

Short-Term and Mid-Term Control of Type 2 Diabetes Mellitus by Laparoscopic Sleeve Gastrectomy with Ileal Interposition

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Abstract

Background Standard surgical procedures used for the treatment of morbid obesity constitute optional treatments for type 2 diabetes mellitus (T2DM). The aim of the present study was to evaluate the short- and mid-term effects of laparoscopic sleeve gastrectomy (SG) with ileal interposition (II) in T2DM patients ($n = 30$).

Methods The variables investigated were the feasibility of the procedure, remission/alleviation of the disease, morbidity, mortality, and weight loss. Patients were followed during a period of 6–18 months after surgery.

Results The average time required for the surgical procedure was 181.47 ± 53.23 min, and the mean duration of postoperative hospital stay was 3.17 ± 0.79 days. There were no intraoperative complications, and none of the patients required conversion to open surgery. Postoperatively, all patients experienced a significant weight loss: i.e., the mean body mass index (BMI) values prior to and following surgery were significantly different ($P = 0.0001$). Postoperative levels of glycosylated hemoglobin, fasting glucose, and fructosamine were significantly reduced ($P = 0.0001$, 0.0001 , and 0.0004 , respectively) from those detected prior to surgery. Remission of T2DM was

observed in 80% of the patients over the follow-up period, and these subjects no longer required treatment with hypoglycemic drugs or diet. The remaining 20% of patients presented significant improvement in their condition but needed an oral hypoglycemic medication.

Conclusions Adequate glycemic control, adjustable weight loss, and absence of nutritional deficiencies were the main benefits offered by the surgical intervention. The results indicate that SG/II treatment could be a promising alternative for patients with T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) is a devastating disease with high morbidity and mortality rates and damaging consequences that include cardiovascular problems, visual deterioration, renal insufficiency, and amputation. The current treatment of T2DM includes diet, control of blood glucose levels, exercise, and the use of medication. However, as the disease progresses, pancreatic beta cell function tends to deteriorate, and the need for drug combinations to control the glycemia increases.

Standard surgical procedures employed in the treatment of morbid obesity are considered a safe optional treatment for T2DM, even in individuals who are not overweight [1]. In a recent review, Roux-en-Y gastric bypass (RYGB) and biliopancreatic derivation (BPD) were reported to induce remission of T2DM in 83.7 and 98.9% of cases, respectively, whereas purely restrictive bariatric surgery (gastric banding) had success rates in only 47.9% of cases [2].

As glycemic control can be observed earlier than weight loss, it has been suggested that T2DM could be regulated by mechanisms involving a group of gastrointestinal hormones known as incretins, which include gastric inhibitory

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polypeptide (GIP), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1) [3–5]. These hormones, in conjunction with the central nervous system, influence glucose metabolism by (1) increasing insulin secretion, (2) suppressing postprandial glucagon secretion, (3) reducing gastric emptying and diminishing food intake, (4) preserving and/or promoting the hypertrophy of pancreatic beta cells, (5) stimulating the differentiation of pancreatic duct cells into insulin-secreting beta cells, (6) reducing peripheral insulin resistance, and (7) limiting beta cell apoptosis [6–11].

Mediated by GIP and GLP-1, the incretin effect accounts for 50–70% of the insulin response, which is essential for glucose homeostasis. It is also responsible for the deposition of two-thirds of the glucose ingested. The serum concentration of GIP is practically normal in early T2DM patients but tends to decrease as the disease progresses. On the other hand, GLP-1 secretion is reduced. The effect of GIP is severely impaired, although the GLP-1 effect is preserved. Continuous infusion of GLP-1 produced lower fasting and average plasma glucose concentrations, decreased glycosylated hemoglobin (HbA1c) levels, and improved insulin sensitivity [11].

Surgical procedures that increase hindgut (ileum) delivery of nutrients stimulate the release of incretins and could promote control of T2DM. Nevertheless, the more extensive the intestinal bypass, the greater are the chances of nutritional and metabolic complications [2, 12–15].

Recent reports have suggested that the same metabolic benefits (e.g., improved glucose tolerance) could be reproduced without restricting gastric size or intestinal resection through a procedure termed ileal interposition (II). II introduces a segment of terminal ileum into the proximal jejunum and allows premature exposure of nutrients to the interposed ileum, thus stimulating GLP-1- and PYY-producing L cells without disrupting intestinal transit or absorption [16]. The raised level of the anorectic peptides and the delay in gastric emptying reduces hunger and provides a longer sensation of satiety, both of which contribute to weight loss [17, 18]. A study involving experimental animals demonstrated that application of the II procedure does not result in problems relating to malnutrition or nutrient absorption [16].

