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Moderate effect of duodenal-jejunal bypass surgery on glucose homeostasis in patients with type 2 diabetes

Samuel Klein¹, Elisa Fabbrini^{1,2}, Bruce W. Patterson¹, Kenneth Polonsky¹, Carlos A. Schiavon³, Jose L. Correa³, Joao E Salles³, Bernardo L. Wajchenberg³, and Ricardo Cohen³

¹Center for Human Nutrition, Washington University School of Medicine, St. Louis, MO, USA

²Center for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele, Rome, Italy

³Center of Excellence of Bariatric and Metabolic Surgery, Hospital Oswaldo Cruz, and Department of Surgery, Hospital Sao Camilo, Sao Paulo, Brazil

Abstract

Gastric bypass surgery causes resolution of type 2 diabetes (T2DM), which has led to the hypothesis that upper gastrointestinal (UGI) tract diversion, itself, improves glycemic control. The purpose of this study was to determine whether UGI tract bypass without gastric exclusion has therapeutic effects in patients with T2DM. We performed a prospective trial to assess glucose and β -cell response to an oral glucose load before and at 6, 9, and 12 months after duodenal-jejunal bypass (DJB) surgery. Thirty-five overweight or obese adults (BMI:27.0 $\pm$ 4.0 kg/m²) with T2DM and 35 sex-, age-, race-, and BMI-matched subjects with normal glucose tolerance (NGT) were studied. Subjects lost weight after surgery, which was greatest at 3 months (6.9 $\pm$ 4.9%) with subsequent regain to 4.2 $\pm$ 5.3% weight loss at 12 months after surgery. HbA1C decreased from 9.3 $\pm$ 1.6% before to 7.7 $\pm$ 2.0% at 12 months after surgery ($P<0.001$), in conjunction with a 20% decrease in the use of diabetes medications ($P<0.05$); 7 (20%) subjects achieved remission of diabetes (no medications and HbA1C <6.5%). The area under the curve after glucose ingestion was ~20% lower for glucose but doubled for insulin and c-peptide at 12 months, compared with pre-surgery values (all $P<0.01$). However, the β -cell response was still 70% lower than subjects with NGT ($P<0.001$). DJB surgery improves glycemic control and increases, but does not normalize the β -cell response to glucose ingestion. These findings suggest that altering the intestinal site of delivery of ingested nutrients has moderate therapeutic effects by improving β -cell function and glycemic control.

Introduction

Overweight and obesity are important risk factors for developing type 2 diabetes mellitus (1). Therefore, it is likely that the increase in the prevalence of overweight and obesity in the last 30 years is an important contributor to the marked increase in the worldwide prevalence rate of type 2 diabetes (2). Diet-induced weight loss improves glucose homeostasis and is recommended by the leading medical societies as the first step of therapy for patients with type 2 diabetes. Unfortunately, effective weight loss with lifestyle intervention is difficult to achieve, and many patients with type 2 diabetes are treated with hypoglycemic agents that

Corresponding author: Samuel Klein, M.D. Washington University School of Medicine 660 South Euclid Avenue Campus Box 8031 St Louis, MO 63110 Phone: (314) 362-8708 Fax:(314) 362-8230 sklein@dom.wustl.edu.

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cause weight gain. Moreover, most patients with type 2 diabetes fail to achieve adequate glycemic control with medical therapy, and ~50% of patients in the general population do not achieve HbA1C <7% (3).

