

# Laparoscopic Duodenal–Jejunal Exclusion in the Treatment of Type 2 Diabetes Mellitus in Patients with BMI < 30 kg/m<sup>2</sup> (LBMI)

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## Abstract

**Background** The association between medical and dietetic–behavioral treatments of type 2 diabetes mellitus (T2DM) has demonstrated to have variable results. The surgical treatment of T2DM is justifiable after the observation of a successful glycemic control in patients submitted to Roux-en-Y gastric bypass and biliopancreatic diversion. Experiments have shown an important role of the proximal intestine in glycemia decrease and diabetes control.

**Methods** Twenty diabetic patients underwent laparoscopic duodenal–jejunal exclusion. The variables studied were body mass index (BMI), fasting glycemia, glycosylated hemoglobin (HbA<sub>1c</sub>), and C-peptide, in the preoperative period and after 3 and 6 months.

**Results** There was a BMI decrease up to the third month and a weight stabilization between the third and sixth months. There was a significant reduction in fasting glycemia (43.8%) and HbA<sub>1c</sub> (22.8%) up to the sixth month ( $p < 0.001$ ). C-peptide did not show any significant alteration until the third month, although there was a considerable increase (25%) between the third and the sixth months ( $p < 0.001$ ). Only two patients were on oral medication after the sixth month.

**Conclusions** Preliminary results have shown an important effect of the laparoscopic duodenal–jejunal exclusion in the treatment of T2DM. Studies with longer follow-up and a larger number of patients are necessary to better define the role of this new and promising procedure.

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**Keywords** Diabetes mellitus · Duodenal–jejunal exclusion · Surgical technique

## Introduction

Diabetes mellitus affects nearly 150 million people all over the world. This number may double by 2025 [1]. In the USA, it is the leading cause of blindness, chronic renal insufficiency, and amputations, multiplying by three the risks of heart diseases and by two the risks of a stroke. The annual health system expenditures amount to 100 billion American dollars [2]. It is type 2 diabetes mellitus (T2DM) that predominates in about 90% of patients, usually associated with intolerance to glucose and overweight. The treatment of T2DM in the past few years has been based upon a combination of dietetic–behavioral proce-

dures and medical therapy with oral hypoglycemics and, in more severe cases, insulinotherapy with variable success rates [3]. The large variability in clinical treatment results and the growing economic impact of the DM treatment and its complications worldwide justify the search for new and efficient treatment methods, whether clinical or surgical. In the past two decades, with the advancement of bariatric surgery and the observation of a successful glycemia control in patients who underwent Roux-en-Y gastric bypass and biliopancreatic diversion (Scopinaro & Duodenal Switch), many groups have been trying to elucidate the mechanisms associated with glycemia control [4–8]. At first, it was thought that glycemia stabilization would be a direct consequence of weight loss induced by surgery. Rubino et al. carried out a study with non-obese diabetic rats which underwent duodenal–jejunal exclusion, having found a significant glycemia decrease in about 40% of them and an improvement in tests of glucose oral tolerance (better result than clinical treatment with rosiglitazone). Independent from any ponderable weight loss, this effect was confirmed within a 3-week postoperative observation [9, 10]. In this setting, a study protocol of 20 patients with low body mass index (LBMI) was designed in which they underwent laparoscopic duodenal–jejunal exclusion, under informed consent, aiming to control glycemia and to improve the conditions associated with T2DM.

## Patients and Methods

### Patients

From August 2006 to October 2007, we started a prospective study in patients with BMI between 20 and 30 kg/m<sup>2</sup>, aged between 18 and 60 years old, with diabetes being diagnosed later than two and earlier than 8 years, without a history of insulinotherapy and with C-peptide levels >1.0 ng/ml. All patients were explained the risks and benefits of this new technique and have provided informed consent term approved by the local Institutional Review Board.

Patients taking hypoglycemics different from metformin, glimepiride, and glitazones, with a previous history of difficult glycemic control or ketoneacidosis, with a weight loss of more than 5 kg in the last 3 months or with HbA<sub>1c</sub> >11% were excluded from this protocol.

### Operative Technique

Positioning of patient, surgical team, and punctures are similar to that in a five-trocar antireflux procedure. The greater omentum is divided at the greater gastric curvature with the use of a harmonic scalpel (Harmonic ACE 5 mm

shears, Ethicon Endo-Surgery, Cincinnati, OH, USA), preserving the gastroepiploic vessels until the head of the pancreas is reached. Once in the retrocavity, the dissection is extended to the lesser curvature for freeing the first duodenal portion (about 2 cm distal to the pylorus), where a 45-mm linear stapler (ETS-Flex Endoscopic Articulating Linear Cutter, Ethicon Endo-Surgery) with a vascular white load is fired (Fig. 1). Pyloric artery ligation is always performed to achieve a tension-free duodenojejunostomy.

