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Laparoscopic treatment of type 2 diabetes mellitus for patients with a body mass index less than 35

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Abstract
Background Type 2 diabetes mellitus (T2DM) is a common disease with numerous complications. Bariatric surgery is an efficient procedure for controlling T2DM in morbidly obese patients. In T2DM, the incretin effect is either greatly impaired or absent. This study aimed to evaluate the preliminary results from interposing a segment of ileum into the proximal jejunum associated with a sleeve or diverted sleeve gastrectomy to control T2DM in patients with a body mass index (BMI) less than 35 kg/m^2.
Methods For this study, 39 patients (16 women and 23 men) underwent two laparoscopic procedures comprising different combinations of ileal interposition into the proximal jejunum via a sleeve or diverted sleeve gastrectomy. The mean age of these patients was 50.3 years (range, 36–66 years). The mean BMI was 30.1 kg/m^2 (range, 23.4–34.9 kg/m^2). All the patients had a diagnosis of T2DM that had persisted for at least 3 years and evidence of stable treatment with oral hypoglycemic agents or insulin for at least 12 months. The mean duration of T2DM was 9.3 years (range, 3–22 years).
Results The mean operative time was 185 min, and the median hospital stay was 4.3 days. Four major complications occurred in the short term (30-days), and the mortality rate was 2.6%. The mean postoperative follow-up period was 7 months (range, 4–16 months), and the mean percentage of weight loss was 22%. The mean postoperative BMI was 24.9 kg/m^2 (range, 18.9–31.7 kg/m^2). An adequate glycemic control was achieved for 86.9% of the patients, and 13.1% had important improvement. The patients whose glycemia was not normalized were using a single oral hypoglycemic agent. No patient needed insulin therapy postoperatively. All the patients except experienced normalization of their cholesterol levels. Targeted triglycerides levels were achieved by 71% of the patients, and hypertension was controlled for 95.8%.
Conclusions The laparoscopic ileal interposition via either a sleeve gastrectomy or diverted sleeve gastrectomy seems to be a promising procedure for the control of T2DM and the metabolic syndrome. A longer follow-up period is needed.

Keywords Arterial hypertension · Dyslipidemia · Ileal interposition · Neuroendocrine brake · Sleeve gastrectomy · Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) and obesity are diseases of epidemic proportions. The association between them is well established, as the majority of patients with T2DM are obese.

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It is postulated that the pathologic sequence of events leading to T2DM is characterized by failure of beta cells to secrete adequate amounts of insulin to compensate for insulin resistance in peripheral tissues and by increased endogenous glucose production [1]. The deterioration of secretion and insulin action is present for many years before the diagnosis of diabetes [2]. However, some patients with T2DM are not obese [3], and for some nonobese T2DM individuals, insulin resistance is not essential to the development of diabetes [4]. Moreover, diabetes still can persist even when complete restoration of normal insulin sensitivity after weight reduction has been achieved, implying an essential role for impaired insulin secretion [5].

In patients with T2DM, the incretin effect is either greatly impaired or absent, and this could presumably contribute to these patients' inability to adjust their insulin secretion to their needs. It is recognized that early-phase plasma insulin response to glucose (0–20 min) is impaired but significantly enhanced by both glucagon-like peptide 1 (GLP-1) and gastric-inhibitory peptide (GIP), as compared with glucose alone. A defective amplification of the so-called late-phase plasma insulin response to glucose (20–120 min) by GIP also is observed, whereas GLP-1 enhances the late-phase plasma insulin response markedly [6]. Loss of early-phase insulin secretion has severe consequences for glucose homeostasis and includes inability to suppress glucagon secretion, free fatty acid secretion, and hepatic glucose output adequately, determining a continued delivery of glucose in the circulation [7].

Findings show that the secretion of GIP generally is normal, whereas the secretion of GLP-1 is reduced. It probably is an even more important observation that the effect of GLP-1 is preserved and that the effect of GIP is severely impaired [8]. After continuous infusion of GLP-1, findings demonstrated a lowered effect on fasting and average plasma glucose concentrations, a decrease in glycosylated hemoglobin (HbA1c) levels, and an improvement in insulin sensitivity [9].

Weight loss has benefits for patients with obesity and T2DM. However, long-term realistic weight loss by nonsurgical methods has a variable impact on glycemic control, and only a proportion of T2DM patients have a worthwhile response [10]. Despite adequate drug therapy with antidiabetic medications, glucose and HbA1c measurements steadily increase with time, reflecting the ongoing deterioration of the beta cell [11].

Bariatric surgery, especially gastric bypass [12] and malabsorptive surgery [13], is effective in controlling T2DM, improving the glucose control in 80% to 100% of patients. Nevertheless, as emphasized by Pinkney and Kerrigan [14], the investigations in this area are not indicated specifically for testing the efficiency of bariatric surgery in the treatment of diabetes and diabetic patients. These patients usually do not resemble the typical clinical population of T2DM with macro- and microvascular problems.