The identification of ghrelin, an orexigenic hormone (appetite stimulant), signaled the importance of mechanisms involved in the decision to eat. Serum levels of ghrelin are elevated before meals and decrease rapidly after food ingestion. It was shown in patients undergoing RYGB that ghrelin levels did not rise before meals [19]. Ghrelin also stimulates the secretion of counterregulatory hyperglycemic hormones (e.g., glucagon, catecholamines, cortisol, growth hormone) and suppresses secretion of the insulin-sensitizing hormone adiponectin by fat cells, consequently blocking insulin signaling in the liver and

inhibiting insulin secretion [20, 21]. In contrast to RYGB, sleeve gastrectomy (SG) foregoes intestinal rerouting but involves removing the fundus, thereby eliminating the diabetic effects of ghrelin.

DePaula et al. [18, 22, 23] have proposed SG + II as a surgical alternative to improve remission of T2DM and its co-morbidities. Following this procedure, the presence of the terminal ileum near the gastric drain would stimulate premature production of incretin hormones, whereas gastric resection would reduce ghrelin levels and accelerate stomach emptying [16, 22]. Initial results are highly encouraging. The aim of the present study was to evaluate the short- and mid-term effects of laparoscopic SG/II in T2DM patients. The variables investigated were the feasibility of the procedure, remission/alleviation of the disease, morbidity, mortality, and weight loss.

Patients and methods

The São José do Avaí Hospital Ethics Committee approved the study registered on the National Information System on Ethics in Human Research (CAAE—0023.0.316.000-10). Informed written consent was obtained from all subjects prior to their inclusion in the study.

Patients

The nonrandomized prospective 1-year study involved 30 T2DM patients who had undergone an SG/II procedure during the period March 2009–March 2010. The time span between the procedure and inclusion of the patient in the study varied from 6 to 18 months (average of 13.0 ± 3.3 months).

Criteria for inclusion/exclusion in the study

The inclusion criteria were as follows: (1) patients diagnosed with T2DM for at least 3 years according to the standards adopted by the American Diabetes Association (ADA) [24]—i.e., fasting glucose ≥ 126 mg/dl, glycosylated hemoglobin (HbA1c) $\geq 6.5\%$, fasting plasma glucose ≥ 200 mg/dl, and 2-h glucose ≥ 200 mg/dl in the 75-g oral glucose tolerance test; (2) evidence of stable treatment with oral hypoglycemic drugs and/or insulin for more than 12 months; (3) age between 18 and 70 years; (4) stable weight (defined by an alteration of $<3.0\%$ during the last 3 months prior to the study); (5) possibility of clinical follow-up for 24 months; (6) serum peptide C >0.5 ng/ml.

The exclusion criteria were (1) positive anti-glutamic acid decarboxylase (anti-GAD) antibodies; (2) type 1 diabetes; (3) active hepatic disease; (4) serum levels of liver

enzymes threefold higher than normal; (5) alcoholism or addiction to illicit drugs; (6) coexisting malignant diseases or occurrence thereof during the last 4 years; (7) glomerular filtration rate <30 ml/h; or (7) American Society of Anesthesiologists (ASA) classification $> III$.

Surgical intervention

Patient was placed on the right side in a 30° reverse Trendelenburg position. Surgeon and assistant camera stayed at the right side and the assistant on the left side. Devascularization of the large gastric curvature was done with ultrasonic scissors, starting 5 cm from the pylorus, moving in the cranial direction, and up to the His angle.

A 32F Fouchet catheter was introduced. Gastric sectioning was performed with a blue cartridge linear stapler beginning in the antrum–body transition, about 5–10 cm from the pylorus, according to the patient's body mass index (BMI). In patients with $BMI <30$ kg/m², the first gastric sectioning was done 10 cm from the pylorus in the cranial direction. In patients with $BMI >30$ kg/m², the starting point was 5 cm from the pylorus. Gastric resection was accomplished with a sharp linear blue load stapler of 45 or 60 mm, until reaching the His angle. A running suture, across the staple line, was done with 3-0 polypropylene thread.

