Effect of Duodenal–Jejunal Bypass Surgery on Glycemic Control in Type 2 Diabetes: A Randomized Controlled Trial

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Objective: To determine whether upper gastrointestinal tract (UGI) bypass itself has beneficial effects on the factors involved in regulating glucose homeostasis in patients with type 2 diabetes (T2D).

Methods: A 12-month randomized controlled trial was conducted in 17 overweight/obese subjects with T2D, who received standard medical care (SC, n = 7, BMI = 31.7 ± 3.5 kg/m2) or duodenal–jejunal bypass surgery with minimal gastric resection (DJBm) (n = 10; BMI = 29.7 ± 1.9 kg/m2). A 5-h modified oral glucose tolerance test was performed at baseline and at 1, 6, and 12 months after surgery or starting SC.

Results: Body weight decreased progressively after DJBm (7.9 ± 4.1%, 9.6 ± 4.2%, and 10.2 ± 4.3% at 1, 6, and 12 months, respectively) but remained stable in the SC group (P < 0.001). DJBm, but not SC, improved: (1) oral glucose tolerance (decreased 2-h glucose concentration, P = 0.039), (2) insulin sensitivity (decreased homeostasis model assessment of insulin resistance, P = 0.013), (3) early insulin response to a glucose load (increased insulinogenic index, P = 0.022), and (4) overall glycemic control (reduction in HbA1c with fewer diabetes medications).

Conclusions: DJBm causes moderate weight loss and improves metabolic function in T2D. However, our study cannot separate the benefits of moderate weight loss from the potential therapeutic effect of UGI tract bypass itself on the observed metabolic improvements.

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Introduction

Bariatric surgery is the most effective available therapy for patients with type 2 diabetes (T2D). In fact, many patients with T2D who undergo bariatric surgery achieve complete remission of their disease (1,2). It has been proposed that, in addition to the known therapeutic effects of weight loss on glycemic control, surgical procedures that involve anatomical bypass of the upper gastrointestinal (UGI) tract, such as Roux-en-Y gastric bypass (RYGB) surgery, have weight loss-independent effects in ameliorating T2D (3). One of the most compelling arguments for weight loss-independent effects of UGI tract bypass surgery is the observation that remission of T2D without weight loss has occurred in patients who have had duodenal–jejunal bypass (DJB) surgery (4,5).

However, these data are based on case reports and small patient series, which can be influenced by inherent bias associated with observational studies. Randomized controlled trials (RCTs) are considered the most robust method for evaluating the efficacy of an intervention and are needed to reliably demonstrate a cause-and-effect relationship between an intervention and a clinical outcome.

The purpose of the present study was to conduct a 1-year RCT to evaluate the effect of modified DJB surgery (DJB with minimal gastric resection) on glycemic control, oral glucose tolerance, insulin sensitivity, β-cell function, and diabetes remission in patients with T2D. This procedure involves creating a duodenojejunostomy, which prevents ingested nutrients from direct contact with the duodenum.
and proximal jejunum, in conjunction with resection of the gastric fundus to reduce the risk of impaired gastric emptying observed after DJB alone. A 5-h modified oral glucose tolerance test (OGTT) was performed in patients randomized to DJB surgery or continued standard care before and at 1, 6, and 12 months after surgery or after beginning standard care.

Methods

Subjects

Between May 2012 and October 2013, a total of 247 potential subjects who were seen at the University Hospital of the Sao Paulo University School of Medicine, Brazil, were screened for this study. Twenty-three of these subjects were considered eligible to participate in the study and were randomized to treatment with either DJB with minimal gastric resection (DJBm) \((n = 12)\) or standard care \((n = 11)\). All subjects had T2D and were overweight (body mass index [BMI] 25.0-29.9 kg/m\(^2\)) or had class I or II obesity (BMI 30.0-39.9 kg/m\(^2\)). Potential subjects who had a history of diabetes for more than 10 years, plasma c-peptide <1 µg/ml, or were being treated with insulin were excluded. Additional exclusion criteria included age \(\geq 65\) years old, previous gastrointestinal surgery, history of cancer in the last 5 years, plasma creatinine \(>1.5\) mg/dl, and alcohol or drug abuse.