The pathophysiologic mechanisms whereby bariatric surgery reaches the described results are not yet well understood. It is suggested that caloric restriction, weight loss, and hormonal changes in the enteroinsulinic axis [15] are possible features of such mechanisms. Gumbs et al. [16] suggested that the improvement of glucose metabolism and insulin resistance after bariatric operations is due to the decreased stimulus of the enteroinsulin axis by the caloric restriction in the short term, and to weight loss and alterations in the secretion of cinins from the adipose tissues in the long term. Pories [17] proposed that the excessive stimulation of intestinal incretins in vulnerable individuals is the cause of T2DM, and that the cure through surgery is related to the loss of this stimulus. Rubino and Gagner [18] maintained that the presence of an intestinal feature derived from excessive stimulus of the upper digestive tract causes a deficient incretin action. Wickremesekera et al. [19] pointed out that the improvement or resolution of T2DM by gastric bypass operations in the short term (e.g., 6 days), well before the effective weight loss, is consistent with a hormonal mechanism. Clement et al. [20] suggested that GIP levels decrease after gastric bypass, and that GIP participates in the control of the T2DM. Mason [21] emphasized the role of GLP-1 in the prevention and resolution of T2DM after gastric bypass. Naslund et al. [22] reported high levels of GLP-1 in patients 20 years after jejunoileal bypass, suggesting that T2DM may be adequately controlled by the performance of the GLP-1 in the long term. Mason [23] finally proposed that the ileal interposition may be the ideal operation for the treatment of T2DM. Patriti et al. [24] performed an ileal transposition in lean diabetic Goto-Kakizaki rats, concluding that the procedure effectively induced an improvement in glucose tolerance without affecting weight or food intake. De Paula et al. [25] performed a technique termed "neuroendocrine break," characterized by a sleeve gastrectomy associated with an ileal interposition, and reported complete resolution of T2DM in morbidly obese patients.

The concepts in relation to the laparoscopic neuroendocrine brake involve providing an early exposure of ingested nutrients to the transposed ileum, with intention to determine an early rise in GLP-1 with its consequent impact on the defective early-phase insulin secretion. They also involve intention to induce an adjustable and long-lasting weight loss, to restrict the caloric intake, and to diminish or abolish excessive stimulation of the duodenum.

This study aimed to evaluate the results from laparoscopically transposing a segment of ileum to the proximal

jejunum associated with either a sleeve gastrectomy or diverted sleeve gastrectomy to control T2DM in patients with a body mass index (BMI) less than 35 kg/m^2.

Materials and methods

For this study, 39 T2DM patients were submitted to laparoscopic ileal interposition associated with either a sleeve gastrectomy or ileal interposition related to a diverted sleeve gastrectomy until March 2006. The patients comprised 23 (59%) men and 16 (41%) women with a mean age of 50.3 years (range, 36–66 years). The preoperative mean BMI ranged from 23.4 to 34.9 kg/m^2 (mean, 30.1 ± 3.5 kg/m^2). In this study, 12.9% of the patients had a BMI less than 25 kg/m^2, 33.3% had a BMI of 25.1 to 29.9 kg/m^2, and 53.8% had a BMI of 30 to 34.9 kg/m^2.

All the patients were taking diabetic medication as prescribed by their endocrinologist. Oral hypoglycemic agents were used by 58.9% of the patients (mean number, 1.3). Insulin therapy (regular and neutral protamine Hagedorn) was required by 7.7% of the patients, and 33.4% were receiving both insulin and oral agents. The preoperative demographic data are summarized in Table 1. The main associated diseases and complications of T2DM are listed in Fig. 1. The most common comorbidity was dyslipidemia.

The inclusion criteria specified type 2 diabetic patients whose disease had been diagnosed for at least 3 years; documentation of HbA1c exceeding 7.5% for at least 3 months; stable weight, defined as no significant change (>3%) over the 3 months before enrollment; and evidence of stable treatment with oral hypoglycemic therapy or insulin for at least 12 months. All the patients had a BMI less than 35 kg/m^2. There were no special criteria for the indication of the two different configurations of the procedures, although we assumed that the diverted version would be more effective in controlling T2DM.

The exclusion criteria specified elderly patients (>66 years), previous major upper abdominal surgery, pregnancy, malignant or debilitating diseases, severe pulmonary or cardiac diseases, severe renal disease (glomerular filtration rate < 30 ml/min), use of appetite suppressant medication, eating disorder such as bulimia or binge eating, and obesity due to any other endocrine disorder.

Preoperative assessment included general clinical history that of T2DM and obesity, physical examination, blood tests, urinalysis, serum chemistries, abdominal sonogram, upper digestive endoscopy, chest x-ray, pulmonary function test, fasting lipid profile, test for microalbuminuria, serum creatinine assessment, estimation of the glomerular filtration rate, Doppler study of the carotid arteries, retinopathy screening, and detailed cardiac evaluation. Other tests specific to certain concomitant diseases and specialty consultations were required as well. Biochemical markers of T2DM were obtained including fasting plasma glucose, postprandial plasma glucose, HbA1c, fasting plasma insulin, and the homeostasis model assessment of insulin resistance (Homa-R) and C-peptide.

The diagnosis of T2DM, goals for glycemia and lipids, and control of blood pressure were based on the criteria established by the American Diabetes Association [26]. Type 2 diabetes mellitus was considered resolved for patients who had a normal fasting plasma glucose (<100 mg/dl), normal HbA1c (<6%), and no need for diabetic medications. Glycemic control was achieved if an HbA1c of less than 7% without diabetic medication was obtained. Patients were considered improved if they showed more than a 25-mg/dl decrease in fasting plasma glucose and a significant reduction in A1C (> 1%). The primary goal in relation to the lipid profile was a low-density lipoprotein (LDL) level lower than 100 mg/dl, a triglyceride level lower than 150 mg/dl, and a high-density lipoprotein (HDL) level exceeding 40 mg/dl. Blood pressure was targeted at less than 130/80 mmHg.