For the II procedure the ligament of Treitz was identified, and the jejunum was divided 30 cm distally. After the cecum was identified, the distal ileum was transected 30 cm proximal to the ileocecal papilla. A total of 170 cm of ileum was measured proximally and transected (Fig. 1). This segment of ileum was interposed in an isoperistaltic

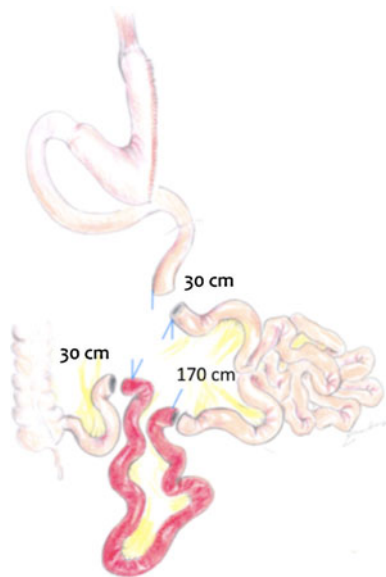


Fig. 1 Sleeve gastrectomy with all three small bowel sections



Fig. 2 Final view

way into the proximal jejunum, previously divided. Next, we performed a three side-to-side enteroanastomosis. The first one was the ileoileostomy, followed by the jejunoileostomy, and finally the ileojejunostomy. All three mesenteric defects were closed with interrupted sutures (Fig. 2).

Evaluation of surgical outcome

Surgical outcomes were evaluated according to ADA proposed criteria [25]. Patients were divided into two groups on the basis of their postsurgical status: (1) those in remission of T2DM, defined by $HbA1c <6.5\%$ without oral hypoglycemic drugs or insulin; and (2) those with alleviation of their T2DM, defined as a reduction of at least 25% in the fasting plasma glucose level and of at least 1% in the $HbA1c$ level with hypoglycemic drug treatment.

Results

Characteristics of the patients

The study population ($n = 30$) comprised 10 women (33.3%) and 20 men (66.7%) with an average age of 49.7 ± 8.9 years (median 49 years, range 33–68 years). The average BMI of the population was 30.8 ± 5.1 kg/m² (median 31.1 kg/m²; range 19.9–40.1 kg/m²), and mean time from T2DM diagnosis was 9.9 ± 4.4 years (range 4–20 years).

Surgical outcome

The mean operating time was 181.47 ± 53.23 min, and the mean postoperative hospital stay was 3.17 ± 0.79 days.

There were no intraoperative complications, and none of the patients required conversion to open surgery. There were no deaths.

Postsurgical complications included metabolic ketoacidosis in one patient (3.3%), urinary infection in one (3.3%), and diarrhea in two (6.6%). Three months after the operation, one patient (3.3%) presented with cholecystolithiasis and another (3.3%) with bowel obstruction caused by adhesions. Both problems were resolved by laparoscopy.

Patients were followed for a period of 6–18 months (average 13 ± 3.3 months) after surgery. All 30 patients evolved with weight loss: i.e., the BMI values of the patients prior to and after surgery were significantly different ($P = 0.0001$) as determined by paired *t* tests (Table 1). Additionally, the mean postsurgical blood levels of HbA1c, fasting glucose, and fructosamine were significantly lower ($P = 0.0001$, 0.0001 , and 0.0004 , respectively) than those determined prior to surgery (Table 2). The distribution of patients according to postsurgical evolution of T2DM is shown in Table 3. All patients evidenced improvement in their T2DM over the months that

Table 1 Body mass index of T2DM patients ($n = 30$) prior to and following laparoscopic SG with ileal interposition

| Time of measurement | BMI (kg/m^2) | | |
|---------------------|--------------------------------|---------|----------------|
| | Minimum | Maximum | Mean \pm SD |
| Preoperative | 19.9 | 40.1 | 30.8 ± 5.1 |
| Postoperative | 18.3 | 34.4 | 25.7 ± 4.0 |

Mean values were significantly different according to the paired *t* test ($P = 0.0001$)

