

Surgery for Nonobese Type 2 Diabetic Patients: An Interventional Study with Duodenal–Jejunal Exclusion

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Abstract

Background A 24-week interventional prospective trial was performed to compare the benefits of open duodenal–jejunal exclusion surgery (GJB) with a matched control group on standard medical care.

Methods One-hundred eighty patients were screened for the surgical approach. Twelve patients accepted to be operated and presented the full eligibility criteria for surgery that includes overweight BMI (25–29.9 kg/m²), T2DM diagnosis for less than 15 years, insulin-treated patients, no history of major complications, preserved beta-cell function, and absence of autoimmunity. A matched control group (CG) of patients whom refused surgical treatment was placed to receive standard care. Patients had age of 50 (5) years, time of diagnosis 9 years (range, 3 to 15 years), time of insulin usage 6 months (range, 3 to 48 months), fasting glucose (FG), 9.8 (2.5) mg/dL, and glycated hemoglobin (A1C) 8.90 (2.12)%.

Results At 24 weeks after surgery, patients experienced greater reductions on FG (14% vs. 7% on CG), A1C (from

8.78 to 7.84 in GJB— $p < 0.01$ and 8.93 to 8.71 in CG; $p < 0.05$ between groups) and reductions on average daily insulin requirement (93% vs. 29%, $p < 0.01$). Ten patients stopped insulin usage in GJB but they remain taking oral medications. No differences were observed in both groups regarding BMI, body distribution and composition, blood pressure, and lipids. **Conclusions** In conclusion, duodenal–jejunal exclusion was an effective treatment for nonobese T2DM subjects. GJB was superior to standard care in achieving better glycemic control along with reduction in insulin requirements.

Keywords Metabolic surgery · Type 2 diabetes · Insulin therapy · Incretin · Insulin resistance · Duodenal–jejunal exclusion · Diabetes surgery

Introduction

Type 2 diabetes mellitus is a common and harmful metabolic disease in westernized countries with an estimated 300 million of people affected in 2025 [1]. There is a strong association between obesity and prevalence of T2DM, and 80% of patients have some degree of obesity [2]. Several underlying physiopathological mechanisms have been described for obesity-associated T2DM, including obesity-related insulin resistance [3], impairment in beta-cell function [4], elevation of inflammatory adipocytokines [5], and an incretin dysfunction [6]. The incretin defect could be named “incretinopathy”.

Bariatric surgery has become a common treatment for obesity-associated T2DM and is currently recognized as an effective treatment considering prevention, control, or reversion of the disease [7]. Because BMI is the dominant factor for diabetes, the antidiabetic effect of surgery has been incorrectly interpreted as an exclusive result of increased insulin sensitivity due to surgically induced

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weight loss [8]. Otherwise, glycemic control often occurs in few days before patients had had a significant weight loss, suggesting that there is a direct effect of surgery rather than a secondary outcome related to reduction in body weight [9].

Both surgeries Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) exert an entero-endocrine effect characterized by an increase in glucagon-like peptide 1 (GLP-1) circulating levels and an enhancement in incretin effect [10, 11]. Considering that this incretin effect is related to a rerouting of intestinal flow and is not dependent on weight loss, Rubino et al. conducted an experimental protocol with duodenal–jejunal exclusion (GJB) in Goto–Kakizaki rats, a spontaneous nonobese model of type 2 diabetes. The GJB resulted in better glucose control in comparison to weight loss from food restriction and to rosiglitazone therapy [12]. The foregut hypothesis was later contested. Recently, using an oral glucose tolerance test in operated Goto–Kakizaki rats, Pacheco et al. demonstrated that gastrojejunal bypass in a nonobese diabetic model improves glycemic control with a significant decrease in leptin levels, without changes in enteroinsular axis (GLP-1, GIP, glucagons, and insulin levels) [13].

Although the hormonal and molecular mechanisms are not still elucidated, these findings had opened an alternative surgical approach for nonobese T2DM. Interested in these hypotheses, we conducted a 24-week interventional controlled study to compare GJB to standard clinical treatment for T2DM in insulin-treated nonobese type 2 diabetic patients.