Treatment of patients who have type 2 diabetes with bariatric surgery frequently results in complete resolution of diabetes, usually defined as discontinuation of all diabetes medications in conjunction with normal fasting blood glucose or HbA1c <7%. However, the remission rate of diabetes is not the same among all bariatric surgical procedures. The results from a meta-analysis of 621 studies involving thousands of patients found that the rate of diabetes resolution was greater in patients who had surgical procedures that involved anatomical diversion of the upper gastrointestinal (UGI) tract (e.g. roux-en-Y gastric bypass [RYGB]) than those that simply restricted the stomach (e.g. laparoscopic adjustable gastric banding) (4). In addition, RYGB surgery often results in rapid improvement or resolution of type 2 diabetes before large changes in body weight have occurred (5, 6). These observations have led to the notion that excluding ingested nutrients from the upper gastrointestinal tract has important therapeutic effects on type 2 diabetes that are independent of weight loss (7). However, the interpretation of these clinical results is confounded by differences in weight loss between surgical treatments and by a marked reduction in energy intake after gastric bypass surgery, which could have important effects on metabolic outcomes. Data from studies that evaluated subjects who had RYGB and those who lost the same amount of weight by diet therapy have reported both greater and the same improvement in glucose tolerance or insulin sensitivity in the RYGB group as in the diet group (8, 9).

The recent innovation of duodenal-jejunal bypass (DJB) surgery provides an opportunity to test the hypothesis that UGI tract diversion without marked weight loss improves glucose homeostasis in patients with type 2 diabetes. This procedure involves creating a duodenojejunostomy, which prevents ingested nutrients from direct contact with the duodenum and proximal jejunum, but does not restrict or exclude the stomach. Different beneficial effects of DJB surgery on metabolic outcomes in small numbers of subjects with type 2 diabetes have been reported previously (10–14), supporting the need for a more comprehensive evaluation in a larger group.

The purpose of the present study was to test the hypothesis that bypass of the UGI tract by DJB surgery improves glucose homeostasis and the β -cell response to ingested glucose in overweight and obese patients with type 2 diabetes. Accordingly, we conducted a longitudinal, 12-month study to evaluate the effect of DJB surgery on glycemic control, oral glucose tolerance, and β -cell function in overweight and obese subjects with type 2 diabetes. In addition, a cohort of subjects with normal glucose tolerance, matched on a sex, age, BMI and race with the subjects with type 2 diabetes, served as a comparison group to determine whether changes induced by DJB surgery resulted in complete normalization of metabolic outcomes.

Methods and procedures

Subjects

A total of 70 subjects participated in this study. The following inclusion criteria were required for eligibility in subjects with type 2 diabetes: 1) between 20 and 65 years old, 2) BMI between 23.0 and 34.0 kg/m², 3) treated with diabetes medications, 4) HbA1C > 7.5%, 4) c-peptide > 1 ng/ml, 5) history of diabetes <10 years, 6) no evidence of anti-GAD65, and 7) no previous abdominal surgery. Forty overweight and obese subjects with type 2 diabetes enrolled in the study and underwent DJB surgery. However, 5 subjects withdrew from the study after surgery for personal reasons, did not return for follow-up evaluations, and are

excluded. All 35 subjects with type 2 diabetes were taking oral hypoglycemic agents (33 metformin, 25 sulfonylureas, 7 meglitinides, 15 pioglitazone, 1 dipeptidyl peptidase-4 inhibitor) and 7 subjects (20%) were also being treated with insulin. Subjects had HbA1C values between 7.6% and 13.6%, plasma c-peptide concentration 1 µg/ml, and a history of type 2 diabetes for 10 y (mean duration of diabetes was 7.8 ± 2 y). Ten subjects also had hypertension. Thirty-five overweight and obese subjects with normal glucose tolerance (NGT), determined by a 2-h oral glucose tolerance test (OGTT) were also studied as a comparison group. Subjects with NGT were selected from a group who were studied previously (15), and were matched with type 2 diabetes subjects on age (53.3 ± 7.6 and 52.5 ± 4.7 yrs old in type 2 diabetes and NGT groups, respectively), sex (15 women and 20 men in both groups), race (1 Asian, 4 Black and 30 White adults in both groups), and BMI 27.0 ± 4.0 and 27.0 ± 3.9 kg/m² in type 2 diabetes and NGT groups, respectively). All subjects provided written informed consent before participating in this study, which was approved by the Institutional Review Boards of Hospital Sao Camilo, Sao Paulo, Brazil and Washington University School of Medicine, St. Louis, MO, USA. This study was registered in the Current Controlled Trials website (<http://www.controlled-trials.com/ISRCTN79580044>).