During the 12-month follow-up, four subjects in the Standard Care group and two in the Surgery group discontinued the study because they no longer wanted to participate in the study for personal reasons and withdrew consent (Supporting Information Figure S1). Therefore, data were collected and final analyses were performed on a total of 17 subjects, 10 in the Surgery group (age 47 ± 8 years old, BMI \(29.7 ± 1.9\) kg/m\(^2\)) and 7 in the Standard Care group (44 ± 5, BMI \(31.7 ± 3.5\) kg/m\(^2\)).

Study protocol

This study was conducted at the Center of Excellence of Bariatric and Metabolic Surgery, Hospital Oswaldo Cruz, and Department of Surgery, University Hospital, University of Sao Paulo, Sao Paulo, Brazil, and Washington University School of Medicine, St. Louis, MO, USA. The surgical procedure and the 5-h OGTT were performed at The University of Sao Paulo Hospital in Sao Paulo, and the analysis of data and mathematical modeling were conducted at Washington University School of Medicine in St. Louis. All subjects provided written informed consent before participating in this study, which was approved by the Institutional Review Board of University Hospital, University of Sao Paulo. This study was registered in the Current Controlled Trials website (http://ClinicalTrials.gov, NCT01771185).

After subjects fasted for 12 h overnight, they were admitted to the outpatient clinical research unit, where a modified 5-h OGTT was performed. A 5-h OGTT, rather than a 2-h OGTT, was performed to permit assessment of the full time-course of the glucose, insulin, and c-peptide response to glucose ingestion including a nearly complete return to baseline. Subjects stopped taking all hypoglycemic medications 2 days before the OGTT. Baseline blood samples were obtained for plasma glucose, insulin, c-peptide, HbA1C, and lipid profile. Subjects then ingested 75 g of glucose given as a liquid drink, and blood samples were obtained at 10, 20, 30, 60, 90, 120, 150, 180, 240, and 300 min after ingestion to determine plasma glucose, insulin, and c-peptide concentrations.

Subjects randomized to the Standard Care group were treated in accordance to the guidelines provided by the Federal Health Authority of Brazil. Patients were instructed to monitor their blood glucose concentrations every day; at each monthly visit the subject’s dietary habits were reviewed and discussed with the study dietitian (T.S.) and a medical evaluation was performed by the study endocrinologist (T.Z.P.), and medications adjusted accordingly.

Subjects randomized to the Surgery group underwent laparoscopic DJB surgery with partial gastrectomy within 2 weeks of the baseline 5-h modified OGTT. All surgery procedures were performed by the same surgeon (R.C.) at University Hospital, University of Sao Paulo. The surgical technique consisted of a Roux-en-Y duodenoejunostomy in conjunction with a minimal proximal gastrectomy over a 62F bougie, equivalent to a “fundectomy” and resulting in about a 15% reduction in gastric volume (Figure 1). A minimal proximal gastric resection was performed to enhance gastric emptying, because delayed gastric emptying was observed in previous patients who had DJB surgery alone. The duodenum was transected 1-2 cm below the pylorus, and the jejunum was transected 80 cm from the ligament of Treitz. The proximal end of the jejunum was anastomosed end-to-end to the subpyloric duodenum, and the distal end of the jejunum was anastomosed end-to-side to the jejunum, 150 cm from the duodenoejunostomy. Venous thromboembolism prophylaxis was provided by

