am after a 12-h fast using an ELISA kit (DY1336-Human Proinsulin-R&D systems and ELH-FGF19-Human FGF19–Raybiotech). For GLP1 and GIP measurements using an ELISA Kit (EZHGIP-54K-Gastric Inhibitory Polypeptide (GIP) ELISA Kit–Linco Legancy and JP27784-GLP-1 (active forms) ELISA-IBL International GmbH), a mixed meal test was performed at baseline and at 24 months with blood samples collected at 8:00 am after 12-h fast and 15, 60, and 120 min after the ingestion of a meal supplement (150 mL (300 kcal) of Nutren 2.0 from Nestlé, Vevey, Switzerland), as previously described [8].

Metabolic Surgery

SG + TB (Fig. 2) was performed with 10 patients by one surgeon (SS), between May 2014 and May 2015. The laparoscopic procedure was described in detail in a previous article [6] and video [9] (Fig. 2). In this study, the gastro-ileo-anastomoses were 3 cm wide and were performed 250 to 260 cm from the ileocecal valve; in these cases, the resulting common channel was 120–130 cm from the ileocecal valve. Patients adhered to a liquid diet for 12 days after discharge that was gradually progressed after this time. No gallstone prevention was prescribed.

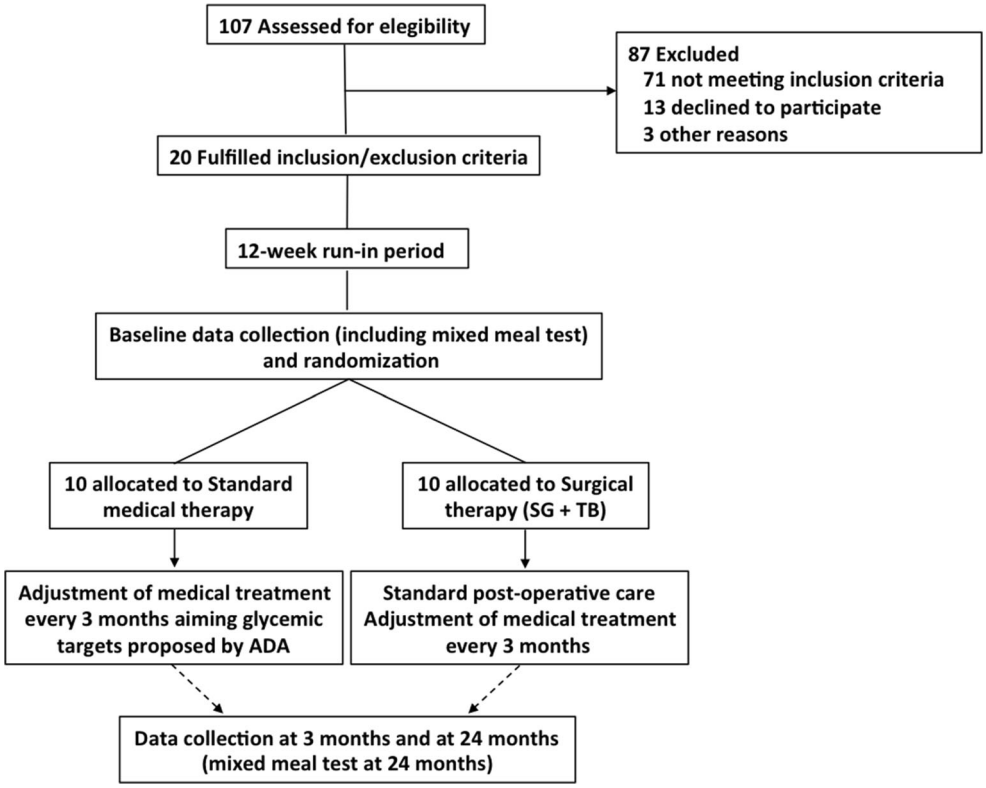

Fig. 1 Flowchart of the study design

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Statistical Analysis

The biochemical values, hormones, and other metabolite concentrations of the groups and time points were analyzed through generalized estimating equations (GEE) with normal marginal distribution using means and standard deviation and identity link function with matrix autoregressive correlation between the first order time points. The same analysis was performed with the areas under the curve (AUCs) for the incretin concentrations after the mixed meal test to compare the various groups and time points. When a significant difference was found in the GEE analysis, the Bonferroni multiple comparison procedure was performed to determine which groups or times were different.