Materials and Methods

This trial began on June of 2006 and was conducted in the General Hospital of University of Campinas—UNICAMP—with patients being recruited from diabetic outpatient clinics. Protocol was approved by the Institutional Review Board and by ANVISA, the Brazilian Health Regulatory Agency. The registration number in National Institute of Health (NIH) is NCT00566358. This trial is part of a cross-sectional research project named BRAINS (Brazilian Incretin Study).

Eligibility criteria were inclusion of patients with T2DM treated with insulin plus oral antidiabetic agents or not from less than 5 years, diagnosis of T2DM for less than 15 years, average A1C 7.5–10%, no history of major complications, documented residual beta-cell function (fasting C-peptide above 1 ng/mL), absence of autoimmunity (negative anti-GAD antibodies), no history of major diseases, and stable weight with BMI from 25 to 29.9 kg/m². Exclusion criteria were history of gastrointestinal surgery, presence of active dyspeptic symptoms or inflammatory disease detected by

an endoscopy, documented beta-cell failure or autoimmunity, and use of incretin mimetics or DPP-IV inhibitors.

All patients presenting for treatment who meet the fully eligibility criteria during the interval from June 2006 to May 2007 were invited to participate in this trial. After having completed the self-selected GJB group ($n=12$), a nonsurgical control group was composed by patients whom refused the surgical procedure that matched selected baseline characteristics (age, BMI, sex, and time of diagnosis) to surgical group in order to minimize the imbalance of two groups matched. For each surgical case, we choose an eligible matched control subject in order to have treated groups as close to each other as possible. All the subjects had written a fully informed consent. No financial or other inducements were offered for participants.

The selection of patients excluded 90% of volunteers. In summary, 180 consecutive T2DM from our outpatient clinics met the clinical eligible criteria. The main reason for exclusion was the rejection to be submitted to an experimental surgery (27%). Other additional reasons include low concentration of fasting C-peptide (23%), presence of positive anti-GAD (11%), and significant amelioration of glucose control (A1C < 7.5%) during pre-operative phase (16%). There are no differences between groups.

In addition to clinical assessment for inclusion, each potential participant were assessed by a dietician (C.S.), a nurse specialized on diabetes education (C.F.), and consultant endocrinologists (S.G., B.G.) to suggest any changes required to maximize current management. A run-in period of at least 2 months was undertaken to made the adjustment on treatment and perform the laboratorial assessment.

During the first 2 months after surgery, visits were weekly. Then, visits were scheduled to be monthly. Patients had open access to clinical health care team within follow-up. Phone contacts and short visits are performed in both groups for collecting self-monitored blood glucose and for adjusting treatment if needed.

Treatment offered to subjects in the control arm was not standardized, but should include pharmacological and nonpharmacological best approach according to current national guidelines [14] that are quite similar to American Diabetes Association–European Association for the Study of Diabetes joint consensus treatment for T2DM [15]. Counseling regarding diet and exercise was made by a nurse, a dietician, and endocrinologists from the clinical team.

The primary end points of the study were changes in glycated hemoglobin (A1C), fasting glucose (FG), and in insulin dosage requirement. Secondary comparisons were changes in anthropometric variables: body weight, distribution and composition, and changes in metabolic variables: lipid profile and liver function and systemic blood

pressure. Participants were considered controlled for diabetes if they had A1C < 6.5% according to consensus of Brazilian Diabetes Society and other international diabetes societies.

Clinical Assessment

Clinical examination, medical history, and application of informed consent were made by consultant endocrinologists. Body weight, height, and circumferences were obtained for a trained dietician. Bioelectrical impedance was used for assessing body composition (BIA-Biodynamics) using standard protocol [16].

Laboratory Methods

After a 12-h overnight fasting period, blood samples were collected for measurements of glucose, cholesterol, HDL-Chol, and triglycerides by enzymatic methods. LDL-Chol was calculated by the Friedwald method. A1C was measured by high-performance liquid chromatography assay periodically calibrated according to worldwide consensus on standardization of the hemoglobin A1C measurement [17].