Figure 1 Diagram of duodenal–jejunal bypass surgery with minimal gastric resection. The duodenum is transected 1-2 cm below the pylorus and the jejunum is transected 80 cm from the ligament of Treitz, forming a 90 cm bilipancreatic limb that is anastomosed to the jejunum, 150 cm from the duodenoejunostomy. The fundus is resected, resulting in a 15% reduction in gastric volume.
| Variable                                | **Standard Care group** | **Surgery group** |
|-----------------------------------------|-------------------------|------------------|
|                                        | Basal       | 1 month | 6 months | 12 months | Basal     | 1 month | 6 months | 12 months |
| Body weight (kg)                        | 95 ± 12     | 95 ± 14 | 95 ± 15  | 94 ± 15   | 85 ± 13   | 79 ± 13 | 77 ± 10 | 77 ± 12   |
| Fasting glucose (mg/dl)                 | 198 ± 59    | 172 ± 43 | 174 ± 55 | 157 ± 50  | 203 ± 64  | 139 ± 22 | 148 ± 45 | 146 ± 26  |
| Fasting insulin (mU/l)                  | 18 (10,31)  | 17 (9,30) | 14 (8,26) | 16 (10,27) | 16 (10,25)| 8 (6,12)| 8 (6,11)| 9 (6,13) |
| HOMA-IR                                 | 8 (4,16)    | 7 (4,11) | 6 (4,9)  | 6 (4,9)   | 8 (5,12)  | 3 (2,4) | 3 (2,6) | 3 (2,5)   |
| HbA1c (%)                               | 8.3 ± 1.0   | 8.4 ± 1.4| 7.6 ± 1.4| 7.7 ± 1.3| 8.7 ± 1.3 | 7.9 ± 1.2| 7.2 ± 1.1| 7.5 ± 1.0 |
| Glucose 2-h OGTT (mg/dl)                | 338 ± 68    | 332 ± 70 | 328 ± 86 | 356 ± 64  | 358 ± 78  | 276 ± 46 | 247 ± 73 | 294 ± 57  |
| Glucose AUC0-300 (mg/dl)                | 87,000 ± 18,000 | 78,000 ± 16,900 | 78,300 ± 23,000 | 80,400 ± 22,100 | 89,200 ± 22,300 | 67,800 ± 11,700 | 66,700 ± 16,800 | 69,000 ± 10,300 |
| OGIS0-180 (ml/min/m²)                  | 244 ± 46    | 272 ± 34 | 264 ± 35 | 260 ± 55  | 266 ± 67  | 324 ± 32 | 298 ± 86 | 306 ± 41  |
| Insulinogenic index0-30                 | 0.19 (0.06, 0.68) | 0.20 (0.06, 0.64) | 0.16 (0.03, 0.77) | 0.19 (0.06, 0.63) | 0.12 (0.05, 0.27) | 0.26 (0.19, 0.36) | 0.30 (0.17, 0.53) | 0.33 (0.19, 0.58) |
| ISR AUC0-300 (pmol/l)                   | 42,700 ± 18,000 | 42,700 ± 20,300 | 39,700 ± 19,800 | 45,300 ± 19,700 | 33,400 ± 14,300 | 36,500 ± 10,300 | 32,000 ± 12,100 | 36,200 ± 12,300 |
| ISR AUC/glucose AUC0-300 (pmol/l/mg/dl) | 0.49 (0.29, 0.83) | 0.54 (0.30, 0.97) | 0.51 (0.26, 1.02) | 0.54 (0.28, 1.03) | 0.36 (0.23, 0.55) | 0.52 (0.39, 0.70) | 0.48 (0.34, 0.69) | 0.50 (0.38, 0.66) |
| Triglyceride (mg/dl)                    | 256 ± 163   | 265 ± 120 | 264 ± 121 | 203 ± 17  | 176 ± 99  | 168 ± 53 | 165 ± 81 | 189 ± 121 |
| HDL-cholesterol (mg/dl)                 | 42 ± 6      | 41 ± 8   | 41 ± 7   | 40 ± 4    | 39 ± 15   | 39 ± 5  | 44 ± 8  | 44 ± 5    |
| LDL-cholesterol (mg/dl)                 | 132 ± 28    | 125 ± 26 | 111 ± 67 | 117 ± 22  | 109 ± 44  | 112 ± 24 | 122 ± 22 | 129 ± 24  |

HOMA-IR = homeostasis model assessment of insulin resistance; OGTT = oral glucose tolerance test; AUC = area under the curve; OGIS = oral glucose insulin sensitivity; ISR = insulin secretion rate.

Values are means ± SD or 95% CI.