Study protocol

After subjects fasted for 12 h overnight, they were admitted to the outpatient clinical research area, where a 2-h OGTT was performed. Subjects with diabetes stopped taking all hypoglycemic medications 2 days before the OGTT. Baseline blood samples were obtained for plasma glucose, insulin, c-peptide, and HbA1C. Subjects then ingested 75 g of glucose given as a liquid drink, and blood samples were obtained at 30, 60, 90, and 120 min after ingestion to determine plasma glucose, insulin and c-peptide concentrations.

Subjects with diabetes underwent laparoscopic DJB surgery within 2 wks of the OGTT. All medications were stopped the day before surgery. All DJB procedures were performed by the same surgeons (R.C. and C.A.S.). A Roux-en-Y duodenojejunostomy with a 50 cm biliopancreatic limb and an 80 cm Roux limb was constructed. The duodenum was transected 1–2 cm below the pylorus, and the jejunum was resected 50 cm from the ligament of Treitz. The proximal end of the jejunum was anastomosed end-to-end to the duodenum, and the distal end of the jejunum was anastomosed end-to-side to the jejunum, 80 cm from the duodenojejunostomy (Figure 1).

After surgery, all subjects consumed clear liquids for 5 days, followed by pureed food for 5 days before advancing to a regular diet. Subjects were discharged from the hospital 2–5 days after surgery. Several complications occurred after surgery. Nausea and vomiting occurred in 7 (20%) subjects during the early postoperative period; 4 of these subjects were readmitted to the hospital for rehydration and anti-emetic therapy. Nausea and vomiting completely resolved in all subjects within 2 weeks after surgery. One subject was hospitalized for 6 days after surgery because of pancreatitis, which resolved with conservative therapy. One subject was hospitalized 7 months after surgery because of intestinal obstruction, which was managed conservatively without surgery.

Subjects returned at 3, 6, 9 and 12 months after surgery to assess body weight and obtain baseline blood samples. In addition, the OGTT test performed before surgery was repeated at 6, 9 and 12 months after surgery. It was assumed that the potential confounding post-operative effects of reduced energy intake and inflammation on metabolic outcome would be minimal by 6 months after the operation.

Sample collection and analysis

Blood samples were collected in chilled tubes containing sodium ethylenediamine-tetraacetate 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 in subjects with NGT were determined by using radioimmunoassay (Linco Research, St.Louis, MO). Plasma c-peptide and insulin concentrations in subjects with type 2 diabetes were determined by using an electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN). Radioimmunoassay and electrochemiluminescence provide similar results for c-peptide and insulin with an intraclass correlation coefficient between the two methods of 0.952 for c-peptide and 0.992 for insulin.

Calculations

The homeostasis model assessment of insulin resistance HOMA-IR [fasting insulin ($\mu\text{U}/\text{mL}$) $\times$ fasting glucose (mmol/L) / 22.5] (16), was used to provide an index of insulin sensitivity. The incremental increase in the area under the curve above baseline (iAUC) for glucose, insulin, and C-peptide during the 120 min after glucose ingestion were calculated by using the trapezoidal rule. Several indices of β -cell function were determined (17): 1) c-peptide secretory response measured as c-peptide iAUC $\div$ glucose iAUC during the 120 min OGTT; 2) total insulinogenic index (IGI120) assessed as the insulin iAUC $\div$ glucose iAUC during the 120 min OGTT; and 3) acute insulinogenic index (IGI30) assessed as the increase in plasma insulin divided by the increase in plasma glucose at 30 min of the OGTT [(insulin₃₀ – insulin₀) $\div$ (glucose₃₀ – glucose₀)]. An index of plasma insulin residence time was calculated as (insulin AUC/c-peptide AUC), assuming that a higher insulin/c-peptide ratio reflects a longer insulin residence time because insulin and c-peptide are secreted at equimolar rates.

A scoring system based on the number of medications being taken and medication dose was used to assess the use of diabetes medications. For each oral agent prescribed, a numerical score was calculated as the daily drug dose relative to the maximum recommended dose (18). For insulin, a numerical score was calculated as the daily insulin dose relative to a standard dose of 1 U/kg/day. A composite diabetes medication score for each subject was calculated as the sum of each drug score.