T2CM type 2 diabetes mellitus; BMI body mass index

Table 2 Laboratory evaluation of T2DM patients ($n = 30$) prior to and following laparoscopic SG with ileal interposition

| Parameter | Period | | <i>P</i> |
|-----------------------------|------------------|------------------|----------|
| | Preoperative | Postoperative | |
| Glycosylated hemoglobin (%) | | | |
| Minimum | 7.6 | 5.0 | 0.0001 |
| Maximum | 13.7 | 8.2 | |
| Mean \pm SD | 9.5 ± 1.7 | 6.2 ± 0.8 | |
| Fasting glucose (mg/dl) | | | |
| Minimum | 98.0 | 73.0 | 0.0001 |
| Maximum | 416.0 | 160.0 | |
| Mean \pm SD | 201 ± 78.5 | 99.6 ± 19.7 | |
| Fructosamine (mg/dl) | | | |
| Minimum | 166.0 | 210.0 | 0.0004 |
| Maximum | 438.0 | 388.0 | |
| Mean \pm SD | 323.4 ± 67.9 | 271.8 ± 41.6 | |

Mean values were significantly different according to the paired *t*-test

Table 3 Postoperative evaluation of T2DM patients ($n = 30$) who underwent laparoscopic SG with ileal interposition

| T2DM status after surgery | No. | % |
|-----------------------------------------------|-----|-----|
| Remission (HbA1c $<6.5\%$ without medication) | 24 | 80 |
| Alleviation | 6 | 20 |
| Total | 30 | 100 |

HbA1c hemoglobin A1c (glycosylated hemoglobin)

followed surgery, and remission was observed in 80% of patients such that these subjects no longer required treatment with antidiabetes drugs. Presurgical BMI was not a determinant factor for the postsurgical remission of T2DM. There were no significant differences between patients in the two outcome groups with respect the presurgical duration of T2DM. In addition, there were no significant differences between the three groups of patients regarding duration of insulin usage prior to surgery.

Discussion

The aim of the present study was to evaluate the feasibility of SG/II in 30 T2DM patients and determine the postsurgical outcomes in terms of morbidity, mortality, weight loss, and disease alleviation or remission.

The effects associated with the increased levels of GLP-1 induced by procedures involving intestinal derivation could be the basis of metabolic surgery as this hormone inhibits acid secretion by the stomach, increases the sensation of satiety, and reduces appetite and gastric motility [26–28]. Additionally, augmentation of GLP-1 leads to increased secretion of insulin and postprandial suppression of glucagon secretion, together with preservation, and possible hypertrophy, of the beta cell mass. Moreover, it is believed that GLP-1 is involved in the differentiation of progenitor duct cells into beta cells, thus limiting apoptosis of these cells [11, 29, 30].

Studies based on meta-analyses, such as those reported by Buchwald et al. [2, 31], reveal a high rate of resolution (78.1%) among diabetic patients who had undergone bariatric surgery. Indeed, the rate of T2DM remission following BPD operations can be as high as 95.0% as indicated in a number of reports [32–34].

Glycemic control following RYGB is well documented [34–36], although some studies have questioned the real efficacy of this procedure in the control of T2DM. For instance, DiGiorgi et al. [37], following evaluation of 42 obese diabetic patients who had undergone RYGB, observed remission of the disease in only 27 individuals (67%). Furthermore, the disease relapsed in 26% of the patients exhibiting T2DM remission; that is, only 41% of the patients achieved glycemic control over the short and

mid term. Recurrence of the disease was associated with low preoperative BMI, indicating that surgical treatment of T2DM may not have the same results in nonobese patients. These authors concluded that additional investigations would be needed before it would be possible to recommend RYGB as a general alternative treatment for T2DM.

Chikunguwo et al. [38] examined 177 obese diabetic patients for an average of 8.6 years following an RYGB procedure and observed disease remission in 89% of the individuals. Within this group, disease recurrence was observed in 43% of the patients; thus, long-term glycemic control was observed in only 46% of the patients. These authors concluded that durable remission of T2DM correlated most closely with an early disease stage at surgery.

The rate of glycemic control in obese patients who undergo RYGB is apparently low over the mid and long term [37, 38], and the search for more efficient procedures for the treatment of T2DM in nonobese individuals was stimulated by results obtained from morbidly obese diabetic patients who underwent bariatric operations [34, 39–41]. A key outcome of these investigations was the development of the SG, a procedure that has been increasingly employed in the treatment of morbid obesity and T2DM. Among 23 obese diabetic patients who underwent SG, 16 (69.6%) had remission of T2DM within a follow-up period of 36 months [42]. Similarly, T2DM was reportedly resolved in 63.0% of cases treated by SG and followed for a period of 6 months [43].