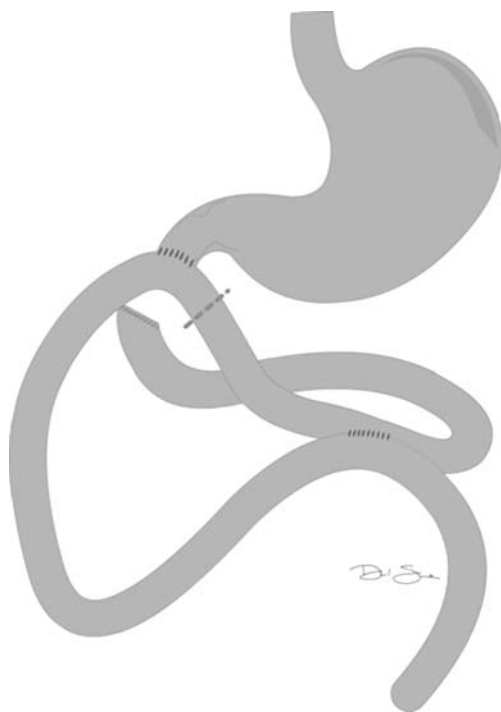
A jejunal omega isoperistaltic loop 200 cm from the Treitz ligament is shown in an antecolic isoperistaltic fashion. A 45-mm linear stapler (vascular) performs the terminolateral duodenojejunostomy. The stapled hole is closed by a layer of continuous suture with PDS 3.0® (Fig. 2).

By mobilizing the alimentary limb on the surgeon's left side, a side-to-side enteroenterostomy is performed with a 45-mm vascular stapler 100 cm distal from the duodenojejunostomy. Roux-en-Y reconstruction is completed through stapling between the duodenojejunostomy and the enteroenterostomy with a 45-mm vascular stapler (Fig. 3). Mesenteric defects are closed with an Ethibond® 3.0 running suture. A tubolaminar drain is left next to the duodenojejunostomy until the seventh postoperative day.

A hypoglycemic/hypolipidemic diet is started on the first postoperative day. Patients are stimulated to walk, being dismissed from the hospital on the second postoperative day. Dosages of fasting glycemia, HbA<sub>1c</sub>, C-peptide, and BMI calculation are taken at postoperative days 30, 90, and 180. Glycemic control at home is maintained as in the preoperative period.



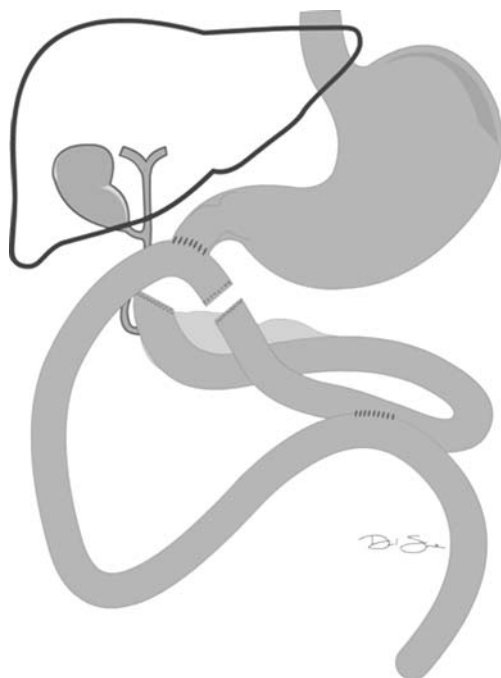
**Fig. 1** Transection of the first duodenal portion



**Fig. 2** Creation of the duodenoenterostomy 200 cm from the Treitz ligament

**Statistical Methods**

BMI, HbA<sub>1c</sub>, fasting glycemia, and C-peptide data were checked using analysis of variance, together with multiple comparisons through the Bonferroni method when neces-



**Fig. 3** Formation of the enteroenterostomy, 100 cm from the previous anastomosis and the jejunal section for the final bypass positioning