Statistical analyses

The effect of DJB surgery was assessed by using two-way repeated measures analysis of variance for fixed effects; time served as the within-subjects factor (before vs. 3, vs. 6, vs. 9, vs. 12 months after surgery); differences between time points after surgery and baseline were assessed with simple contrast. The statistical significance of differences between values obtained from subjects with NGT and values obtained from subjects with type 2 diabetes 12 months after DJB surgery were evaluated by using t-test for independent samples. A p-value <0.05 was considered statistically significant. Unless otherwise stated, all results are mean $\pm$ SD. Analyses were performed by using SPSS 18.0 (SPSS Inc., Chicago, IL).

Results

Body weight

Body weight decreased after DJB surgery (Table 1). Weight loss was greatest ($6.9 \pm 4.9\%$) in the first 3 months after surgery with a gradual increase subsequently toward baseline. Five subjects weighed more at 12 months than before surgery.

Glycemic control

Values for plasma HbA1C decreased from $9.3 \pm 1.7\%$ before surgery to $6.5 \pm 1.2\%$ at 3 mos after surgery ($P < 0.001$), but increased progressively thereafter to $7.4 \pm 1.7\%$ at 12 months (Table 1). Nonetheless, plasma HbA1C at 12 months after surgery was still lower than preoperative values ($P < 0.001$). The composite score for the use of diabetes medications decreased by 29% ($P < 0.01$), 34% ($P < 0.001$), 24% ($P < 0.01$) and 20% ($P < 0.05$) at 3, 6, 9, and 12 months after surgery, respectively, compared with the value obtained before surgery (Table 2). Seven subjects, who were being treated with oral agents for diabetes (metformin alone or in combination with sulfonylureas, pioglitazone, and/or repaglinide) achieved “remission” of diabetes and discontinued the use of all diabetes medications by 12 months after surgery (medications were stopped in 2 subjects at 3 months, 3 subjects at 6 months, and 2 subjects at 12 months). These subjects had a mean HbA1C of $8.5 \pm 0.9\%$, before surgery while being treated with diabetes medications and a mean HbA1C of $5.8 \pm 0.5\%$ (all had HbA1C $< 6.5\%$ and 3 had HbA1C $< 6.0\%$) at 12 months after surgery without diabetes medications. However, mean fasting blood glucose was 139 ± 36 mg/dL for this group, and only one subject had a fasting blood glucose value < 126 mg/dL. There was no relationship between the decrease in HbA1C (expressed as either absolute or relative change from baseline HbA1c) and the percent decrease in body weight at 3, 6, 9 or 12 months (Pearson correlation coefficients, $P > 0.05$), or when evaluated by both weight change tertiles, and a repeated measures mixed model approach (p values for the interaction time $\times$ percent weight change ranged from 0.13 to 0.68). In addition, percent weight loss was not different in the 7 subjects who were able to stop all diabetes medication compared with 7 subjects who had the highest HbA1C values at 12 months.

Oral glucose tolerance

Glucose concentration during the OGTT was lower, whereas insulin and c-peptide concentrations were higher, at all postoperative time points (6, 9, and 12 months after surgery data are averaged together) (Figure 2). The iAUC of plasma glucose concentrations after 75 g glucose ingestion during the OGTT was $\sim 20\%$ less at 6, 9, and 12 mos after DJB surgery than before surgery ($P < 0.01$) (Table 1). There was no relationship between the decrease in glucose iAUC and % decrease in body weight at 6, 9 or 12 months (Pearson correlation coefficients, $P > 0.3$) or when evaluated by weight change tertiles.