Since significant differences were found between the baseline values of the SG + TB and SMT groups, some analyses were repeated adjusting for the baseline BMI, glucose, and triglyceride values. Tests were performed using the

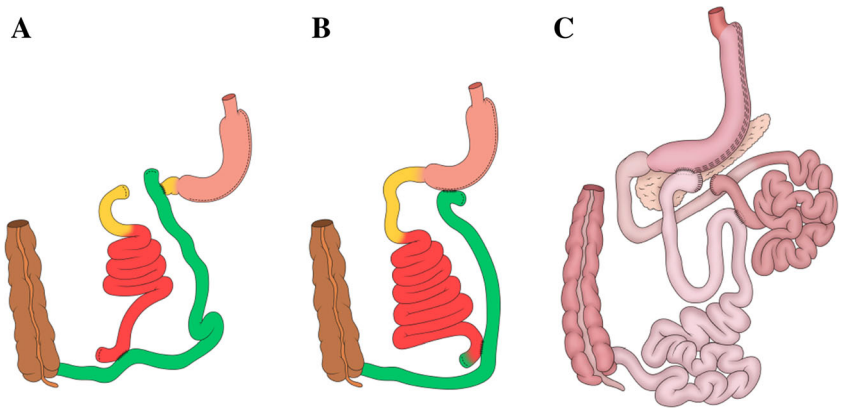

Fig. 2 **a**, **b** Didactic schemes illustrating the surgical techniques of a classic sleeve gastrectomy with duodenal switch (**a**) and of a sleeve gastrectomy with a transit bipartition (SG + TB) (**b**) for comparison. A more technically detailed scheme of SG + TB is provided in panel **c**

Excel 2003 and SPSS20.0 software, and a 5% significance level was adopted.

Results

A total of 107 patients were screened. Twenty patients were randomized, and all patients completed the study. Patient characteristics at baseline are shown in Tables 1 and 2. The surgeries lasted 125 ± 12 min (110–150 min). Mean hospital stay was 46 ± 2 h. No early postoperative complications occurred. One patient developed cholelithiasis after 6 months and underwent elective cholecystectomy, and one patient presented transient anemia and hypoalbuminemia that resolved after 3 months of treatment.

Glycemic Control

At 3 months, the mean HbaA1c values were lower in the SG + TB group (Table 2). A further decrease in HbaA1c values was observed at 24 months in the SG + TB group, but this value was increased in the SMT group (Table 2 and Fig. 3a).

At 24 months, HbaA1c values of ≤ 6.0% were present in 9 out of 10 patients (90%) in the SG + TB group compared with 1 out of 10 patients (10%) in the SMT group. As depicted in Table 2, despite the need of insulin and metformin in all patients ($n = 20$) in both groups and sulfonylureas in 80% ($n = 16$) at baseline, 100% ($n = 10$) of the SG + TB patients achieved glycemic control without using insulin or sulfonylureas and only 2 (20%) of them were still using metformin (criterion for withdrawing metformin was HbA1c < 5.8%), at this point.

Weight Loss

At 3 months, the mean BMI values were lower in the SG + TB group than in the SMT group (27.4 ± 2.8 kg/m^2 versus 30.6 ± 2.0 kg/m^2; $P = 0.047$, weight loss = − 6.0 and + 0.3 kg/m^2, respectively). A further decrease was observed at 24 months in the SG + TB group, but this value remained stable in the SMT group (25.3 ± 2.8 versus 30.9 ± 2.5 kg/m^2; $P = < 0.001$, weight loss = − 8.1 and + 0.6 kg/m^2, respectively) (Fig. 3b).

Lipid Profile and Cardiovascular Medications

The number of patients requiring treatment for hyperlipidemia decreased only in the SG + TB group (80% at baseline, 0% at 3 months, and 0% at 24 months). The HDL-cholesterol levels significantly increased at 3 and 24 months in the SG + TB group only (33 ± 8 mg/dL at baseline versus 38 ± 11 versus 45 ± 15 mg/dL, respectively, $P < 0.001$). The number of patients receiving antihypertensive drugs was reduced only in the SG + TB group (Table 2).