Table 1 Preoperative demographic data for 39 patients[a]

	Surgeries			*p* Value
	Total	II-SG	II-DSG	
Patients	39	23	16	
Age (years)	50.3 ± 6.7 (36–66)	51.1 ± 7.9 (36–66)	49.2 ± 4.3 (41–55)	0.342
Sex: Male: *n* (%)	23 (59)	16 (69.5)	7 (43.7)	0.185[b]
Female: *n* (%)	16 (41)	7 (30.5)	9 (56.3)	
BMI: kg/m^2 (range)	30.1 ± 3.5 (23.4–34.9)	30.9 ± 3.4 (23.4–34.9)	28.9 ± 3.4 (24.2–34.8)	0.085
Mean no. of years of T2DM diagnosis: *n* (%)	9.3 ± 4.7 (3–22)	7.8 ± 4.2 (3–19)	11.4 ± 4.6 (6–22)	0.016
Oral hypoglycemic agents: *n* (%)	22 (56.4)	16 (69.6)	6 (37.5)	
Insulin: *n* (%)	3 (7.7)	1 (4.3)	2 (12.5)	0.130[b]
Both: *n* (%)	14 (35.9)	6 (26.1)	8 (50.0)	

II-SG, sleeve gastrectomy; II-DSG, diverted sleeve gastrectomy

[a] Data are mean ± standard deviation or percentage

[b] Fisher's exact test

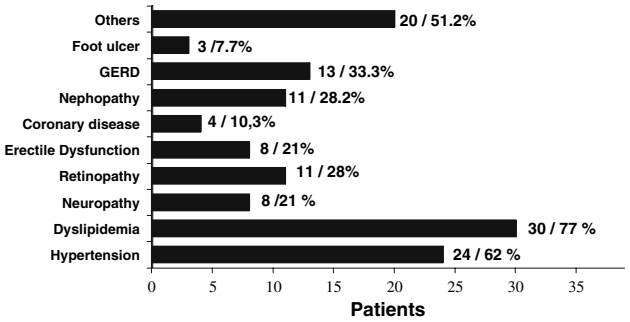

Fig. 1 Associated diseases and complications

A careful evaluation was carried out before the operation because frequent serious concomitant health problems needed to be stabilized on an individual basis. The preoperative preparation for surgery included clear liquids for 48 h before the operation in association with regular insulin according to capillary glucose. Preoperative bowel cleansing, perioperative antibiotics, and low-molecular-weight heparin were administered.

Technique

Two different techniques were performed: ileal interposition associated with a sleeve gastrectomy (II-SG) and ileal interposition associated with a diverted sleeve gastrectomy (II-DSG). A standard five- to six-port laparoscopic technique was used after establishment of pneumoperitoneum.

The first technique, II-SG, started with division of the jejunum 50 cm from the ligament of Treitz using a linear stapler. An ileal segment of 100 cm was created 50 cm proximal to the ileocecal valve, interposing it peristaltically into the proximal jejunum. All three anastomoses were performed functionally side by side using 45-mm linear staplers, with care taken to close mesenteric defects with interrupted 3-0 polypropylene sutures. For standardization purposes, intestinal measurements were performed with traction along the antimesenteric border using a 10-cm marked atraumatic grasper. The sleeve gastrectomy was performed after devascularization of the greater curvature, beginning in the distal portion of the antrum (5 cm proximal to the pylorus) using the ultrasonic scalpel. A 30-Fr Fouchet orogastric calibration tube was placed by the anesthesiologist along the lesser curvature toward the pylorus. The gastric resection was performed starting at the antrum and continuing up to the angle of His using a linear 45- or 60-mm stapler. A 3-0 polypropylene running invaginating suture covered the staple line (Fig. 2).

The second technique, II-DSG, was an ileal interposition associated with a diverted sleeve gastrectomy. The sleeve gastrectomy was performed as mentioned earlier. After that, the devascularization along the greater curvature of the stomach continued to the duodenum, 3 to 4 cm beyond

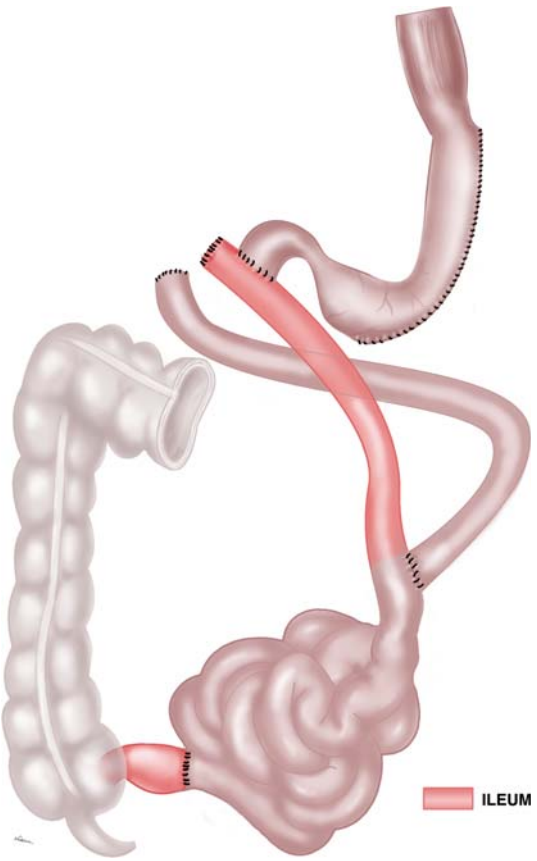

Fig. 2 Ileal interposition with diverted sleeve gastrectomy

the pylorus. The duodenum was transected using a 60-mm linear stapler. A 3-0 polypropylene running invaginating suture covered the duodenal staple line. The gastric pouch and proximal duodenual then were transposed to the lower abdomen through the mesocolon. An ileal segment of 100 cm was created 50 cm proximal to the ileocecal valve, interposing and anastomosing it peristaltically to the proximal duodenum. A point in the jejunum 50 cm from the ligament of Treitz was measured and anastomosed to the distal part of the interposed ileum. All anastomoses were performed functionally using 45-mm linear staplers, with care taken to close mesenteric defects using interrupted 3-0 polypropylene sutures (Fig. 3). The trocar openings were closed.