β -cell function

The iAUC of plasma c-peptide and insulin concentrations after glucose ingestion during the OGTT at 6, 9, and 12 mos after surgery was approximately double the value obtained before surgery ($P < 0.001$) (Table 1). The increase in plasma insulin concentration during the OGTT after surgery was not likely caused by alterations in insulin residence time from plasma, because the ratio of insulin AUC to c-peptide AUC did not change (Table 1). All indices of pancreatic β -cell response to glucose ingestion were also 2–3 fold higher at 6, 9 and 12 months after surgery than before surgery, including the c-peptide secretory response (c-peptide iAUC $\div$ glucose iAUC) ($P < 0.001$), total insulinogenic index (IGI120) ($P < 0.001$), and the acute insulinogenic index at 30 min (IGI30) ($P < 0.05$ at 6 mos, $P < 0.001$ at 9 and 12 mos) (Figure 3).

Insulin resistance

Mean values for HOMA-IR after surgery were not different than the mean value obtained before surgery (Table 1).

Excluding the 7 subjects who were being treated with insulin at baseline did not change the statistical significance of any data on body weight, glycemic control, OGTT, β -cell function or insulin sensitivity (data not shown).

Comparison of DJB surgery and NGT groups

The NGT group had normal fasting blood glucose (93 ± 7 mg/dL) and normal plasma glucose at 2 h after ingesting a 75 g glucose load (115 ± 16 mg/dL). Despite the improvement in glucose and insulin response to an oral glucose load after DJB surgery in subjects with diabetes, values for glycemic control (HbA1C) (Table 1), HOMA-IR (Table 1), glucose, insulin and c-peptide after an oral glucose load (Table 1, Figure 2), and pancreatic β -cell response (Figure 3) were considerably better in the NGT group than the DJB surgery group (all $p < 0.001$). Subjects with type 2 diabetes had faster insulin clearance rates than subjects with NGT both before and after surgery, as indicated by a lower insulin AUC/c-peptide AUC ratio ($P < 0.001$) (Table 1).

Discussion

Type 2 diabetes has become a major public health problem in many countries throughout the world because of its high and increasing prevalence rates, causal relationship with serious medical complications, adverse effects on quality-of-life, and economic burden (19). Data from patients who have had RYGB surgery suggest that bypass of the UGI tract itself has important weight loss-independent effects on glucose homeostasis in obese patients with type 2 diabetes (5, 6). However, this hypothesis has never been adequately tested in people. In the present study, we evaluated the efficacy of UGI bypass without gastric restriction or resection on glycemic control and β -cell function in overweight and obese subjects with type 2 diabetes. Our data demonstrate that DJB surgery causes moderate weight loss and improves, but does not normalize, glucose tolerance, the β -cell response to an oral glucose load, and HbA1C. Although 7 subjects (20%) maintained an HbA1C value of $< 6.5\%$ and discontinued all diabetes medications, most of these subjects still had fasting hyperglycemia. Therefore, DJB surgery did not result in the high rate of diabetes remission reported after RYGB surgery, suggesting that marked weight loss or gastric exclusion or both have important therapeutic effects. These findings have important implications in understanding the mechanisms responsible for glucose control induced by RYGB surgery and in considering potential treatment options for patients with type 2 diabetes.

It is likely that enhanced beta-cell function, not an increase in whole-body insulin sensitivity contributed to the improvement observed in glycemic control after DJB surgery. All indices of β -cell responsiveness to glucose ingestion (plasma insulin and c-peptide concentrations during the OGTT, c-peptide secretory response, total insulinogenic index, acute insulinogenic index, and insulinogenic index relative to insulin resistance) increased 2–3 fold after DJB surgery, but was still much lower than in our subjects with NGT. In addition, DJB surgery did not restore the early-phase of insulin secretion observed after RYGB surgery (8). Therefore, these results suggest that UGI tract bypass, itself, increases the insulin response to oral glucose ingestion, but does not normalize, β -cell function.

