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Original Article

Pilot Clinical Study of an Endoscopic, Removable Duodenal-Jejunal Bypass Liner for the Treatment of Type 2 Diabetes

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Abstract

Background: Bariatric surgery is associated with the rapid improvement of type 2 diabetes (T2DM). Here we report an exploratory trial of a completely endoscopic, removable, duodenal-jejunal bypass liner (DJBL) intended to treat T2DM.

Methods: Obese T2DM subjects were randomized to receive a DJBL ($n = 12$) or sham endoscopy ($n = 6$) in a 24-week study, extended up to 52 weeks. Measurements included weights, hemoglobin A1c (HbA_{1c}), meal tolerance testing, fasting glucose, and seven-point glucose profiles. Subjects' diets were adjusted in the first 2 weeks to obtain similar weight loss during this period.

Results: Subjects had baseline HbA_{1c} of $9.1 \pm 1.7\%$ and body mass index of $38.9 \pm 6.1\,kg/m^2$ ($\pm$SD). In the completer population by week 1, change in fasting glucose in the DJBL arm was $-55 \pm 21\,mg/dL$ versus $+42 \pm 30\,mg/dL$ in the sham arm ($P \leq 0.05$; $\pm$SE); the seven-point glucose profiles were reduced in the DJBL arm but not in the sham arm. Mean postprandial glucose area under the curve was reduced in the DJBL arm by 20% and increased 17% in the sham arm ($P = 0.016$). At week 12, HbA_{1c} change was $-1.3 \pm 0.9\%$ in the DJBL arm and $-0.7 \pm 0.4\%$ in the sham arm ($P > 0.05$), and at 24 weeks, values were $-2.4 \pm 0.7\%$ in the DJBL arm and $-0.8 \pm 0.4\%$ in the sham arm ($P > 0.05$). Device migrations required endoscopic removal prior to reaching 52 weeks.

Conclusions: The DJBL rapidly normalized glycemic control in obese T2DM subjects, a promising development in the search for novel therapies less invasive than bariatric surgery.

Introduction

In 2004, 66% of U.S. adults were overweight or obese, with 5% classified as morbidly obese (body mass index [BMI] $\geq 40\,kg/m^2$).[1] Overweight and obesity are risk factors for increased morbidity, mortality, and incidence of type 2 diabetes mellitus (T2DM).[2–4] A meta-analysis examining the correlation between baseline BMI and subsequent mortality in 57 prospective studies found that at a BMI $>25\,kg/m^2$, each $5\,kg/m^2$ increase in BMI was associated with $\sim$30% higher overall mortality, a 40% increase from cardiovascular disease (CVD) mortality, and a 60–120% increase from diabetes, renal, and hepatic mortality.[3] Conversely, a 12-year mortality analysis of overweight T2DM patients found that intentional body weight loss was associated with a 25% reduction in total mortality and a 28% reduction in CVD and diabetes mortality.[5] Furthermore, weight reductions of 9.1–13.2 kg were associated with a 33% reduction in mortality.

Bariatric surgery has emerged as an effective means of producing durable, clinically meaningful weight loss in obese patients.[6] Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) reroute chyme in such a way that the duodenum and proximal jejunum are bypassed, effectively promoting the delivery of chyme directly to the distal jejunum. Bariatric surgery has also shown notable effectiveness in reversing T2DM. In particular, RYGB and BPD produce sustained normalization of plasma glucose, insulin, and hemoglobin A1c (HbA_{1c}) in 80–100% of obese T2DM patients.

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Insulin sensitivity can increase four- to fivefold after RYGB.[7] In addition, RYGB surgery can prevent progression from impaired glucose tolerance to T2DM[8] and reduce mortality from this condition.[9] Improvement in glycemic control precedes clinically significant weight loss by weeks, suggesting these improvements may occur independent of caloric restriction and weight loss. This seeming paradox has been attributed to neurohormonal regulatory factors triggered by the bypass of the duodenum and the delivery of chyme to the distal gastrointestinal tract.

Concerns regarding morbidity and mortality associated with the RYGB and BPD surgical procedures have prevented wide-scale adoption.[10] However, despite its inherent risks, bariatric surgery is associated with a lower rate of mortality than untreated obesity over the long term.[6] A possible alternative to bariatric surgery is the duodenal-jejunal bypass liner (DJBL) (EndoBarrier™ gastrointestinal liner, GI Dynamics, Lexington, MA), an endoscopically placed and removable liner. As shown in Figure 1, the DJBL is a 60-cm, impermeable, fluoropolymer liner anchored in the proximal duodenum that prevents chyme from contacting the proximal intestine, similar to RYGB. Bile and pancreatic secretions pass along the outer wall of the liner and mix with the chyme distal to the liner in the jejunum.