Postoperatively, chest x-rays and iodine contrast radiography of the upper digestive tract were performed for all patients before resumption of oral feeding and discharge from the hospital. Outcomes measures were collected prospectively. The main parameters included fasting and postprandial glucose, HbA1c, diabetes medication usage (agents, doses, frequency), weight loss (expressed in BMI and percentage of weight loss), resolution or improvement of associated diseases and complications, the reoperation rate, and the morbidity–mortality of the procedure. Patient and laboratory evaluation was scheduled for every 3

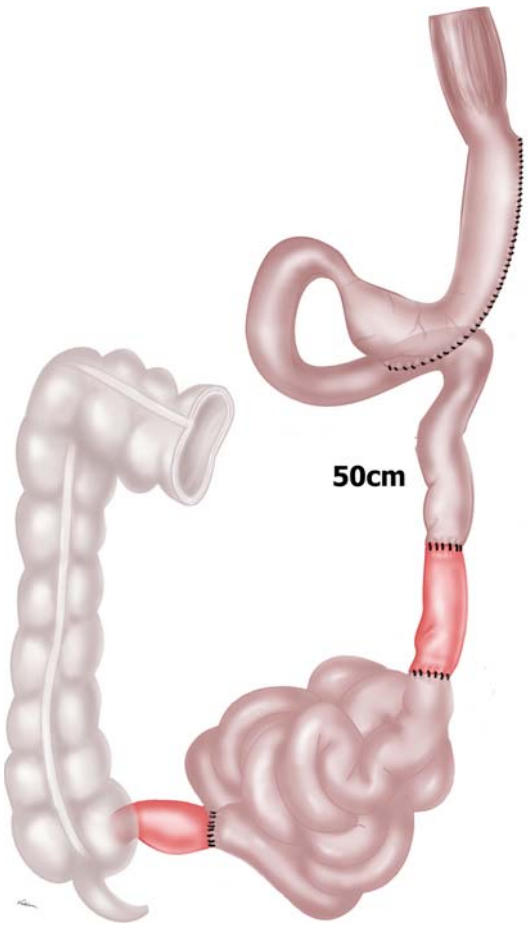

Fig. 3 Ileal interposition with sleeve gastrectomy

months until 18 months after the operation. Tests for microalbuminuria and serum creatinine as well as estimation of the glomerular filtration rate, retinopathy screening, and Doppler of the carotid arteries were performed at 6-month intervals.

The Ethics Committee of the Hospital approved the study, and all the subjects gave written informed consent.

Statistical analysis

Statistical analysis was performed using Fisher's exact test and Student's *t*-test according to the data. A significance level of 0.05 ($\alpha = 5\%$) was adopted, and levels below this were considered significant.

Results

Laparoscopic II-SG was performed for 23 patients and II-DSG for 16 patients. These laparoscopic operations were completed successfully for all 39 patients. Associated procedures included seven cholecystectomies with cholangiography and six hiatal hernia repairs. Severe adhesions present in nine patients were treated with careful lysis. One patient had a Meckel's diverticulum approximately 90 cm from the cecum, which was treated with resection of the segment of ileum and enteroanastomosis.

The mean operative time was 170 min (range, 140–220 min) for the II-SG and 190 min (range, 170–270 min) for the II-DSG. Overall, the mean operative time was 185 min. The median hospital stay was 4.3 days (range, 2.5–58 days).

The intraoperative complications (7.7%) included resection of an ischemic transposed ileum [1], cardiac arrhythmia [1], and hypertensive crisis [1]. Major postoperative complications were experienced by four patients (10.3%) including gastric leak ($n = 2$) and acute renal failure ($n = 2$). Both gastric leaks were late events on postoperative days 12 and 13. The patients were already on liquid diets and at home. Both had normal iodine contrast studies on postoperative day 3. They underwent reoperation (5.1%) and had a prolonged hospital stay. Both acute renal failures also were late problems on postoperative days 10 and 11. One of the patients with acute renal failure died (2.6%). The other patient needed four sessions of hemodyalisis. Minor postoperative complications developed in six additional patients (15.4%) and included cardiac arrhythmia ($n = 2$), urinary tract infection, trocar-site infection, and prolonged ileus ($n = 2$).

During the first postoperative month, the most frequent complaints were nausea, anorexia, early satiety, heartburn, and discomfort in the lower abdomen. Most patients were able to resume work 8 days after surgery. A routine upper digestive endoscopy performed 30 days after surgery demonstrated erosive esophagitis in 11.5% of the patients after II-SG and in 6.3% of the patients after II-DSG, despite 40 mg/day of proton pump inhibitors (PPIs).

Eight clinical late complications (21.1%) had occurred 30 days after surgery including gout attack ($n = 2$), prolonged emesis ($n = 3$), urinary tract infection ($n = 2$), and fungal esophagitis ($n = 1$). After the first month, the most common complaint was anorexia and food intolerance. Some physical limitation also was frequent. Heartburn was reported by three patients (7.9%). There were three late hospitalizations, one due to persistent nausea and vomiting, which resolved spontaneously, and two urinary tract infections treated with appropriate antibiotics. In the II-DSG group, iron deficiency was demonstrated in 12.5% of the patients. Despite routine iron supplementation until weight stability in the II-SG group, this deficiency was found in 4.5% of the patients. Vitamin supplementation was not routine for this group of patients.

A total of 30 patients were followed for a mean of 7 months (range, 4–16 months). Both operations had an important impact on these T2DM patients. Mean HbA1c

decreased from 8.8% ± 1.7% to 6.3% ± 0.9% ($p < 0.001$) (Fig. 4), fasting plasma glucose from 210.7 ± 66.6 to 116.7 ± 33.1 mg/dl ($p < 0.001$) (Fig. 5), postprandial plasma glucose from 259.3 ± 92.6 to 141.7 ± 56.6 mg/dl ($p < 0.001$), fasting plasma insulin from 15.5 ± 17.4 to 8.9 ± 8.8 mU/ml ($p = 0.003$), homeostasis model assessment of insulin resistance from 5.4 ± 4.4 to 2.6 ± 2.9 ($p < 0.001$), and C-peptide from 3.1 ± 2.2 to 2.9 ± 1.6 ng/ml ($p = 0.525$). Table 2 shows these results in relation to both types of operations.