The precise mechanism responsible for the enhanced insulin response cannot be determined from our study, but could be due to rapid jejunal delivery and absorption of ingested glucose, an augmented incretin response, particularly an increase in GLP-1 secretion that has been shown previously after RYGB and DJB surgery (8, 14), improved glycemic control with potential amelioration of β -cell glucose toxicity (20), or other, yet unknown, mechanisms. In contrast, we did not detect a beneficial effect of DJB surgery on “insulin sensitivity”, determined by HOMA-IR. This observation is consistent with data from studies conducted in rodent models that found DJB surgery did not affect hepatic or skeletal muscle

insulin sensitivity, determined by using the hyperinsulinemic-euglycemic clamp technique (21, 22). Insulin clearance rate did not change after DJB surgery, but the subjects with type 2 diabetes had faster insulin clearance rates than the NGT group, consistent with previous reports that hepatic insulin extraction is greater in subjects with type 2 diabetes than in normal volunteers (23).

Weight loss improves glycemic control and is an important therapeutic goal in the management of overweight and obese patients with type 2 diabetes. Therefore, we cannot exclude the possibility that DJB surgery-induced weight loss in our subjects was responsible for their improvement in glycemic control or β -cell function. However, we were unable to detect a significant relationship between percent weight loss and improvement in any metabolic outcome. In fact, there was no difference in improved glucose homeostasis between subjects who were in the highest and lowest tertiles of weight loss. In addition, data obtained from other studies conducted in patients with type 2 diabetes demonstrate that the amount of weight loss achieved by our subjects does not increase the insulin response to an oral glucose load (8), usually results in a smaller reduction in HbA1C (24), and does not increase skeletal muscle insulin sensitivity (25). However, moderate weight loss can improve hepatic insulin sensitivity and decrease endogenous glucose production (25), so it is likely that weight loss contributed to the beneficial effects observed in our subjects.

Our study has several important limitations. First, we did not study a weight loss-matched control group, which would have allowed us to separate the effects of moderate weight loss from UGI tract bypass on our study endpoints. Second, our study did not involve sensitive methods, such as the hyperinsulinemic-euglycemic clamp technique, to evaluate insulin sensitivity, so an effect of DJB on insulin sensitivity could have been missed. However, data from carefully performed studies in rodent models found DJB surgery does not alter hepatic or skeletal muscle insulin action (21, 22). Third, we stopped our subjects' diabetes therapy for 2 days before each testing period, so there might have been residual medication effects on glucose metabolism in the 16 subjects (46%) who were taking pioglitazone or a dipeptidyl peptidase-4 inhibitor. Although the effect of these medications on the baseline studies might have made it more difficult to detect a beneficial effect of surgery, no differences in outcomes were observed between subjects treated and not treated with a TZD or a DPP-4 inhibitor. Fourth, we did not measure incretins or other factors that could have helped explain the mechanism responsible for the augmented insulin response to glucose ingestion. Data from other studies have found that DJB increases the GLP-1 response to an oral glucose load (14), which likely contributed to the increase in insulin observed in our subjects.

In summary, DJB surgery improves β -cell function and glycemic control in overweight and class I obese subjects with type 2 diabetes. These findings have important implications in understanding the factors involved in the pathogenesis of type 2 diabetes, and suggest that altering the intestinal site of delivery of ingested nutrients has therapeutic effects, but cannot exclude the potential contribution of moderate weight loss on our study outcomes. Further studies are needed to further elucidate the mechanism(s) responsible for the link between UGI tract-nutrient interactions and the regulation of metabolic function. The results from our study should not be considered as an endorsement of DJB surgery in clinical practice; randomized, controlled trials that compare DJB surgery with optimal medical management or other bariatric surgical procedures are needed to carefully evaluate the safety and efficacy of DJB surgery as a potential therapy for diabetes.

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Figure 1.
Schematic representation of duodenal-jejunal bypass surgery

Figure 2. Glucose (A), insulin (B) and c-peptide (C) concentrations during a 75 g oral glucose load. Values from the three postoperative studies, obtained at 6, 9 and 12 months after surgery, are averaged together. Results are mean $\pm$ SEM. Value significantly different from correspondent pre-operative time point, * $P < 0.001$, ‡ $P < 0.05$

Figure 3.