**Significant interaction between time and group (P < 0.04).
**Value significantly different from the corresponding value in the Standard Care group, *P* ≤ 0.05 and **P**=0.064.

Value significantly different from the corresponding basal value, *P < 0.05.*
using sequential compressive devices and subcutaneous injections of low molecular-weight heparin during hospitalization. After surgery, all subjects consumed clear liquids for 5 days, followed by pureed food for 5 days, before advancing to a regular diet. All subjects were treated with a proton pump inhibitor for one month after surgery. One subject had a postoperative complication: a duodenal–jejunal anastomotic leak occurred 36 h after surgery, which was surgically repaired without further complications.

Both the Standard Care group and the Surgery group returned at 1, 6, and 12 months to assess body weight, use of diabetes medications, and plasma lipids, and to complete the 5-h modified OGTT test.

Sample collection and analysis
Blood samples were collected in chilled tubes containing sodium ethylenediamine-tetra-acetate and placed on ice. Plasma was separated by centrifugation within 30 min of collection and stored at −80°C until final analyses were performed. Glucose was measured by using the glucose oxidase method. Glycosylated hemoglobin was determined by using HPLC and the Variant II Hemoglobin Testing System (Bio-Rad Laboratories Diagnostic Group, Hercules, CA). Plasma c-peptide and insulin concentrations were determined by using radioimmunoassay (Linco Research, St. Louis, MO).

Calculations
The homeostasis model assessment of insulin resistance (HOMA-IR) \[ \text{fasting insulin (mU/ml)} \times \frac{\text{fasting glucose (mmol/l)}}{22.5} \] (6) was used to provide an index of insulin sensitivity. Insulin sensitivity was also evaluated by using the oral glucose insulin sensitivity (OGIS) index which uses blood samples obtained before and at 120 and 180 min after the 75 g oral glucose load to estimate the glucose clearance rate (ml/min/m²), which has been shown to correlate with values achieved by using the hyperinsulinemic-euglycemic clamp procedure (7). The area under the curve (AUC) for glucose during the 300 min after glucose ingestion was calculated by using the trapezoidal rule (8). Several indices of β-cell function were determined: (1) insulin secretion rate (ISR) calculated by deconvolution of plasma c-peptide concentrations (9); (2) ISR AUC/glucose AUC during the 300 min after glucose ingestion, which is an overall index of β-cell response or sensitivity to glucose (10); and (3) acute insulinogenic index, assessed as the increase in plasma insulin divided by the increase in plasma glucose at 30 min of the OGTT \[ \frac{\text{insulin}_{30} - \text{insulin}_0}{\text{glucose}_{30} - \text{glucose}_0} \] (11).

A scoring system based on the number of medications being taken and medication dose was used to assess the use of diabetes medications (12). For each oral agent prescribed, a numerical score was calculated as the daily drug dose relative to the maximum recommended dose. A composite diabetes medication score for each subject was calculated as the sum of each drug score.

Diabetes remission
The definition of partial and complete remission of diabetes was based on the recommendations of an expert consensus conference held in June 2009 (13). Complete remission was defined as A1C <6.0% and fasting glucose <100 mg/dl (5.6 mmol/l) in the absence of active pharmacologic therapy. Partial remission was defined as A1C <6.5% and fasting glucose 100-125 mg/dl (5.6-6.9 mmol/l) in the absence of active pharmacologic therapy.

Statistical analyses
All data sets were tested for normality according to Shapiro–Wilks, and non-normally distributed variables were log-transformed for analysis and back-transformed for presentation. The difference between DJBm surgery and standard therapy on diabetes control and metabolic variables was assessed by using repeated measures analysis of variance (ANOVA), with time as the within-subjects factor and group (surgery or standard care) as the between-subjects factor. When significant interactions between time and group were found, the effect of time within each group was evaluated by one-way repeated measures ANOVA, and differences between groups at each time point were evaluated by Student’s independent t-test. Results are presented as means with SDs (for normally distributed variables) or 95% CIs (for not-normally distributed variables), unless otherwise indicated. A P-value ≤0.05 was considered statistically significant. Analyses were performed by using SPSS version 19 (SPSS Inc.).