An important reduction in antidiabetic medications was observed. Nearly 87% of the patients permanently discontinued preoperative oral hypoglycemic agents, insulin, or both. Five patients (13.1%) still were using a single oral hypoglycemic agent. A rapid normalization of fasting plasma glucose (first 2 weeks) was achieved by 29% of the patients: 22.7% after II-SG and 37.5% after II-DSG. No event of severe hypoglycemia was documented.

The mean percentage of weight loss was 22% ± 6% of the initial weight (range, 10–33.3%). The mean BMI decreased from 30.1 ± 3.5 kg/m^2 preoperatively to 24.9 ± 3.7 kg/m^2 (range, 18.9–31.7 kg/m^2), as demonstrated in Fig. 6. All the patients were considered to be in good shape. Two patients (5.2%) had a BMI less than 20 kg/m^2. The serum albumin level was normal in all the patients.

There was a significant change in the lipid profile with both operations. Total cholesterol decreased from a mean of 215.1 ± 49.9 mg/dl to 167.5 ± 27.6 mg/dl ($p < 0.001$) (Fig. 7), HDL from a mean of 40.1 ± 10.1 to 46.6 ± 9.5 mg/dl ($p = 0.015$), LDL from a mean of 129.5 ± 51.7 to 92.8 ± 21.5 mg/dl ($p = 0.015$), and triglycerides from a mean of 250.5 ± 168.4 to 131.3 ± 80.2 mg/dl ($p<0.001$) (Fig. 8). Table 3 shows these results for both the II-SG and II-DSG operations.

Overall, the targeted HbA1c level lower than 7% was achieved by 86.9% of the patients without antidiabetic medication. Normalization (HbA1c < 6%) was reached by 47.4% of the patients. Glycemic control, HbA1c between

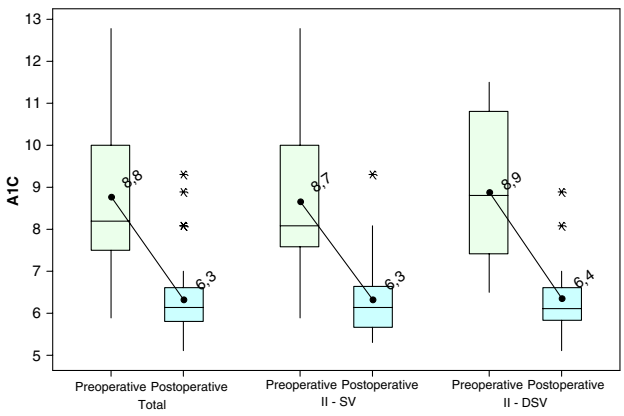

Fig. 4 Pre- and postoperative HbA1c according to type of surgery

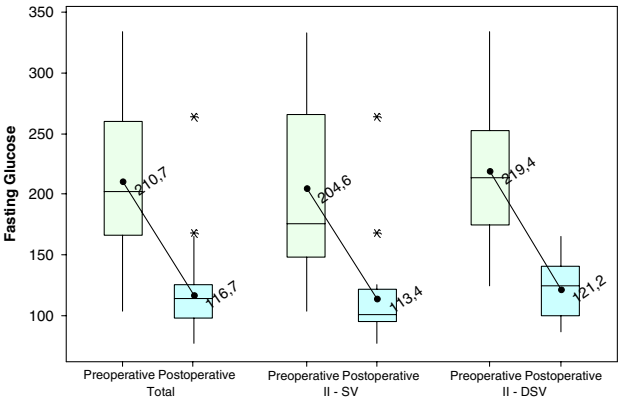

Fig. 5 Pre- and postoperative fasting glucose according to type of surgery

6% and 7% by 39.5% of the patients, and improvement was attained by 13.1% of the patients. Table 4 shows that II-SG and II-DSG both were effective ($p < 0.001$), although patients submitted to II-DSG had a longer period of disease (mean, 11.4 ± 4.6 years vs 7.8 ± 4.2 years; $p = 0.016$). Also, a higher percentage of II-DSG patients were using insulin (62.5% vs 30.4%). Resolution (HbA1c < 6%) was more frequent among patients with fewer than 5 years of T2DM and those receiving oral agents preoperatively. Those with more than 10 years of disease who were taking insulin or insulin plus oral agents were less likely to achieve resolution or glycemic control (Table 5). Resolution and glucose control were more frequent among patients with a BMI of 30 to 35 kg/m^2. Weight loss was not a reliable predictor of resolution or glucose control.

Resolution or improvement in associated diseases or complications was remarkable. The targeted LDL level of less than 100 mg/dl was achieved by 66% of the patients, and 31.4% had an LDL level between 100 and 130 mg/dl. Only one patient (2.6%) still had an LDL level exceeding 130 mg/dl and a total cholesterol level higher than 200 mg/dl. This patient was the one who had to have the transposed ileum segment resected due to ischemia. Hypertriglyceridemia was present in 79.5% of the patients preoperatively. Postoperatively, triglyceride levels lower than 150 mg/dl were achieved by 71% of these patients, with the diverted version more effective. An HDL level exceeding 40 mg/dl was observed for 81.2% of the patients.

Hypertension was present in 61.5% of the patients preoperatively according to a casual blood pressure measurement. All the patients were using antihypertensive medications (mean, 2.2). The blood pressure normalized (<130/80 mmHg) without medication in 83.3% of the patients (casual blood pressure measurement). Most of the patients (95.8%) were not receiving medication.