The DJBL has undergone preliminary clinical studies for weight reduction in morbidly obese subjects.[11–13] In the case report from Gersin et al.[11] a 119.5-kg woman (baseline BMI 45.2 kg/m^2) lost 9.1 kg by the end of the 3-month treatment period. Additional clinical experience with the DJBL was reported by Rodriguez-Grunert et al.[12] In a 12-week, open-label study in obese subjects, the DJBL was associated with a mean weight reduction of 10.2 kg in the 10 subjects completing the entire treatment period, corresponding to a mean 24% decrease in excess body weight. Additionally, three of the four T2DM subjects had normalization of blood glucose concentrations within 24 h of DJBL implantation. In a second 12-week study in obese subjects who were randomized to either DJBL plus a low caloric diet ($n=25$) or diet-alone ($n=14$),[13] mean excess weight loss at 12 weeks was 22% (10.3 kg) in the DJBL arm and 5% (2.6 kg) in the control arm. Of the three T2DM subjects in the DJBL arm, all had improved glycemic control 1 week after device implantation. Based on these data, a pilot, sham-controlled, clinical trial was conducted to assess the utility and safety of the DJBL in restoring glycemic control in obese subjects with T2DM, independent of weight loss.

FIG. 1. The DJBL (EndoBarrier Gastrointestinal Liner). Color images available online at www.liebertonline.com/dia.

Materials and Methods

Study population

Obese T2DM subjects were enrolled in a randomized, single-blind, sham-controlled, trial of a DJBL (Fig. 1). A total of 18 T2DM subjects were randomized in a two-to-one ratio to receive either a DJBL ($n=12$) or a sham procedure ($n=6$) in which subjects received an upper gastrointestinal endoscopic examination without device implantation (Fig. 2). The study was performed from January 2007 to February 2008 at a single site, the Hospital DIPRECA in Santiago, Chile. The trial was conducted according to the principles of Good Clinical Practice and in compliance with the Medical Device Regulations for Chile, and included Ethics Committee approval and subject consent.

Subjects were age $\geq$18 and $\leq$55 years with T2DM for $\leq$10 years and had an HbA_{1c} $\geq$7% and $\leq$10%, fasting plasma glucose (FPG) $\leq$240 mg/dL, and BMI $\geq$30 kg/m^2 and $\leq$50 kg/m^2. The only T2DM medications were metformin and/or a sulfonylurea. Women were postmenopausal, surgically sterile, or not pregnant and taking oral contraceptives. Subjects were excluded if they had weight loss >4.5 kg (10 lb) in the 3 months prior to screening or were using weight loss medications or a history of gastrointestinal tract abnormalities. All subjects were required to discontinue nonsteroidal anti-inflammatory drugs, corticosteroids, and drugs known to affect gastrointestinal motility.

Study design and end points

The study design is shown in Figure 3. The original treatment period was designed to be 24 weeks in duration and was extended up to 52 weeks for the safety and efficacy analysis. The primary efficacy end point was improvement in glycemic

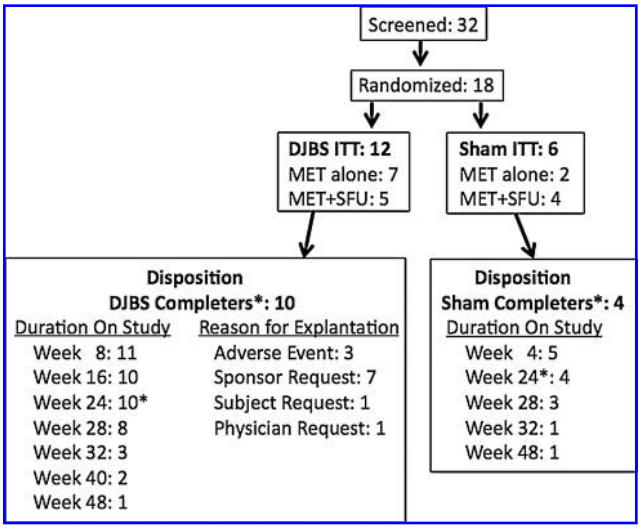

FIG. 2. Subject flow chart and disposition in the duodenal-jejunal barrier study (DJBS). The completer population (asterisks) was defined as all subjects who completed at least 6 months in the study (week 24). MET, metformin; SFU, sulfonylurea.