Results
Subject characteristics
Baseline age, BMI, and duration of diabetes of subjects in the Surgery group (47 ± 8 years old, BMI 29.7 ± 1.9 kg/m² [range 25.1-33.8 kg/m²], and duration of diabetes 6 ± 3 years) were not different.
than those in the Standard Care group (44 ± 5 years old and 31.7 ± 3.5 kg/m² [range 26.3-37.6 kg/m²], and duration of diabetes 5 ± 3 years). Baseline metabolic variables, including measures of glycemic control, HOMA-IR, β-cell function, and plasma lipid profile were also not different between groups; OGIS was 9% higher in the Surgery than Standard Care group (P < 0.05) (Table 1).

**Effect of intervention**

**Body weight.** Body weight decreased progressively after DJBm; body weight decreased by 7.9 ± 4.1% at 1 month, 9.6 ± 4.2% at 6 months, and 10.2 ± 4.3% at 12 months (Table 1, Figure 2). In contrast, mean body weight remained within 1% of initial body weight for 12 months in the Standard Care group.

**Glycemic control.** Fasting plasma glucose concentrations were lower than baseline values at 1, 6, and 12 months in both the Standard Care and Surgery groups (P-value for effect of time = 0.011) (Table 1), without any significant differences between groups. In contrast, fasting plasma insulin concentration decreased in the Surgery group at 1, 6, and 12 months but did not change in the Standard Care group (P-value for interaction time × group = 0.027) (Table 1). Plasma HbA1c decreased significantly in both Standard Care and Surgery groups at 6 and 12 months, but there were no significant differences between groups at either time point (Table 1).

**Oral glucose tolerance.** Plasma glucose concentrations obtained 2 h after the oral glucose load were lower at 1, 6, and 12 months after than before surgery, but did not change in the Standard Care group (P-value for interaction time × group = 0.039) (Table 1). The AUCs of plasma glucose concentration during the entire 5-h OGTT were lower at 1, 6, and 12 months than at baseline in both groups (P-value for effect of time = 0.012); although there was a trend toward a greater decline in glucose AUC in the Surgery than the Standard Care group. 

Figure 3 Glucose and insulin time-course during a 5-h oral modified glucose tolerance test (OGTT), in the Standard Care and Surgery groups, before and at 1, 6, and 12 months after surgery or beginning standard care. Data are means ± SEM. There was a significant ANOVA 3-way interaction (OGTT time-course × time × group) for both glucose (P-value = 0.01) and insulin (P-value < 0.001) concentrations; therefore analyses were repeated at each time point separately. Glucose and insulin time-course during the OGTT was different between Standard Care and Surgery groups at 6 months (P-value for interaction OGTT time-course × group for glucose = 0.002 and for insulin = 0.06) and at 12 months (P-value for interaction OGTT time-course × group for both ≤0.03) months.
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The insulinogenic index during the first 30 min after glucose ingestion, which provides an overall index of β-cell response to glucose, was greater at 1, 6, and 12 months after surgery than at baseline in both groups without any differences between groups (P-value for interaction time × group = 0.013) (Table 1). Values for the OGTT index, a measure of glucose clearance, were higher in the Surgery group than the Standard Care group at baseline, and remained greater in the Surgery group than the Standard Care group throughout the study (Table 1).

**Insulin sensitivity.** Mean values for HOMA-IR were lower at 1, 6, and 12 months in the Surgery group than at baseline but did not change in the Standard Care group (P-value for interaction time × group = 0.005) (Table 1). Values for the OGIS index, a measure of β-cell function, were higher in the Surgery group than the Standard Care group at baseline, and remained greater in the Surgery group than the Standard Care group throughout the study (Table 1).