Surgical Procedure

In the open surgery for gastrojejunal bypass, the gastric volume is maintained intact, while the entire duodenum and proximal jejunum is bypassed. Surgery has gastroenterotomy with an alimentary limb measuring of 100 cm, a biliopancreatic limb of 80 cm from the Treitz ligament, and a common limb comprising the remainder of the small intestine. The details of the procedure are illustrated in Fig. 1.

Statistical Analysis

Because we have 100% of follow-up in this small sample of subjects, we performed per-protocol analysis for comparisons. Data were expressed by mean and standard deviation (SD). Counts and percentages are displayed for categorical data.

Results

Participants recruited from nonsurgical group were matched for the following variables: age (50 vs.

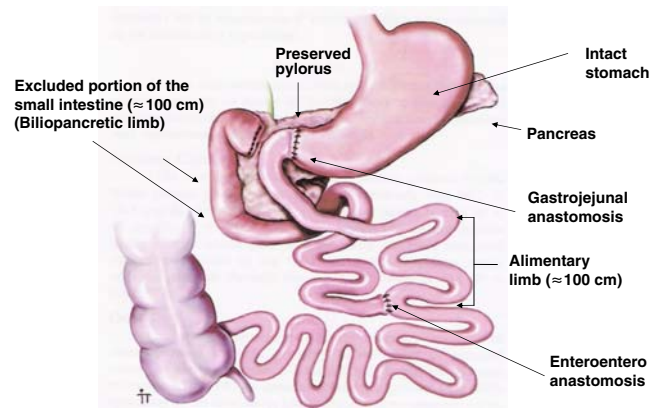


Fig. 1 Gastrojejunal bypass (GJB). The duodenum is separated from the stomach, and the bowel continuity is interrupted at 80 cm from the ligament of Treitz. Distal jejunum is connected to the preserved pylorus, and the biliopancreatic limb is reconnected to the alimentary limb at a distance of 100 cm from the gastrojejunal anastomosis. Adapted with permission from Rubino and Marescaux [12]

49.8 years, GJB and CG respectively), gender (nine male in each group), BMI (26.1 vs. 26.3 kg/m²), baseline A1C (8.78% vs. 8.91%), fasting C-peptide (4.0 vs. 3.7 ng/mL), time of diagnosis (9 vs. 8 years), time of use of insulin (6.0 vs. 5.5 months), and total insulin dosage requirements (39 vs. 49 U/day). No significant differences were observed among these parameters (Table 1).

At baseline and during follow-up, no differences were found among participants in regard to anthropometric measurements (BMI, fat distribution, and body composition) and some biochemical variables (lipid profile and liver function). Besides, no changes on blood pressure were observed (Table 2).

There was a significant improvement on glucose control in both fasting glucose and A1C in surgical group (Fig. 2). Fasting plasma glucose reduced in GJB group [10.2 (2.3) mmol/L at baseline, 7.72 (2.42) at 12 week, and 8.67 (2.22) at 24 week, (Kruskal–Wallis Test, $p=0.015$)]. Hemoglobin A1C reduced in GJB group [8.78 (1.01)% at baseline, 7.32 (0.88)% at 12 weeks, and 7.84 (1.06)% at 24 weeks (Kruskal–Wallis Test, $p=0.008$)] (Fig. 3). At the end of follow-up, two of 12 patients were on target A1C level (below 6.5%) in the GJB group meanwhile none in CG group. Post hoc analysis showed reduction in A1C in GJB group at 24 weeks in comparison to baseline (Mann–Whitney Test, $p=0.045$), but not in fasting glucose levels ($p=0.052$).