GLP-1 and GIP Levels at 24 Months

The GIP and GLP1 response after the mixed meal test at baseline and 24 months are shown in Fig. 4. At baseline, no differences were observed between the two groups in the AUC of GIP or GLP1 concentration (Table 3). After 24 months, the AUC of GLP1 was increased in the SG + TB group only (14,869.2 ± 3891.6 versus 5396.3 ± 2514, respectively; $P < 0.001$). The AUC of the GIP concentrations was lower in the SG + TB group than in the SMT group after 24 months (37,286.7 ± 16,519.1 versus 84,153.3 ± 27,120.1, respectively; $P < 0.001$), but the decrease in AUC between the pre- and postoperative periods was not different (52,804.8 ± 25,847.5 versus 37,286.7 ± 16,519.1, respectively; $P = 0.228$).

Fasting Levels of FGF19 and Proinsulin

The FGF19 levels at baseline and after 3 months were not different in the SMT group: 63.3 ± 59.6 and 62.1 ± 58.5 pg/mL, respectively. Conversely, at 3 months after surgery, the SG + TB group presented with a marked increase in FGF19 levels (from 74.1 ± 45.8 to 237.3 ± 234 pg/mL; $P = 0.001$) that represented more than two-fold the levels of the normal volunteer group that remained stable during this period.

Table 1 Baseline characteristics of the patients

Measure	SMT group ($n = 10$)	SG + TB group ($n = 10$)	P
Age, mean ± SD (years)	**56 ± 7**	**45 ± 10**	*0.035*
T2DM duration, mean ± SD (years)	8.5 ± 3.2	7.5 ± 2.0	0.868
Body weight, mean ± SD (kg)	88.5 ± 11.7	102.2 ± 12.2	0.073
BMI, mean ± SD (kg/m^2)	**30.3 ± 2.1**	**33.4 ± 2.6**	*0.023*
WC, mean ± SD (cm)	106.0 ± 6.0	112.0 ± 8.0	0.055

T2DM type 2 diabetes, *SD* standard deviation, *BMI* body mass index, *WC* waist circumference, *HbA1c* glycated hemoglobin, *P* level of statistical significance

Table 2 Use of medications and biochemical variables at baseline and at the 3- and 24-month follow-up periods

	Medical therapy group ($n = 10$)			SG + TB group ($n = 10$)		
	Baseline	3 Months	24 Months	Baseline	3 Months	24 Months
Medications						
Insulin and/or sulfonylureas (%)	100	100	100	100	0	0
Metformin (%)	100	90	90	100	20	20
Lipid-lowering drugs (%)	90	90	100	80	0	0
Antihypertensive drugs (%)	100	100	100	90	10	0
Biochemical variables						
HbA1c	8.0 ± 1.5	7.6 ± 1.2	8.3 ± 1.1	9.3 ± 2.1	6.2 ± 0.6	5.5 ± 1.1* **
Glucose (mg/dL)	145 ± 71	149 ± 77	182 ± 81	217 ± 103	102 ± 22**	95 ± 25* **
Total cholesterol (mg/dL)	172 ± 45	166 ± 55	209 ± 85	183 ± 45	140 ± 13	144 ± 21*
LDL-cholesterol (mg/dL)	95 ± 33	88 ± 37	98 ± 28	86 ± 17	75 ± 13	75 ± 17
HDL-cholesterol (mg/dL)	41 ± 10	39 ± 9	37 ± 7	33 ± 8	38 ± 11**	45 ± 15**
Triglycerides (mg/dL)	202 ± 185	233 ± 230	556 ± 977	369 ± 25	131 ± 43	121 ± 62
C-Peptide (ng/mL)	3.36 ± 1.38	–		3.96 ± 1.07	–	
Proinsulin (pM)	15.0 ± 14.4	17.6 ± 23.6	83.6 ± 99.7	12.7 ± 9.1	1.7 ± 1.1	7.8 ± 5.2**
FGF19 (pg/dL)	63.3 ± 59.6	62.1 ± 58.5	–	74.1 ± 45.8	237.3 ± 234*	–

** $P < 0.05$ among groups; * $P < 0.05$ from baseline within the same group

The baseline proinsulin fasting levels among the groups of patients with diabetes were not different but were higher than those of the healthy volunteer group (12.72 ± 9.11; 15.09 ± 14.45; 1.16 ± 1.01 pM, respectively). At 3 months, the proinsulin levels for the SG + TB group, healthy volunteer group, and SMT group were 1.76 ± 1.14, 1.52 ± 0.98, and 17.59 ± 23.62 pM, respectively ($P < 0.001$ for SMT group versus healthy).