**β-cell function.** The AUC of ISR during the 5-h OGTT was not different between groups at baseline and did not change throughout the study in either group (Table 1). The ratio between ISR AUC and glucose AUC during the 300 min after glucose ingestion, which provides an overall index of β-cell response to glucose, was greater at 1, 6, and 12 months after surgery than at baseline, but did not change in the Standard Care group (P-value for interaction time × group = 0.022) (Table 1). Plasma insulin concentrations during the first 90 min after glucose ingestion increased at 1, 6, and 12 months after surgery but did not change in the Standard Care group (P-value for interaction between insulin time-course during the OGTT and group at 12 months ≤0.03) (Figure 3).

**Medication score.** There was a significant interaction between time and group (P < 0.01) in the composite score for the use of diabetes medications, because the score increased in the Standard Care group by 26%, 52%, and 70% (P = 0.057), whereas it decreased in the Surgery group by 29%, 33% and 19% (P = 0.068), at 1, 6, and 12 months, respectively (Figure 4). The inability to detect a statistically significant increase in medications in the Standard Care group alone and a statistically significant decrease in medications in the Surgery group alone is likely due to inadequate power because of the small number of subjects.

**Discussion**

We conducted a 1-year RCT to help determine whether bariatric surgical procedures that bypass the UGI tract have important weight loss-independent therapeutic effects in patients with T2D. Accordingly, overweight and obese patients with T2D were randomized to receive either standard care or undergo DJBm. Compared with standard care, DJBm demonstrated several beneficial effects on glucose homeostasis, specifically an improvement in: (1) oral glucose tolerance (decreased 2-h OGTT glucose concentration), (2) insulin sensitivity (decreased HOMA-IR and increased OGIS), (3) the early insulin response to a glucose load (increased insulinogenic index), and (4) overall glycemic control (reduction in HbA1c with less diabetes medications).

The results from the present study provide additional insights into the mechanism responsible for RYGB-induced weight loss. Although both RYGB and DJBm involve anatomical bypass of the UGI tract, weight loss after RYGB is usually threefold greater than the weight loss we observed after DJBm. Furthermore, weight loss after DJBm was greater than the weight loss we previously found after DJB alone (12). In total, these findings suggest that resection or bypass of the stomach per se, rather than bypass of the UGI tract, is primarily responsible for weight loss induced by RYGB surgery.

The potential importance of the stomach in regulating food intake is further supported by the considerable weight loss observed after sleeve gastrectomy (1), which removes a large portion of the stomach but does not divert ingested food away from the UGI tract.

The results from several RCTs have demonstrated that RYGB surgery is more effective than intensive medical therapy in achieving successful glycemic control in patients with T2D, and about half of the patients who have RYGB surgery with a marked 25-30% weight loss achieve complete remission of diabetes (defined as HbA1c <6.0% without diabetes medications) by 1 year after surgery (1,2). In contrast, none of our subjects who had DJBm with moderate 10% weight loss achieved diabetes remission. It is unlikely that the absence of diabetes remission in our subjects was due to severe and refractory diabetes; none of our subjects had any features that have been associated with poor remission rates, including being treated with insulin, a long duration of diabetes, or age ≥65 years old (1). Therefore, these results suggest that >10% weight loss is needed to achieve diabetes remission in patients who have had UGI tract bypass.
bypass. Nonetheless, our data do not mean that UGI tract bypass itself does not contribute to an improvement in glycemic control observed after RYGB.

An important limitation of our study is the absence of a weight loss-matched control group, which would have been able to separate the effects of moderate weight loss from UGI tract bypass on our different assessments of metabolic function. Nonetheless, this limitation does not affect our observation that DJBm did not induce diabetes remission in any subject, despite experiencing a 10% weight loss. In addition, our study demonstrates the importance of including a control group in this type of study. Subjects randomized to standard care demonstrated improvements in glycemic control without a change in body weight, presumably caused by an increase in the use of diabetes medications.

In summary, we found that DJBm surgery improved metabolic function and glycemic control in overweight and obese subjects with T2D. However, this procedure also caused a 10% weight loss, so it is not possible to separate the effect of UGI tract bypass from weight loss itself on the therapeutic effects of surgery. DJBm did not induce diabetes remission in any subject, which suggests that another factor(s), possibly the nearly threefold greater weight loss observed after RYGB than DJBm, is an important contributor to glycemic control after RYGB surgery.

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