There was also a significant reduction on insulin requirements (Fig. 2). In fact, in the GJB group, at 12 and 24 weeks after surgery three and two of 12 patients remained on insulin therapy. All patients in CG remained on insulin therapy. Other medications such as metformin and glibenclamide were adjusted according to patients'

Table 1 Main clinical characteristics of patients

Baseline characteristics	Control group	Gastrojejunal bypass group
Age (years)	49.8 (4.6)	50.0 (5.3)
BMI (kg/m ²)	26.3 (1.2)	26.1 (1.7)
Time of diagnosis (years)	8 (3)	9 (2)
Fasting glucose (mmol/L)	9.7 (2.8)	10.2 (2.3)
HbA1C (%)	8.93 (2.14)	8.78 (1.01)
Insulin dosage (units/day)	49 (14)	39 (12)

Data are shown as mean (standard deviation). There are no differences between groups

requirements until the usual maximum dosage of 2.55 g for metformin and 15 mg of glibenclamide in both groups.

Adverse Events

Two patients developed superficial mild wound infection, which resolved with oral antibiotics. Ten patients experienced eating difficulties and persistent nausea during the first 2- to 4-week period after surgery. Among them, six patients presented clinically relevant vomiting. Dietary counseling in conjunction with proton-pump blockers had improved the symptoms. Minor hypoglycemic events occurred in three operated patients before insulin withdrawal.

In the control group, minor hypoglycemic events are the main adverse effects experienced for ten of 12 patients during follow-up.

Discussion

The major finding of this study is to demonstrate that duodenal–jejunal exclusion is an effective treatment for

nonobese type 2 diabetic subjects during 24 weeks after surgery. Patients that are submitted to this surgical technique had achieved better glucose control along with reduction on insulin requirement. Some improvement on glycemic control was also observed in control group due to optimization of current medical therapy.

Several studies examining thousands of people with T2DM undergoing RYGB had demonstrated improvement of glycemic control in almost all patients, meanwhile patients enjoyed a complete resolution of their disease in above 80% of cases [18]. Diabetic control must be related to improvement in insulin resistance secondary to caloric restriction and weight loss [19]. An attractive candidate mediator of the antidiabetic effect of RYGB is GLP-1. After RYGB, ingested nutrients reach the hindgut readily, bypassing part of the foregut. This morphofunctional modification in gastrointestinal transit leads to an improvement in GLP-1 production stimulating insulin secretion [20]. Exploring this hypothesis, Rubino and Mariscaux [12] provide additional data operating Goto–Kakizaki rats, a spontaneous nonobese model of T2DM using a gastrojejunal bypass. In the present study, we also submitted T2DM patients to a surgery that isolated the effects of

Table 2 Evolution of anthropometric and metabolic parameters after 24-week interventional surgical study

	Control group		Surgical group	
	Baseline	24weeks	Baseline	24weeks
BMI (kg/m ²)	26.3 (1.2)	24.2 (1.6)	26.1 (1.7)	25.6 (1.2)
Waist/hip ratio	0.96 (0.05)	0.94 (0.08)	0.98 (0.04)	0.94 (0.06)
% Fat mass	26 (8)	25 (9)	27 (6)	25 (7)
Fasting glucose (mmol/L)	9.7 (2.8)	9.4 (3.0)	10.2 (2.3)	8.7 (2.2)
Glycated hemoglobin (%)	8.8 (1.0)	8.7 (0.9)	8.9 (2.1)	7.8 (1.1)*
Total cholesterol (mg/dL)	192 (24)	189 (32)	188 (26)	173 (40)
HDL-Cholesterol (mg/dL)	37 (8)	39 (9)	40 (7)	36 (6)
LDL-Cholesterol (mg/dL)	108 (27)	107 (31)	109 (34)	91 (33)
Triglycerides (mg/dL)	234 (128)	216 (103)	250 (136)	236 (187)
Systolic BP (mmHg)	128 (18)	125 (14)	134 (26)	123 (12)
Diastolic BP (mmHg)	83 (17)	80 (10)	87 (16)	78 (8)
Uric Acid (mg/dL)	5.4 (2.2)	5.2 (1.9)	5.6 (2.1)	5.3 (1.8)
AST (IU/L)	22 (10)	23 (11)	23 (6)	20 (4)
ALT (IU/L)	27 (10)	25 (9)	29 (12)	24 (5)
GammaGT (IU/L)	30 (12)	28 (5)	32 (11)	26 (11)