Preoperative nephropathy was present in 28.2% of the patients. Microalbuminuria was diagnosed for 20.5% of the

Table 2 Pre- and postoperative analysis of different diabetes markers according to both types of surgeries[a]

		Total		II-SG		II-DSG	
			p Value		*p* Value		*p* Value
HbA1c	Preop	8.8 ± 1.7	<0.001	8.7 ± 1.7	<0.001	8.9 ± 1.7	<0.001
	Postop	6.3 ± 0.9		6.3 ± 0.9		6.4 ± 1.0	
Fasting glucose	Preop	210.7 ± 66.6	<0.001	204.6 ± 68.3	<0.001	219.4 ± 65.3	<0.001
	Postop	116.7 ± 33.1		113.5 ± 39.0		121.2 ± 23.4	
Postprandial glucose	Preop	259.3 ± 92.6	<0.001	228.2 ± 70.7	<0.001	303.9 ± 103.8	<0.001
	Postop	141.7 ± 56.6		136.4 ± 60.5		149.1 ± 51.8	
Insulin	Preop	15.5 ± 17.4	0.003	13.8 ± 11.0	<0.001	18.1 ± 24.3	0.166
	Postop	8.9 ± 8.8		8.3 ± 6.9		9.7 ± 11.2	
Homa-R	Preop	5.4 ± 4.4	<0.001	5.3 ± 4.6	0.006	5.6 ± 4.3	0.001
	Postop	2.6 ± 2.9		2.5 ± 2.1		2.8 ± 3.7	
C-peptide	Preop	3.1 ± 2.2	0.525	3.6 ± 2.6	0.598	2.5 ± 1.4	0.699
	Postop	2.9 ± 1.6		3.2 ± 1.9		2.4 ± 1.1	

II-SG, sleeve gastrectomy; II-DSG, diverted sleeve gastrectomy; HbA1c, glycosylated hemoglobin; preop, preoperative; postop, postoperative; Homa-R, homeostasis model assessment of insulin resistance

[a] Data are mean ± standard deviation

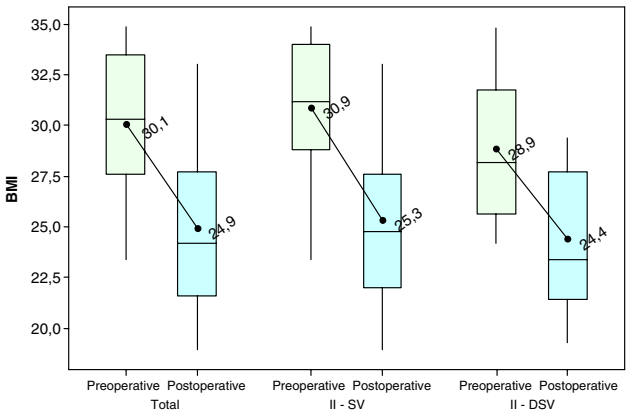

Fig. 6 Pre- and postoperative body mass index (BMI) according to type of surgery

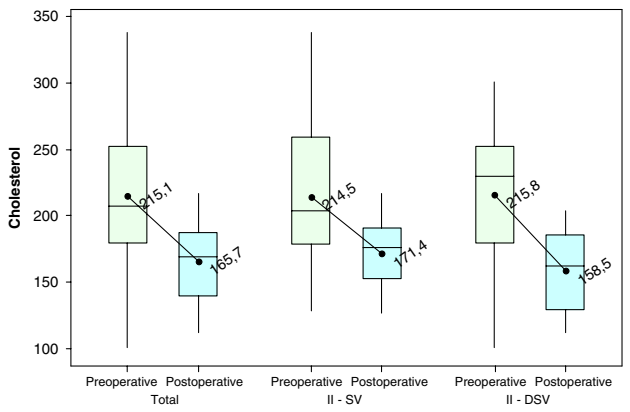

Fig. 7 Pre- and postoperative total cholesterol according to type of surgery

patients, and 7.7% had macroalbuminuria. A glomerular filtration rate of 60 to 89 ml/min was exhibited by 23.1% of the patients and a rate of 30 to 59 ml/min by 7.7%. Postoperatively, there was a substantial improvement in the renal function. Microalbuminuria still was present in four patients (10.5%) and macroalbuminuria in one patient (2.6%). All the patients with a glomerular filtration rate of 60 to 90 ml/min normalized their rate (>90 ml/min). Those with a glomerular filtration rate of 30 to 59 ml/min did not change.

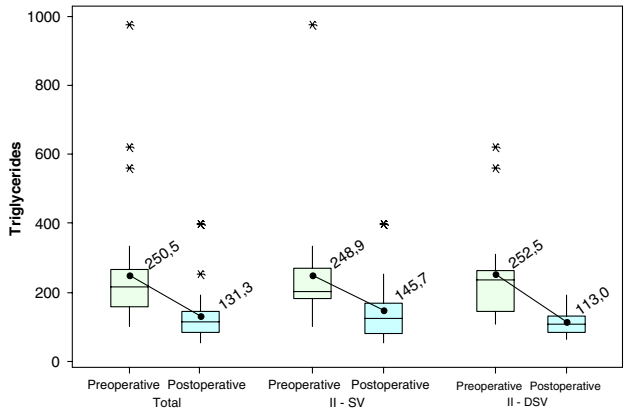

Fig. 8 Pre- and postoperative triglycerides according to type of surgery

Retinopathy was present in 11 patients (28%), glaucoma in 13.2%, and cataracts in 7.9% preoperatively. These eye lesions were more frequent in the group that underwent surgery via II-DSG. Objective improvement in retinopathy was demonstrated in four patients (36.4%). Symptomatic improvement was observed in all 11 patients.

Distal polyneuropathy was present in 20.5% of the patients preoperatively, and clinical improvement occurred in 62.5%. Electrophysiologic testing was not routinely performed. Autonomic neuropathy was suspected in 15.4% of the patients, as characterized by resting tachycardia, gastroparesis, and constipation.