Discussion

Mechanical restrictions and induced malabsorption (R&M) used to be the pillars of BS. Nutritional deficiencies may occur. To minimize malabsorption, SG + TB procedure was originally designed to be functionally restrictive. The concept of a functional restriction means a metabolically driven reduction in the rate of gastric emptying and intestinal transit, rather than a physical restriction. Altogether, this rationale supports the concept of a primarily metabolic surgery [7]. The SG + TB treatment establishes a new balance: gastroileal anastomosis enhances distal gut activity by rapidly bringing food to the ileum, which is similar to the observed in biliopancreatic derivation (BPD), and reduces proximal gut activity via diverting food away from this location [6].

The anatomical alterations promoted by SG + TB are associated with changes in GIP and GLP1 release and secretion, which may be related to the metabolic changes previously described [10, 11]. In our study, the SG + TB treatment was associated with a reduction in post-prandial GIP, which may be contributing to metabolic improvement since this incretin is obesogenic [12] and induces inflammation and insulin resistance in adipocytes. GLP1, in contrast to GIP, lowers glucagon secretion, decreasing glucose levels [13, 14]. In addition,

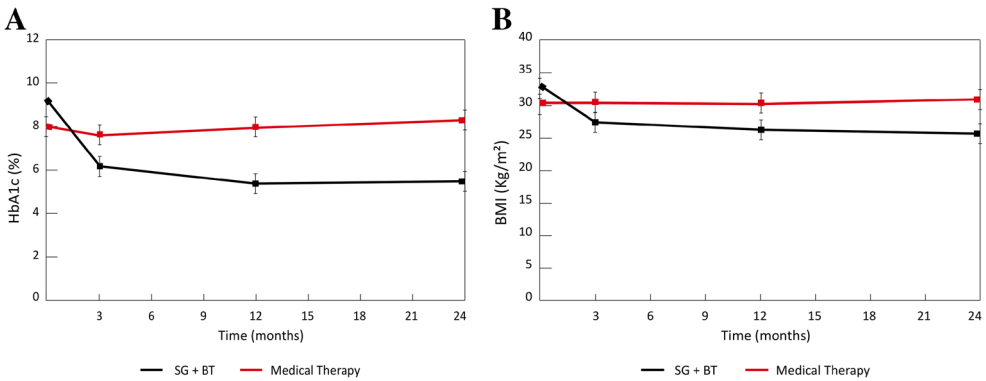

Fig. 3 Changes in glycated hemoglobin and BMI throughout the study

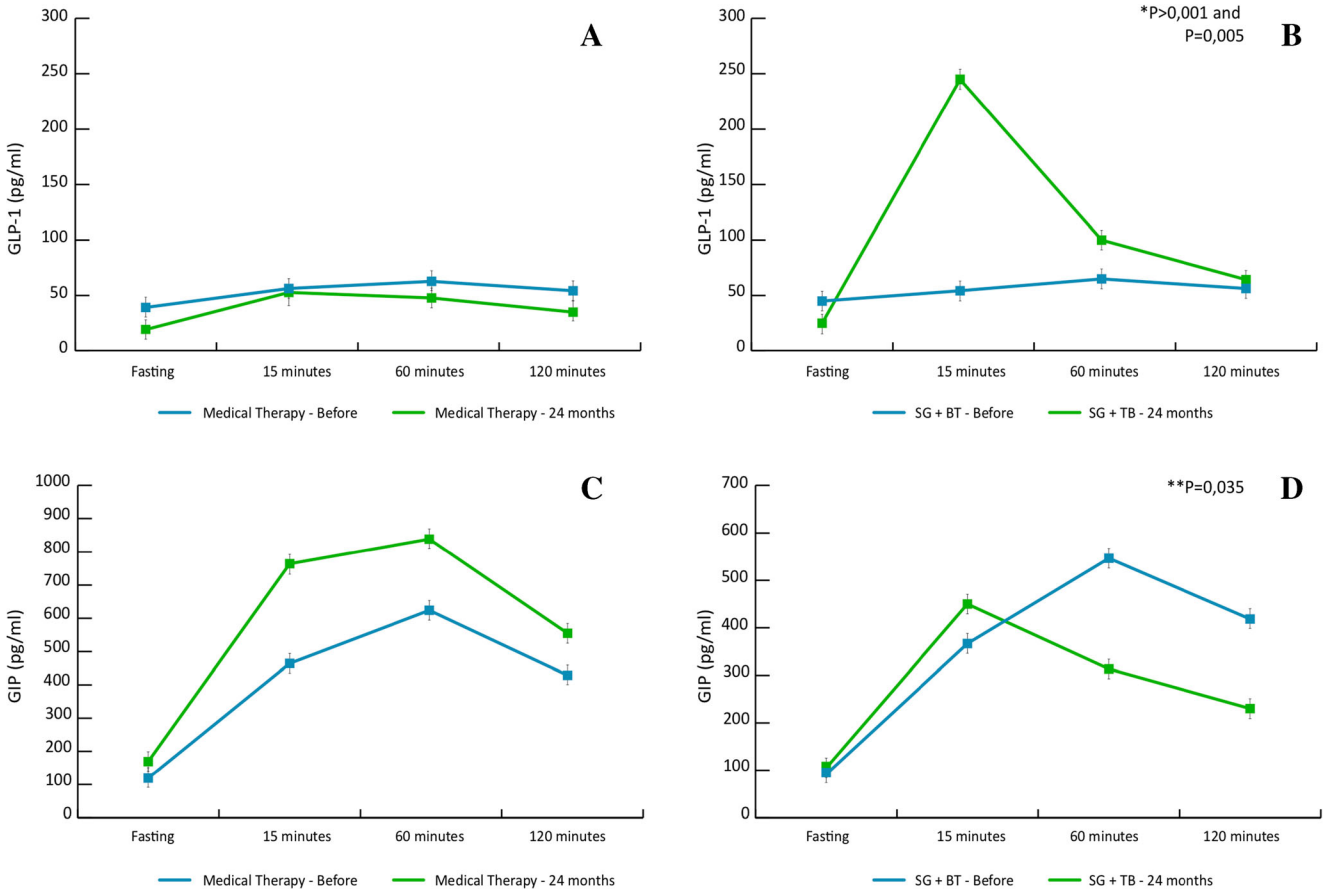