Data are shown as mean (SD)

BMI body mass index, HDL high-density lipoprotein, LDL low-density lipoprotein, BP blood pressure, AST aspartate aminotransferase, ALT alanine aminotransferase, GammaGT gamma-glutamyltransferase

* $p < 0.05$ (difference between baseline and 24 weeks)

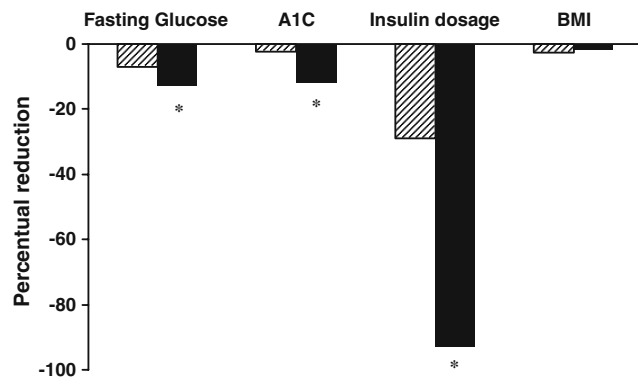


Fig. 2 Glucose control, insulin requirements, and BMI after 24-week intervention study in controls (CG; hatched bar) and surgically treated patients (GJB; filled bars). $p < 0.01$ between groups (95%CI)

RYGB that are related to gastric restriction and bypass. The stomach was not perturbed, but food was diverted from pyloric area to proximal jejunum with a gastrojejunal anastomosis exploring the hypothesis that a modulatory effect on incretin production could lead to better glycemic control independent of weight loss.

Our patients were not obese, and we did not expect a significant weight loss after surgery. In fact, they lost some amount of weight in the first period of 12 week closely related to dyspeptic symptoms, but at 24 weeks, both groups had the same BMI and no significant changes in comparison to baseline. The residual weight loss of about 2% could also influence the diabetic control. Some patients experienced adverse symptoms probably related to a pyloro paresis after surgical manipulation. The use of proton pump inhibitors for 3 months had prevented or treated these problems with success in all patients.

Glycemic control was improved in both groups. Control group had significant reduction on fasting glucose, but a nonsignificant reduction on A1C and on insulin requirement after 24-week follow-up. This modest clinical improvement was probably related to intensive follow-up, glucose monitoring, and greater adherence to recommendations similar as reported in clinical trials placebo-controlled [21]. Surgical group had the same follow-up and beneficial influences of self-monitoring and intensive clinical assistance, but the magnitude of the clinical effect overcame the findings observed in control group. The reduction on A1C remained significant in GJB group at 24 weeks in comparison to baseline. Otherwise, just only two of 12 patients reached target A1C below 6.5%. Insights from this and other studies will facilitate the development of new treatments that can achieve some beneficial effects in other diabetic phenotypes.

The design had some bias in sample collection. One obvious limitation of the present study is that the two treatments were not randomly assigned. This was why the ethics committee did not approve of a randomized design for a new developing surgical procedure. Both groups were matched for age, sex, BMI, and time of diagnosis. Furthermore, people who volunteer for clinical studies often differ from those who decline to participate. Volunteers may be more inclined to trust the health care system. We have tried to minimize this problem, giving them the same frequency of visits and similar nonpharmacological approach and counseling regarding to diet, exercise, and self-monitoring assessments.

A potential confounding factor was the presence of dyspeptic symptoms just after surgery, leading to caloric restriction and additional improvements on glucose control and reduction on insulin requirement. In fact, GJB experienced better outcomes in the first 12-week period, probably related to difficulties in eating with caloric restriction and consequent weight loss. Otherwise, after 24 weeks, both groups had the same BMI, and there are no differences in food consumptions, but the GJB group had still better glycemic control and reduced insulin requirement.