Table 3 Pre- and postoperative analysis of lipid profile according to both types of surgeries[a]

		Total		II-SG		II-DSG	
			p Value		*p* Value		*p* Value
Total cholesterol	Preop	215.1 ± 49.9	<0.001	214.5 ± 50.6	0.003	215.8 ± 50.9	<0.001
	Postop	165.7 ± 27.6		171.4 ± 24.8		158.5 ± 30.2	
HDL	Preop	40.1 ± 10.1	0.015	37.1 ± 8.5	0.046	45.6 ± 11.3	0.240
	Postop	46.6 ± 9.5		44.9 ± 10.8		48.3 ± 7.9	
LDL	Preop	129.5 ± 51.7	0.015	142.8 ± 48.1	0.235	116.3 ± 54.9	0.042
	Postop	92.8 ± 21.5		97.9 ± 17.7		87.3 ± 24.3	
Triglycerides	Preop	250.5 ± 168.4	<0.001	248.9 ± 186.2	0.006	252.5 ± 149.1	0.001
	Postop	131.3 ± 80.2		145.7 ± 100.8		113.0 ± 38.4	

II-SG, sleeve gastrectomy; II-DSG, diverted sleeve gastrectomy; HDL, high-density lipoprotein; LDL, low-density lipoprotein

[a] Data are mean ± standard deviation

Table 4. Resolution of type 2 diabetes mellitus according to procedures: glycosylated hemoglobin (HbA1c)

	Resolution	Glycemic control	Improvement	*P* Value
Total: *n* (%)	18 (47.4)	15 (39.5)	5 (13.1)	<0.001[a]
Mean	5.7 ± 0.28	6.5 ± 0.26	8.3 ± 0.88	<0.001
II-SV: *n* (%)	10 (45.5)	10 (45.5)	2 (9.0)	<0.001[a]
Mean	5.6 ± 0.22	6.5 ± 0.27	8.7 ± 0.84	<0.001
II-DSV: *n* (%)	8 (50.0)	5 (31.3)	3 (18.8)	0.001[a]
Mean	5.7 ± 0.34	6.4 ± 0.19	8.0 ± 0.95	<0.001

[a] Statistically significant

Residual food was diagnosed in 7.7% of preoperative upper digestive endoscopies despite adequate fasting. Two of these patients experienced prolonged ileus during the postoperative period. Erectile dysfunction was reported by 21% of the patients in the preoperative period, whereas 62.5% of these patients reported some improvement postoperatively. Cholelithiasis developed in two patients during the follow-up period.

Discussion

This is the first report of a laparoscopic surgical treatment for patients with T2DM and a BMI less than 35 kg/m^2. All the patients had at least 3 years (mean, 9.3 years; range, 3–22 years) of documented T2DM stable treatment, with oral hypoglycemic agents, insulin, or both for at least 12 months, and multiple associated diseases and complications. Insulin was used by 41% of the patients. Dyslipidemia (77%) and hypertension (62%) were the most frequent associated diseases. Complications of T2DM were very common, with nephropathy and retinopathy diagnosed in 28% of the patients, neuropathy in 21%, coronary disease in 10%, and foot ulcer in 7.7%. Therefore, all the patients were categorized as a typical T2DM clinical population with micro- and macrovascular disease.

The procedures were designed specifically for the treatment of diabetes. Impaired insulin secretion and insulin resistance usually characterize classic T2DM. There is also a relative insensitivity of the beta cell to glucose and a greatly impaired or absent incretin effect. The lack of amplification by the incretin hormones determines a further aggravation of insulin deficiency [27]. In nonobese subjects with impaired glucose tolerance and T2DM, defective early insulin secretion after an oral glucose is a key factor. This defective beta cell function is associated with, and may be caused by, a reduced early GLP-1 response [28]. Postprandial glucose homeostasis is determined not only by stimulation of insulin secretion and suppression of hepatic glucose production, but also by the velocity of gastric emptying. Glucagon-like peptide 1 has an inhibitory action on gastric emptying. The deceleration of gastric emptying depends strictly on the respective GLP-1 blood level [29]. Therefore, the first characteristic of these operations is early exposure of ingested nutrients to the transposed ileum, allowing an early rise of GLP-1 and consequently correcting the early phase of defective insulin secretion. Caloric restriction, independent of adipose tissue mass, and weight management are vital for the individual with diabetes in terms of preventing or delaying further morbidities [30]. Persistent high caloric intake may be another factor detrimental to diabetes remission because insulin sensitivity is impaired in the presence of high caloric intake [31].

The second characteristic of these operations is caloric restriction and an adjusted weight loss, which was successfully achieved by a sleeve gastrectomy. The patients experienced a 22% ± 6% (range, 10–33.3%) mean loss of their initial weight. It was demonstrated as an adjusted weight loss, with 5.2% having a BMI below 20 kg/m^2. Resolution and glucose control were more frequent among patients with a BMI of 30 to 35 kg/m^2. Weight loss was not a reliable predictor of resolution or glucose control. As suggested by the original work of Pories et al. [32], the normalization of blood glucose levels occurred soon in the postoperative period for some patients, before significant

Table 5. Resolution of type 2 diabetes mellitus according to preoperative medication and duration of disease

Total	Resolution	Glycemic control	Improvement	*p* Value
Oral hypoglicemic agent: *n* (%)	12 (54.5)	8 (36.4)	2 (9.1)	<0.001
Mean	5.7 ± 0.2	6.5 ± 0.3	8.1 ± 0.0	
Insulin: *n* (%)	1 (33.3)	1 (33.3)	1 (33.3)	—
Mean	5.1	6.4	7.0	—
Both: *n* (%)	5 (38.5)	6 (46.2)	2 (15.4)	0.001
Mean	5.7 ± 0.3	6.6 ± 0.3	9.1 ± 0.3	
T2DM (3–5 years): *n* (%)	7 (87.5%)	1 (12.5%)	—	
Mean	5.7 ± 0.2	6.5		—
T2DM (5–10 years): *n* (%)	6 (37.5)	9 (56.3)	1 (6.3)	<0.001
Mean	5.7 ± 0.4	6.5 ± 0.3	9.3	
T2DM (>10 years): *n* (%)	5 (35.7)	5 (35.7)	4 (28.6)	0.057
Mean	5.7 ± 0.3	6.5 ± 0.3	8.0 ± 0.8	

T2DM, type 2 diabetes mellitus

weight loss. This could be demonstrated for 29% of the patients in this series, and was more common after II-DSG in relation to II-SG. It is not clear how much weight loss is needed to determine metabolic improvement for T2DM patients. Rubino et al. [33] demonstrated that bypassing a short segment of the proximal intestine directly ameliorates T2DM, independently of effects on food intake, body weight, malabsorption, or nutrient delivery to the hindgut. Gault et al. [34] also demonstrated a role for the inhibition of GIP receptors in obesity-related glucose intolerance and its effect on insulin action independent of enhanced insulin secretion, indeed, determining a marked improvement in insulin sensitivity.