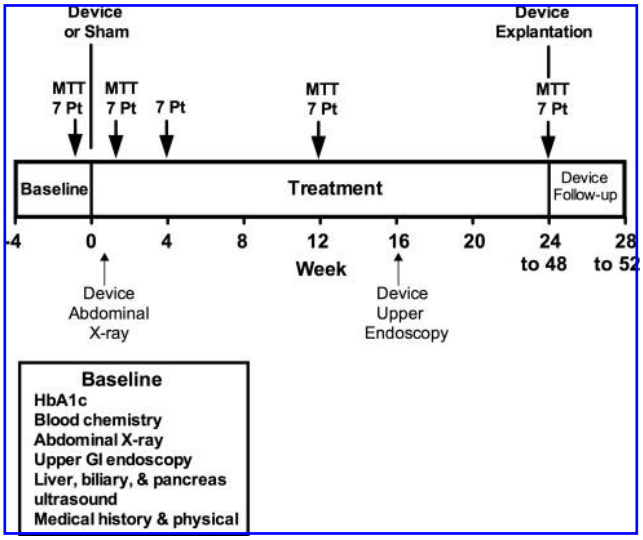

FIG. 3. Study design. Subjects received counseling at baseline, week 1 post-implant, and at every subsequent study visit until week 24. Body weight was recorded at each visit. 7 Pt, seven-point glucose profile; GI, gastrointestinal.

control as measured by HbA_{1c} change from baseline at weeks 12 and 24. Secondary efficacy end points included change in FPG concentration, postprandial seven-point blood glucose profile, meal tolerance test (MTT), body weight, and oral antidiabetic drug (OAD) use. Safety was assessed as the incidence and severity of adverse events.

All subjects completed a nutritional survey for a period of 3 days prior to their procedures, and the study nutritionist determined their baseline caloric intake. All subjects were maintained on their baseline caloric intake for the first 2 weeks after the endoscopic procedure and subsequently counseled about low calorie diet, exercise, and lifestyle modification. This was done to minimize weight loss differences between the two treatment arms early in the study to permit analysis of glycemic impact of the DJBL separate from weight loss. Subjects ingested a liquid diet for the first week postimplantation, pureed food during week 2, and solid foods thereafter. Recommended caloric intake after week 2 was a maximum of 1,200 calories/day for women and 1,500 calories/day for men.

Subjects monitored their blood glucose using a provided Precision Xtra® glucometer (Abbott Diabetes Care, Alameda, CA). Sampling for the seven-point glucose profile was performed by subjects at home before and 2 h after each meal and once prior to bedtime. Both groups underwent standardized meal challenge tests (Ensure Plus®, Abbott Diabetes Care) comprising 25–30% of baseline daily caloric intake in the morning after a 12-h fast. The liquid meal was 50% carbohydrates, 30% protein, and 20% fat.

The protocol stated that all device subjects taking sulfonylureas should have had their dose decreased by 50% at implant. Further reductions were planned if there were episodes of hypoglycemia with blood glucose concentrations <70 mg/dL. Metformin doses were to remain unchanged.

DJBL implantation and explantation

The DJBL has been previously described in detail.[11–13] Subjects underwent general anesthesia for the delivery and removal of the device. Subjects in the DJBL group underwent follow-up endoscopy at 3 days and 4 weeks after device removal.

Statistical analysis

The "intent-to-treat" (ITT) population was defined as all treated subjects. The "completer" population was defined as all subjects who completed at least 6 months on study (week 24), with week 28 data used for the last time point for the subjects who missed the week 24 visit. Continuous variables were summarized utilizing descriptive statistics. Categorical variables were summarized using frequency. Analyses were performed using SAS® (Cary, NC) version 9.2 software or later. Student's *t* test or Fisher's exact test was used for comparisons between arms.