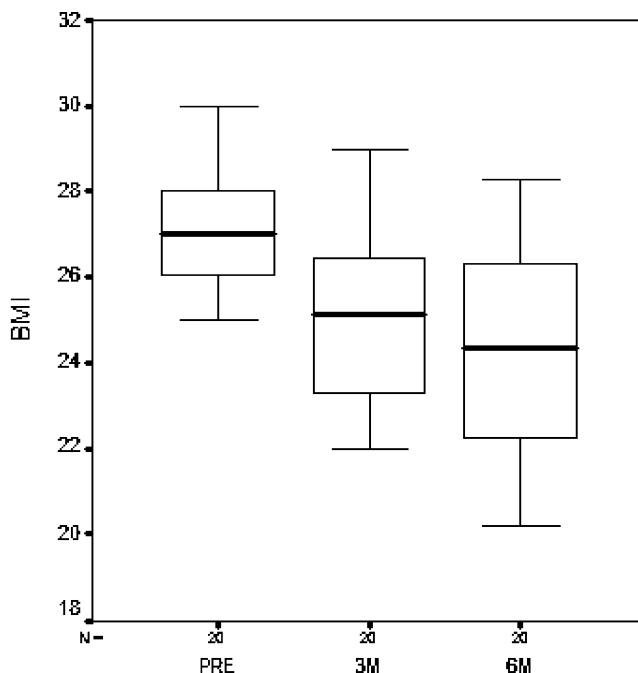
sary. It was necessary to use the logarithmic transformation in the variable fasting glycemia. Values of  $p < 0.05$  were considered significant [11]. The statistical analysis were made by the software “Statistical Package for Social Sciences” version 11.0 for Windows.

**Results**

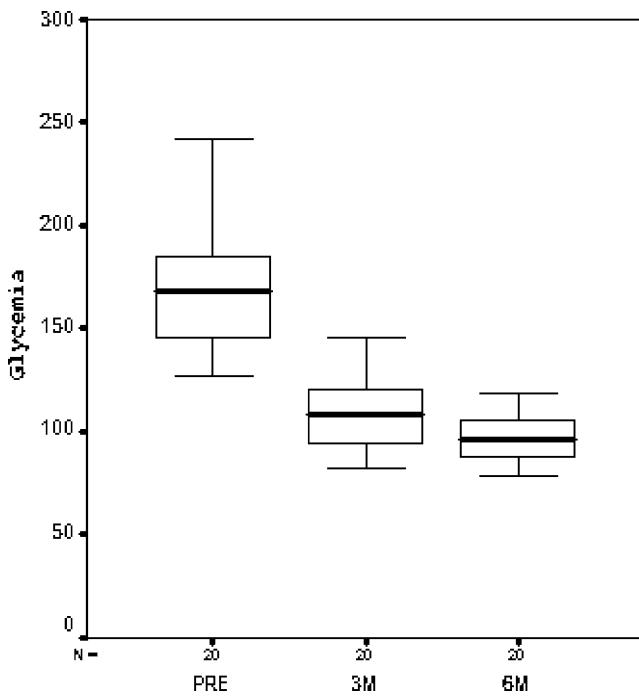
Twenty patients were included in the study (11 men and nine women). Mean age was 43 (29–60) years old. The mean T2DM diagnosis time was 5.3 (2–8) years. Mean preoperative BMI was 27.1 (25–30). Mean BMI in the third and sixth postoperative months were respectively 25 (22–29) and 24.4 (20.2–28.3). A statistically significant difference was observed between BMI in the preoperative period and in the third month ( $p < 0.001$ ). However, there was no difference between the third and the sixth months ( $p = 0.732$ ), showing a weight loss stabilization, around 7.8% below the initial weight (Fig. 4).

Preoperative fasting glycemia level was 171.3 (127–242). After the third and the sixth postoperative months, there was a decrease to 107.1 (82–145) and 96.3 (78–118), with a reduction of 37.5% and 43.8% ( $p < 0.001$ ), respectively. Comparing the third and the sixth postoperative months, there was a significant difference ( $p = 0.047$ ; Fig. 5).

Concerning HbA<sub>1c</sub>, the mean value in the preoperative period was 8.8% (7.5–10.2). There was a decrease to 7.8



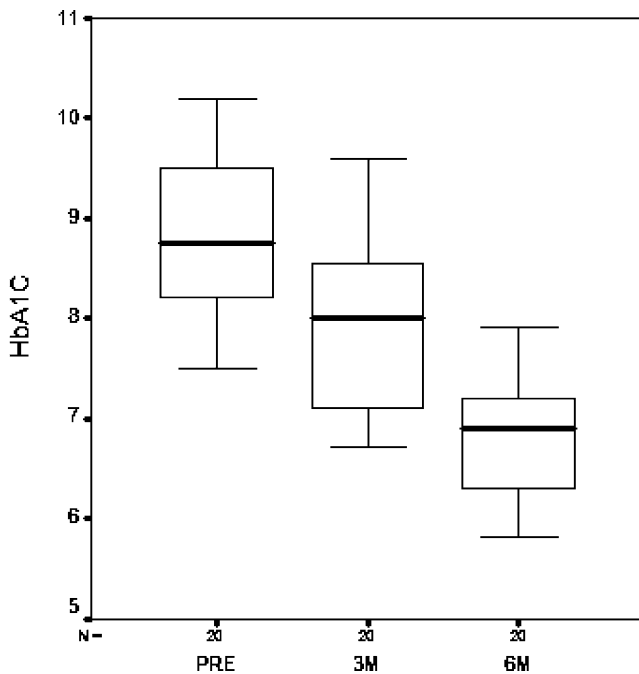
**Fig. 4** BMI evolution up to the sixth postoperative month. PRE preoperative data, 3M 3 months, 6M 6 months