As observed by Rubino et al. using an animal model, our patients had their diabetes improved with better results than clinical approaches. Goto–Kakizaki rats were considered cured for diabetes after surgery. In our trial, there is no patient that could be considered cured for diabetes. In fact, 100% of them had experienced improvements in glycemic control, but all of them were still taking oral antidiabetic medications. Considering that insulin resistance is a major defect on T2DM, the present operation probably did not contribute to enhancement on insulin sensitivity. Limitations of our study do not allow to establish which

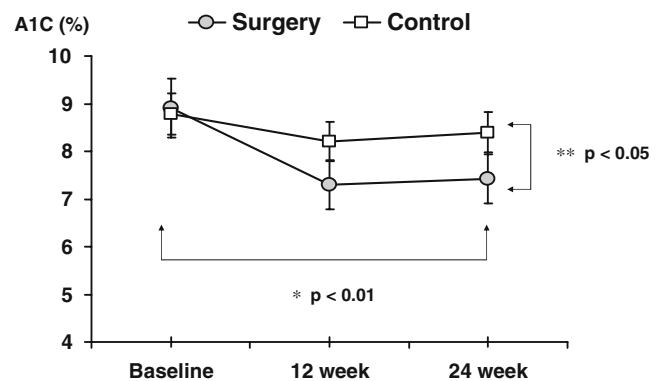


Fig. 3 Hemoglobin (A1C) changes in nonobese T2DM controls with standard care (CG) and nonobese T2DM submitted to duodenal-jejunal exclusion (GJB). There is significant reduction in surgical group within follow-up (Kruskal–Wallis Test). At 24 weeks, GJB had reduced A1C in comparison to CG (Mann–Whitney U Test)

underlying physiopathological mechanisms are affected. There is a report demonstrating beneficial findings for T2DM submitted to GJB [22]. In this communication, authors presented two patients who ameliorated their diabetic control after surgery, but they were on oral agents alone and had preoperative A1C well controlled. In our study, we selected just only patients taking insulin with no satisfactory glycemic control, in which some additional measure or intensification of treatment would be necessary.

The adverse events observed in this trial were partially expected. Dispeptic symptoms were quit high leading to extra medical care and use of medications. In fact, the surgical procedure could modulate the antro-pyloric motility by affecting gut hormone production, such as raising GLP-1 levels. Furthermore, some degree of diabetic autonomic dysfunction is commonly observed in patients with uncontrolled T2DM contributing to dyspeptic symptoms.

In addition to superior glycemic control, this study demonstrated significant reduction on insulin requirements. Only two of 12 patients were still on insulin therapy. This reduction on insulin use and total daily dosage could not be explained by reduction on weight, caloric restriction, or raise on oral medications. In fact, both groups had no changes on weight, and they used similar dosage of oral antidiabetic agents during follow-up. The antidiabetic effect by the surgery itself could be considered superior to any current antidiabetic single agent other than insulin. The results achieved by the surgical group resemble those found in intensive medical therapies using multiple hypoglycemic strategies. Multiple pharmacological therapies have additional problems regarding to low rates of adherence and high rates of side effects and hypoglycemic events [23]. On the other hand, low rates of adherence could also be expected regarding to prescribed supplements of vitamins and oligoelements after surgeries.

The choice of diabetic therapies will likely continue to expand in the coming years. Conventional gastrointestinal operations (RYGB and BPD) provide new opportunities to treat T2DM. Although the impact of bariatric surgery on T2DM in obese patients is impressive, this evidence comes from diabetic who have undergone bariatric surgery primarily for other reasons related to obesity. An expanding indication for a metabolic surgery for nonobese type 2 diabetic patients is a new frontier for the surgical approach. Gastrointestinal tract coordinates the largest collection on endocrine and immune cells in the body. Then, the indication of surgical approach for nonobese T2DM must be viewed with caution [24]. Whether duodenal–jejunal exclusion will prove therapeutically and safe for treatment of human type 2 diabetes in nonobese requires careful assessment in properly controlled clinical trials. Hence, long-term assessment will be important to define potential

advantages or disadvantages for glycemic control and ultimately for long-term diabetic complications.

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