Results

Study population and antidiabetes medications

Selection and disposition of the study population is shown in Figure 2. Treatment duration was 200 ± 22 days in the DJBL arm and 190 ± 44 days in the sham arm (mean $\pm$ SE). Total procedure time for the device implantation was 31 ± 4 min, and total fluoroscopic time was 12 ± 2 min. Total

Table 1. Baseline Demographics and Subject Characteristics in the ITT Population

	All (n = *18*)	*DJBL* (n = *12*)	*Sham* (n = *6*)	P *value*[a]
Age (ys)	47 ± 10	45 ± 7	51 ± 13	> 0.05
Gender (% male/% female)	39/61	33/67	50/50	> 0.05
Ethnicity (% white)	100	100	100	NA
Body weight (kg)	104.3 ± 20.8	103.4 ± 21.3	106.2 ± 21.6	> 0.05
BMI (kg/m^2)	38.9 ± 6.1	38.9 ± 5.9	39.0 ± 7.2	> 0.05
HbA_{1c} (%)	9.1 ± 1.7	9.2 ± 1.7	9.0 ± 2.0	> 0.05
FPG (mg/dL)	195 ± 77	199 ± 71	185 ± 94	> 0.05
Postprandial glucose AUC (mg/dL · min)		$31{,}226 \pm 11{,}570$	$27{,}558 \pm 11{,}480$	> 0.05
Duration of diabetes (years)	3.7 ± 2.4	3.5 ± 2.5	4.2 ± 2.1	> 0.05
Co-morbidities (%)				
Hypertension	50	58	33	
Hyperlipidemia	33	25	50	
Hepatosteatosis	83	92	67	

Data are mean $\pm$ SD values. NA, not applicable.
[a]Comparison between DJBL and sham groups.