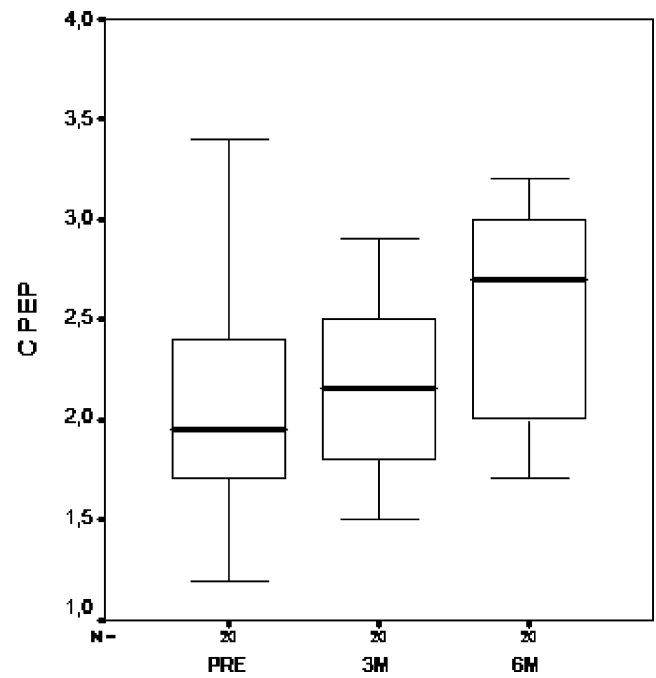
**Fig. 5** Fasting glycemia up to the sixth postoperative month. *PRE* preoperative data, *3M* 3 months, *6M* 6 months

(6.7–9.6) and 6.8 (5.8–7.9) in the third and sixth postoperative months, respectively ( $p < 0.001$ ; Fig. 6).

The mean value of C-peptide levels in the preoperative period was 2.0 ng/ml (1.2–3.4). In the third and sixth postoperative months, there was an increase to 2.1 (1.5–2.9)



**Fig. 6** HbA<sub>1c</sub> up to the sixth postoperative month. *PRE* preoperative data, *3M* 3 months, *6M* 6 months



**Fig. 7** C-peptide up to the sixth postoperative month. *C PEP* C-peptide, *PRE* preoperative data, *3M* 3 months, *6M* 6 months

and 2.5 (1.7–3.2). However, there was no statistical significance up to the third month ( $p = 0.247$ ). In the sixth month, there was an increase of 25% in the C-peptide levels ( $p < 0.001$ ; Fig. 7). Results are summarized in Table 1.

Only two patients (10%) included in this study were kept on oral medication (metformin) after the sixth postoperative month. Patients are still on clinical follow-up aiming a long-term analysis. There have been no postoperative complications, such as fistulae or abscesses in this group of patients. No mortality was observed.

**Table 1** Comparative results between BMI, HbA<sub>1c</sub>, glycemia, and C-peptide in different collection moments

	Conclusion
BMI	PRE > 3M ( $p < 0.001^a$ ) PRE > 6M ( $p < 0.001^a$ ) 3M = 6M ( $p = 0.732^a$ )
HbA <sub>1c</sub>	PRE > 3M ( $p < 0.001^a$ ) PRE > 6M ( $p < 0.001^a$ ) 3M > 6M ( $p < 0.001^a$ )
Glycemia	PRE > 3M ( $p < 0.001^a$ ) PRE > 6M ( $p < 0.001^a$ ) 3M > 6M ( $p = 0.047^a$ )
C-peptide	PRE = 3M ( $p = 0.848^a$ ) PRE < 6M ( $p < 0.001^a$ ) 3M < 6M ( $p < 0.001^a$ )