DePaula et al. [17, 18, 23] demonstrated that SG coupled with II is also effective in the control of T2DM and associated diseases along with their complications in non-obese patients (BMI <30 kg/m²). Under these circumstances, the short- and mid-term resolution of T2DM was successful in as many as 95.7% of the cases. These authors also reported that SG/II induced an elevation in serum levels of GLP-1, GIP, and PYY and a reduction in serum ghrelin. The fundamentals of the control of the metabolic syndrome following SG/II have been stated as [17]: (1) premature increase in GLP-1 levels resulting from the response of L cells (from the interposed ileum) to the presence of nondigested food, thus normalizing first-phase insulin secretion (up to 30 min); and (2) GIP-mediated correction of the defect relating to the amplification of second-phase insulin secretion (from 20 to 120 min) in response to glucose caused by the diminution or absence of stimuli on duodenal K cells. SG can also control the obesity exhibited by up to 60% of T2DM patients by caloric restriction and adjusted weight loss.

In the present study, 80% of T2DM patients who underwent SG/II exhibited remission during the 6- to 18-month follow-up period. Thus, during the follow-up period they no longer required antidiabetes medication. Furthermore, 20% of the T2DM patients exhibited

considerable improvement after surgery, although medication was still required in such cases. These findings are similar to those reported by DePaula et al. [44], who also used the ADA evaluation criteria for T2DM [24]. Their study involved 72 patients with a mean T2DM duration of 24.5 months and an average BMI that was slightly high (27 kg/m²). In all, 50% of the patients exhibited total remission, 36.1% showed partial remission, and 13.9% experienced alleviation of their condition.

On the basis of the available evidence, improved status of treated patients could be occasioned by a combination of factors including hormonal alterations, caloric restriction, and weight loss. The identification of a predominant factor is likely to be extremely complex owing to the multifaceted physiology of T2DM. Some studies have demonstrated that the duration of T2DM and the use of insulin are determinant factors for control of the disease after RYGB [34–36]. Our results did not find an association of the duration of T2DM and the possibility of disease control after surgery. The average duration of the disease among the studied subjects was 9.9 ± 4.4 years, a value that was similar to that presented by patients showing alleviation of the T2DM (10.7 ± 5.5 years) and to those exhibiting remission (10.0 ± 4.4 years). Similarly, the presurgical use of insulin was not a determinant factor for diabetes control after SG/II as, prior to surgery, the average HbA1c values were high ($9.5 \pm 1.75\%$) indicating inadequate control of the disease even though some of the patients had probably required the use of insulin before surgical intervention. It is possible that a more expressive casuistry and a longer follow-up period would allow a more consistent relation to be established.

Even though the differences in BMI values before and after surgery were statistically significant (Table 1), the procedure did not induce the excessive weight loss that has been reported in previous studies [17, 22, 23]. Presurgical BMI values (i.e., >30 or <30 kg/m²) were not a determining factor for the postsurgical remission of T2DM.

The SG/II procedure employed in the present study was performed using a laparoscopic procedure. As emphasized by other researchers [17, 18, 22, 23, 45], weight control and amelioration of the metabolic syndrome are the foremost benefits of this type of surgery. However, it is essential to consider the technical difficulties and potential complications before opting for this approach. The average operating time (181.5 ± 53.2 min) was similar to that required for RYGB and BPD procedures [46, 47]; and considering the clinical conditions of the patients and the magnitude and complexity of the procedure, it was well within acceptable limits. Similar considerations can be applied to the relatively short hospital stay (3.2 ± 0.8 days).

Although the present study involved a limited number of patients and a short- to mid-term follow-up, the findings

presented herein are valuable in that they suggest excellent possibilities for the development of metabolic surgery, and they confirm the results obtained from similar operations performed on rats, dogs, and humans [48–55]. Despite the weight of evidence in favor of SG/II, however, two key points must be considered: Will the long-term (>8 years) outcome be comparable with the optimistic results shown in the short to mid term? Is glycemic control similar to that observed after bariatric surgery (RYGB) in which some recent results show a recurrence rate close to 50% [37, 38]? It is evident that longer postsurgical follow-up of patients is essential to answer these critical issues.

Conclusions

The SG/II procedure can produce adequate glycemic control and satisfactory weight loss with no clinical signs of nutritional deficiencies. Such findings indicate that this operation, which interferes with glucose metabolism, is a promising alternative for patients with T2DM. Laparoscopic SG/II is an effective, safe, reproducible technique that produces few short- or mid-term complications. However, a much longer postsurgical follow-up is essential to answer the critical issues relating to the maintenance of glycemic control in treated patients.

Conflicts of interest The authors declare that they have no conflicts of interest.

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