Fig. 4 GLP1 and GIP secretion behavior during mixed meal test before and 24 months after randomization. GLP1: Glucagon-like peptide 1; GIP: gastric inhibitory polypeptide. A-GLP1 levels during mixed meal test in the medical therapy group; B-GLP1 levels during mixed meal test in the SG + TB group; C-GIP levels during mixed meal test in the medical therapy group; D-GIP levels during mixed meal test in the SG + TB group. * in the SG + TB group, at 15 and 60 min, before vs. 24 months; ** in the SG + TB group, at 60 min, before vs. 24 months

GLP1 promotes satiety, blocks gastric emptying, and stimulates the clearance of sugar and lipids from the blood [15, 16] In our study, SG + TB treatment was associated with an early and potent increase in GLP1 levels without causing undernutrition, hypoproteinemia, or anemia, which was also observed in a previous study [6].

Another important finding in this study was that SG + TB treatment was associated with an increase in plasma FGF19 concentrations 3 months after surgery. FGF19 interferes in lipid metabolism several ways. First, FGF19 appears to increase fatty acid oxidation [17, 18]. Second, patients with higher FGF19 concentrations present with a reduced

Table 3 Multiple comparisons of the areas under the curve for GIP and GLP1 concentration among the groups and time points evaluated, according to the results of the comparative analysis

Variables	Time	SG + TB ($n = 10$)	Medical therapy ($n = 10$)	p Group	p Time	p Group*Time
AUC GIP				*0.003*	0.815	*0.004*
	Pre	52,804.8 ± 25,847.5[a]	61,840.3 ± 28,909.9[a]			
	24 months	37,286.7 ± 16,519.1	84,153.3 ± 27,120.1			
AUC GLP-1				*< 0.001*	*< 0.001*	*< 0.001*
	Pre	6865.1 ± 2793.2	7117.7 ± 2953.6			
	24 months	14,869.2 ± 3891.6	5396.3 ± 2514			

Data are expressed as mean ± SD

[a] Not all patients completed the curve; EEG with normal marginal distribution and identity function