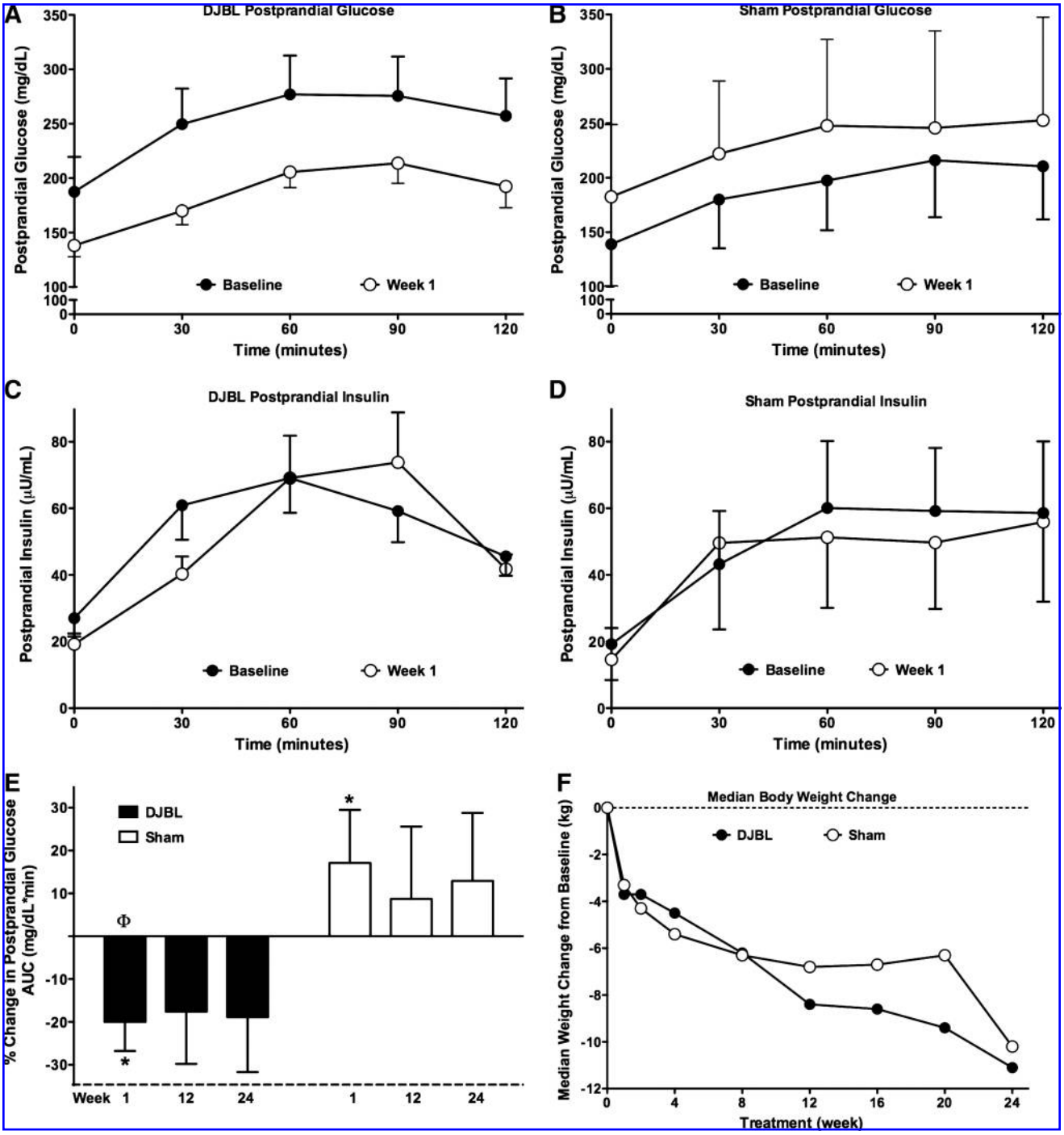

FIG. 4. Postprandial (**A** and **B**) glucose and (**C** and **D**) insulin concentrations during mixed MTTs at baseline and week 1 in the completer population. (**E**) Glucose AUC percentage change from baseline in the completer population. Baseline AUC values were $30{,}761 \pm 4{,}027$ mg/dL · min in the DJBL arm and $23{,}048 \pm 5{,}572$ mg/dL · min in the sham arm ($P > 0.05$ between arms). Week 24–28 value is the last value available before DJBL explantation. $^{*}P = 0.016$ between treatment arms; $^{\Phi}P = 0.034$ for change from baseline. Data are mean ± SE values. (**F**) Median weight change in the completer population. Because of a skewed distribution of weight loss values, means were not reflective of weight change in the overall population.

procedure time for explantation was 15 ± 2 min. Upon explantation, the anchor position was normal in seven subjects, migrated in four subjects, and both turned and migrated in one subject.

A summary of baseline characteristics and subject demographics is shown in Table 1. At baseline, all subjects were being treated for T2DM with at least one OAD. In the DJBL arm, seven subjects were treated with metformin alone, and five were treated with both metformin and a sulfonylurea. In the sham group, two subjects were treated with metformin monotherapy, and four were treated with both OADs. At week 12 in the ITT population, 42% of the DJBL subjects had