The third characteristic of these operations is reduction (II-SG) or even abolishment (II-DSG) of the excessive duodenum stimulation, although this study was not designed to compare the two techniques.

The preliminary data of this study demonstrated that the majority of the patients (86.9%) achieved an adequate glycemic control (HbA1c < 7%) during a mean follow-up period of 7 months (range, 4–16 months). Nearly 50% reached levels of resolution (HbA1c < 6%). It is possible that an even better outcome may be achieved with a longer follow-up period. These preliminary data are similar to those for morbidly obese patients with T2DM treated using laparoscopic adjustable gastric banding [35], laparoscopic Roux-Y gastric bypass [36], bilio-pancreatic diversion (BPD) procedures [37], or longitudinal gastrectomy associated with an ileal interposition [38], despite the variable characteristics of patients, severity of diseases, or methodology.

A significant reduction in the use of oral hypoglycemic agents also was observed, with 13% still using these agents in the postoperative period. No patients needed insulin in the postoperative period (41% had used insulin preoperatively). There was no documented episode of hypoglycemia, probably due to the effect of GLP-1, which stimulates insulin secretion only in the presence of glucose-stimulatory concentrations [39]. Although patients submitted to II-DSG had a longer duration of T2DM (11.4 ± 4.6 to 7.8 ± 4.2) and were using insulin more often (62.5–30.4%) than those submitted to II-SG, suggesting more severe T2DM in the former group, both operations were effective.

It is possible that the diverted version may be more effective for the treatment of T2DM, probably due to a partial inhibition of the GIP signaling. Zhou et al. [40] demonstrated that GIP plays a crucial role in the switch from fat oxidation to fat accumulation under the diminished insulin action and inhibition of GIP, signaling ameliorated insulin resistance.

A dramatic improvement in some associated diseases and related complications was observed. Type 2 diabetes mellitus is an independent risk factor for macrovascular disease. Hypertension is a major risk factor for cardiovascular disease and microvascular complications such as retinopathy and nephropathy. Randomized trials have demonstrated the benefit of lowering blood pressure to less than 140 mmHg systolic and less than 80 mmHg diastolic in individuals with T2DM [41]. These levels of control for arterial hypertension were reached by 95.8% of the patients via a casual blood pressure measurement.

Although this work was not designed specifically for this objective, these findings deserve merit. In the study of Sugerman et al. [42], hypertension was controlled in approximately 70% of morbid obese patients who underwent a gastric bypass. Hypercholesterolemia resolution was almost universal, except for one patient who needed resection of his transposed ileal segment. In a study in rats, Tsuchiya et al. [43] demonstrated that ileal transposition to the upper jejunum affected lipid and bile salt absorption, attenuating cholesterol absorption and transport, possibly by promoting premature absorption of bile salts. Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and lowering triglycerides reduced

macrovascular disease and mortality in patients with T2DM, particularly in those who had prior cardiovascular events [44].

Despite the relatively short follow-up period, partial improvement in microvascular complications from T2DM was observed. Preoperative nephropathy was present in 28.2% and microalbuminuria in 20.5% of the patients. Microalbuminuria is a well-established marker of increased cardiovascular disease risk [45]. After a mean follow-up period of 7 months, microalbuminuria was still present in 10% of the patients. Retinopathy was present in 28% of the patients preoperatively, and objective improvement was demonstrated in 36.4%. Symptomatic improvement was observed in all the patients. The achievement of near normoglycemia has been shown to prevent or delay the onset and progression of diabetic retinopathy [46]. Neuropathy was present in 20.5% of the patients preoperatively. Symptomatic improvement was reported by 62.5%.

The laparoscopic approach was the preferred access, and there was no need for conversion. Certainly, open surgery is technically feasible, although probably needing long incisions. Ileal interposition involved a significant technical complexity, and the need of three enteroanastomoses had the potential to increase the risk of leaks, intestinal obstructions, and internal hernias. The use of suture techniques, closure of all possible internal hernia sites, and oversewing of stapler lines probably represented additional safety issues, averting complications in this initial series. The major morbidity and mortality rates of 10.3% and 2.6%, respectively, seem reasonable for such a high-risk group of patients. Ileal interposition and sleeve or diverted sleeve gastrectomy has the potential to cause nutritional problems. The patients submitted to II-SG were surprisingly well despite significant weight loss. Vitamin deficiencies were not diagnosed. The diverted version also was associated with significant weight loss, but caused iron deficiencies. Calcium metabolism may be a problem with a longer follow-up period. Furthermore, the potential incretin effect from moving ileum proximally may cause hypertrophy of the pancreas, with attendant nesidioblastosis [47].

The limitations of the current study were the small numbers of patients ($n = 39$), the brevity of the follow-up period (most < 12 months), and the lack of relevant control groups. The remarkable findings are adequate control of glucose, dyslipidemia, and arterial hypertension in the majority of the patients, independent of weight loss. We hypothesize that these operations maybe considered for treatment of the metabolic syndrome. It is not clear nor was it the goal of this study to define the proportional participation of caloric restriction, weight loss, and neurohormonal mechanisms.

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