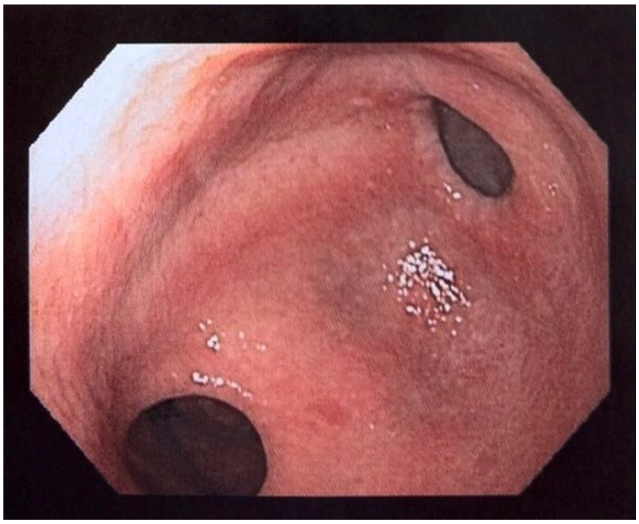

Fig. 5 Endoscopic view after sleeve gastrectomy + transit bipartition. At the right upper side, the pylorus and at the left bottom side the gastro-ileal anastomosis

production of Lp (a), a highly atherogenic particle [19]. Clinical studies have reported an inverse association between FGF19 concentration and coronary artery disease severity [4].

The impact of BS on FGF19 concentration is controversial. Gerhard et al. observed an increase in the FGF19 concentration 12 months after Roux-en-Y gastric bypass surgery; this increase was greater in patients with diabetes who presented with post-surgical remission [20]. Jorgensen did not observe an increase in FGF19 values in diabetic individuals in the short or in the long term [5]. Twelve months after Roux-en-Y gastric bypass surgery, Sachdev observed an increase in this protein during both fasting and post-prandial periods in uncompensated diabetic individuals, which was similar to the assessments in our study that used a shorter period of observation [21]. The reason for the increased FGF19 concentration, which is usually attributed to changes in the bile route (that do not properly occur following SG + TB treatment), requires further clarification [20, 21].

SG alone accelerates gastric emptying at the beginning of a meal. A band around the pouch or a narrower residual gastric pouch is mean to add mechanical restriction to a SG. TB does the opposite as it drains the gastric pouch by adding a gastro-ileal anastomosis in the antrum (Fig. 5). In spite of this drainage, the early, potent secretion of distal gut hormones like GLP1 may reduce gastric emptying, promoting a physiological restriction and satiety, mimicking a natural restriction [7].

Adequate glycemic control was achieved after 2 years in the STAMPEDE trial [22] in 6/18 (33.3%) patients after gastric bypass surgery and in 2/19 (10.5%) patients after SG surgery alone. In the present study, after 24 months, it was achieved in 9/10 (90%) patients who underwent SG + TB treatment. Only surgeries that promote the early delivery of nutrients to the ileum (like BPD) show potent results such as those reported in this study. BPDs leads to T2D remission in approximately 90% of patients [23, 24] and substantially reduces blood lipid levels and arterial hypertension, but may induce severe malnutrition [25, 26] SG + TB treatment has shown long-term results that are comparable (86% T2D remission) to the published BPD results [6].

One of the main mechanisms underlying these results is certainly the reduction in insulin resistance, as reflected by the lower proinsulin concentrations after surgery, also described previously [27] In addition, improvement in lipid profile was observed in our study, as we observed an increase in HDL-cholesterol levels after intervention. Similar results have been seen in studies with different surgical techniques [27–29].

Finally, in the present study, among the patients who presented with hypertension before surgery, none required treatment 24 months thereafter. This outcome is similar to previous studies and may be associated with weight loss and decreased insulin resistance [30].

The main limitation of this study was the small number of patients included in the sample. The small number is related to the strict selection of patients in this conceptual clinical study. As a consequence, the results may not apply to other groups of patients. On the other hand, these interesting and promising findings should be promptly tested in larger samples of patients.

In conclusion, SG + TB treatment plus standard medical therapy was superior to standard medical therapy alone and was associated with remission in the metabolic and cardiovascular risk variables. These findings support the concept of a primarily metabolic surgery.

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Compliance with Ethical Standards

The study was approved by the Institutional Ethics Committee (CAPPesq 0355/11) and registered with ClinicalTrials.gov (NCT01581099).

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

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