Pancreatic β -cell function was assessed by the response to a 75 g oral glucose load, determined as the c-peptide secretory response [c-peptide iAUC ($\mu\text{g}/\text{mL} \times 120 \text{ min}$) $\div$ glucose iAUC ($\text{mg}/\text{dL} \times 120 \text{ min}$)] (A), the total insulinogenic index over 120 min [IGI120: insulin iAUC ($\mu\text{U}/\text{mL} \times 120 \text{ min}$) $\div$ glucose iAUC ($\text{mg}/\text{dL} \times 120 \text{ min}$)] (B), and the acute insulinogenic index at 30 min [IGI30: $\Delta \text{insulin}_{30-0}$ ($\mu\text{U}/\text{mL}$) $\div$ $\Delta \text{glucose}_{30-0}$ (mg/dL)] (C) before and at 6, 9 and 12 months after duodenal-jejunal bypass surgery. Values at 12 months are also expressed as a percent of the value obtained in subjects with normal glucose tolerance (NGT), matched on age, sex, race and body mass index (white bar, right axis). Results are mean $\pm$ SEM. Value significantly different from basal pre-operative value, * $P < 0.001$, ‡ $P < 0.05$

Table 1

Metabolic variables during basal conditions and during an oral glucose tolerance test in subjects before and after duodenal-jejunal bypass surgery and subjects with normal glucose tolerance

	Before Surgery	3 months DJB	6 months DJB	9 months DJB	12 months DJB	Normal Glucose Tolerance
Weight (kg)	79.4 ± 11.9	73.8 ± 11.3 *	74.7 ± 10.9 *	75.5 ± 11.2 *	75.9 ± 12.4 *	81.2 ± 16.3
BMI (kg/m ²)	27.0 ± 4.0	25.2 ± 3.8 *	25.5 ± 3.7 *	25.8 ± 3.8 *	25.9 ± 6.2 *	27.0 ± 3.9
Fasting glucose (mg/dL)	188 ± 75	152 ± 41 ‡	154 ± 39 ‡	161 ± 43 ‡	175 ± 58	93 ± 7 *
Fasting C-peptide (µg/mL)	2.71 ± 0.94	3.06 ± 0.93 ‡	3.61 ± 0.84 *	3.06 ± 0.97	3.16 ± 1.08	1.98 ± 1.04 *
Fasting insulin (µU/mL)	11.9 ± 6.7	13.2 ± 5.3	15.1 ± 7.6	14.1 ± 6.4	14.5 ± 4.9	8.3 ± 9.0 *
HOMA-IR	5.2 ± 3.1	4.9 ± 2.3	5.7 ± 3.2	5.6 ± 2.6	6.4 ± 3.3	1.95 ± 2.18 *
HbA1C (%)	9.3 ± 1.6	6.5 ± 1.2 *	7.1 ± 1.1 *	7.1 ± 1.2 *	7.7 ± 2.0 *	ND
Medication score	1.38 ± 0.54	0.96 ± 0.73 ‡	0.93 ± 0.67 *	1.04 ± 0.72 ‡	1.15 ± 0.84 ‡	ND
Glucose iAUC (mg/dL × 120 min)	16300 ± 4600	ND	13700 ± 4400 ‡	12500 ± 3900 *	11700 ± 4000 *	5990 ± 1900 *
C-peptide iAUC (µg/mL × 120 min)	158 ± 62	ND	306 ± 66 *	376 ± 112 *	363 ± 90 *	634 ± 255 *
Insulin iAUC (µU/mL × 120 min)	882 ± 360	ND	1560 ± 700 *	1540 ± 620 *	1630 ± 610 *	6560 ± 4060 *
Insulin residence time index (insulin AUC/C-peptide AUC)	4.9 ± 1.9	ND	4.6 ± 1.2	4.4 ± 1.0	4.6 ± 1.0	8.1 ± 2.8 *

Values are mean ± SD. DJB=duodenal-jejunal bypass surgery; BMI=body mass index; HOMA-IR=homeostasis model assessment of insulin resistance; iAUC=incremental area under the curve; ND=not done.

* p<0.001,

‡ p<0.01,

‡ p<0.05 vs. Before Surgery; Normal Glucose Tolerance vs. 12 month DJB.