*PRE* preoperative data, *3M* 3 months, *6M* 6 months

<sup>a</sup> Analysis of variance (ANOVA)  $p$  value

## Discussion

In recent years, some procedures have been proposed in the literature for the treatment of T2DM in non-obese and obese patients, as the duodenal–jejunal exclusion [12] and the ileal interposition [13]. We have chosen the duodenal–jejunal exclusion based on the consistent results on glycemia control reported by Rubino et al. in an experimental protocol in Goto–Kakizaki non-obese diabetic rats [9]. The option for creating a biliopancreatic limb ranging 200 cm from Treitz and an alimentary limb of 100 cm was based in the literature data [14] and our group's experience in bariatric surgery with the Roux-en-Y gastric bypass in morbidly obese patients who also had hyperlipidemia and T2DM or glucose intolerance. We have observed a reduction in blood levels of glucose and cholesterol and the resolution of T2DM in most of our cases (unpublished data). The choice for the laparoscopic method was due to its benefits in terms of postoperative recovery, surgical infection, and cosmesis.

The inferential results showed that the BMI behavior ( $p < 0.001$ ), HbA<sub>1c</sub> ( $p < 0.001$ ), fasting glycemia ( $p < 0.001$ ), and C-peptide ( $p < 0.001$ ) are not statistically the same in the different moments of postoperative follow-up. We verified a weight loss of approximately 7.8% of the total body weight up to the third month and stabilization from the third to the sixth months. There was an important decrease in fasting glycemia up to the third month, followed by a lower reduction after the sixth month. The reduction of HbA<sub>1c</sub> levels was more stable, 11.4% and 22.8% in the third and the sixth postoperative months, respectively. C-peptide levels increased in the sixth month dosage, probably reflecting a slower recovery of the pancreatic function and insulenic activity in the postoperative period.

Six months after the duodenal–jejunal exclusion, only 10% of the patients were still taking oral hypoglycemics. One of those has had the diagnosis of T2DM for 8 years, the longest in our series. The other patient, although after only 4 years of his T2DM diagnosis, showed no improvement in the C-peptide levels, demonstrating a lack of improvement in insulenic secretion. Cohen et al. pointed the better response to surgery in a subset of patients with shorter disease time and higher pre-operative levels of C-peptide [12].

Concerning the association between weight loss and glycemic reduction and the improvement in the levels of HbA<sub>1c</sub> and C-peptide, it can be said that weight loss and glycemic reduction were combined events up to the third month. However, there was no combination up to the sixth month, showing a possible hypoglycemic effect through the increase of incretins. Many publications have pointed the importance of these gut hormones (GLP-1, PYY, GIP)

in the regulation of glucose metabolism [12, 13, 15]. The HbA<sub>1c</sub> reduction was the result of a better glycemic control and the C-peptide increase was the result of improvement of the pancreatic function, probably as a consequence of incretinic stimulation.

The idea of bypassing the duodenum and proximal jejunum as a means of achieving glycemic control was first developed in animal models [9, 10]. This concept has evolved leading to the pioneers well-succeeded attempts of surgical [12] and endoscopic [16] duodenal–jejunal exclusions. In the former study [12], which included two patients, by the fifth week after surgery, both were euglycemic and free of all antidiabetic medications. The HbA<sub>1c</sub> levels were <6% at the last follow-up visit, 9 months postoperatively. In the latter trial [16], glycemia control occurred already 24 h after the initial procedure. De Paula et al. proposed a procedure combining an ileal interposition with sleeve gastrectomy in the treatment of T2DM. An important reduction in antidiabetic medications was observed. Nearly 87% of the patients permanently discontinued preoperative oral hypoglycemic agents, insulin, or both. A rapid normalization of fasting plasma glucose was achieved by 29% of the patients on the first 2 weeks. However, it is a technically challenging procedure, with major morbidity and mortality rates of 10.3% and 2.6%, respectively [13].

Generally, the goals to be reached in the clinical treatment of T2DM are a fasting glycemia around 100–110 mg/dl and HbA<sub>1c</sub> at the most 1% above the upper limit of the reference value [17]. In the present study, the duodenal–jejunal exclusion was efficient by achieving these goals. Despite having no clinical randomization or sample pairing for comparison with a group of patients submitted to clinical treatment in the same institution, the present study showed a remarkable hypoglycemic effect of laparoscopic duodenal–jejunal exclusion in the treatment of T2DM in this subset of patients.

## Conclusions

The laparoscopic duodenal–jejunal exclusion is a safe procedure with low postoperative complication rates and an incretinic effect, shown through the reduction of glycemia and HbA<sub>1c</sub> and the increase of C-peptide secretion in a subset of patients. Further studies with larger samples, randomization, and longer follow-up are necessary to clarify its role in the treatment of T2DM.

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