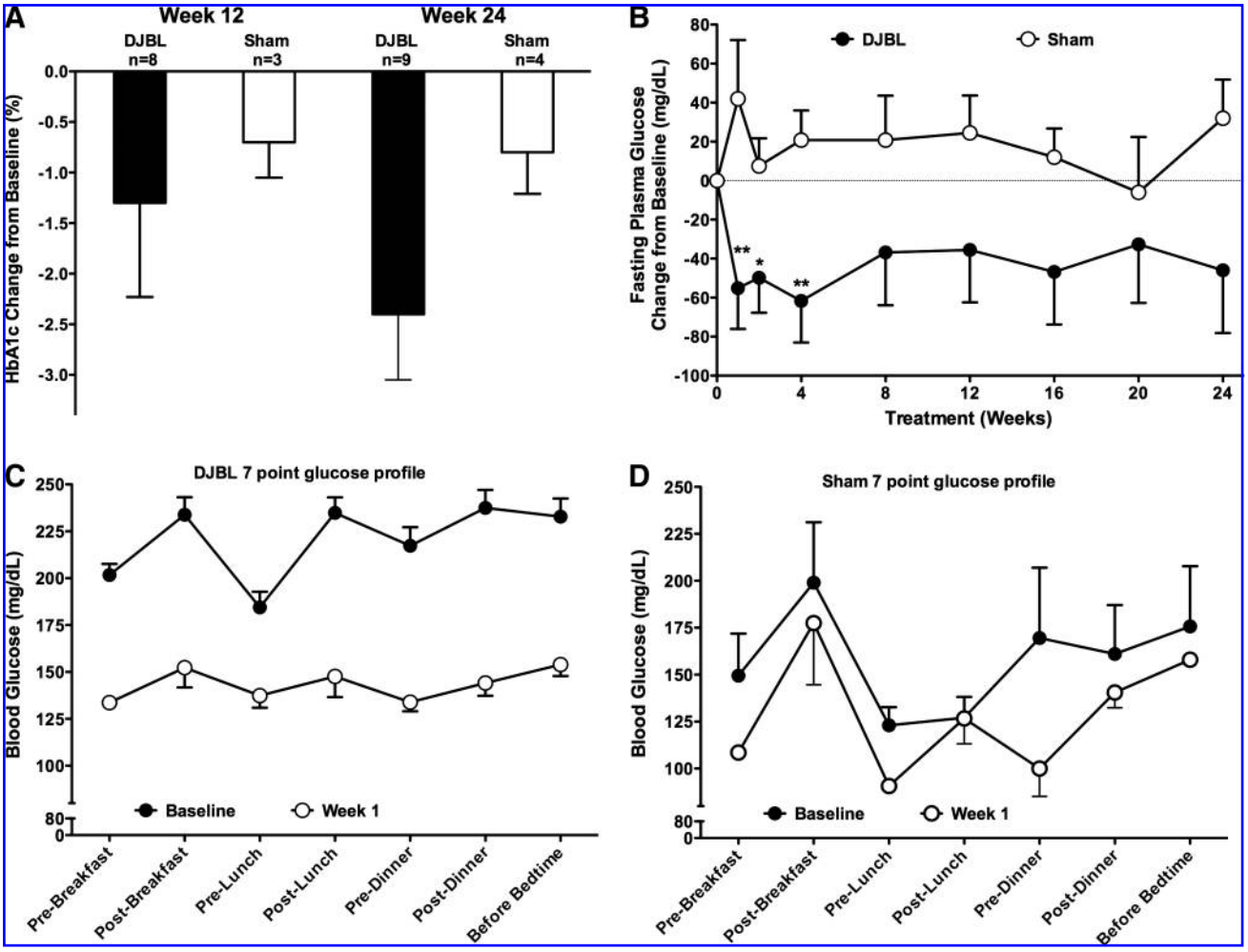

FIG. 5. Glycemic control in the completer population. (**A**) HbA_{1c} change from baseline. In the DJBL arm, baseline HbA_{1c} was $9.3 \pm 0.6\%$ versus $8.8 \pm 1.2\%$ in the sham arm. (**B**) FPG concentrations. Baseline values were 193 ± 24 mg/dL in the DJBL arm and 140 ± 38 mg/dL in the sham arm. $^*P \leq 0.08$; $^{**}P \leq 0.05$. (**C** and **D**) Seven-point glucose profiles. Data are mean ± SE values.

ceased treatment with any OAD, whereas in the sham arm 17% had ceased OAD use. In the completer population at week 12, 50% and 25% had ceased OAD use, respectively. By week 24, 40% of the DJBL subjects and 25% of the sham subjects remaining on study had ceased OAD therapy.

Body weight and glycemic control

Mean body weight loss was equivalent between treatment arms throughout the first 12 weeks of the study for both ITT and completer populations ($P > 0.05$ for mean comparisons). At week 1, mean ITT weight change was -4.0 ± 0.4 kg in the DJBL arm versus -4.0 ± 0.6 kg in the sham arm. Although not statistically significant, the DJBL arm tended towards more weight loss than the sham-treated arm beyond week 12. At week 20, the mean ITT weight change was -10.2 ± 1.3 kg in the DJBL arm versus -7.1 ± 4.3 kg in the sham arm. By week 24, there were only three sham subjects remaining in the study. Therefore median weight loss in the completer population is shown in Figure 4F.

Mean baseline HbA_{1c} values for the ITT DJBL and sham arms were 9.2% and 9.0%, respectively ($P > 0.05$). ITT HbA_{1c} change in the DJBL arm was $-1.3 \pm 0.9\%$ at week 12, compared with $-0.8 \pm 0.3\%$ in the sham arm ($P > 0.05$). Week 24 ITT HbA_{1c} change was $-2.4 \pm 0.7\%$ in the DJBL arm and $-0.8 \pm 0.4\%$ change in the sham arm ($P > 0.05$). Completer HbA_{1c} change is shown in Figure 5A ($P > 0.05$ between arms).

Both treatment arms had equivalent baseline FPG concentrations. However, by week 1 ITT fasting plasma glucose change in the DJBL arm was -50 ± 18 mg/dL and in the sham arm $+25 \pm 29$ mg/dL ($P = 0.042$). ITT FPG change at week 12 was -45 ± 26 mg/dL in the DJBL arm and -8 ± 35 mg/dL in the sham arm ($P > 0.05$). FPG changes at week 24 were -83 ± 39 mg/dL and $+16 \pm 42$ mg/dL, respectively ($P > 0.05$). FPG change from baseline in the completer population is shown in Figure 5B.

In the DJBL arm in the completer population, the seven-point glucose profile was reduced and flattened at week 1 compared with baseline but was not changed in the sham arm (Fig. 5C and D, respectively).

Postprandial plasma glucose and insulin concentrations at baseline and week 1 are shown in Figure 4A–D for the completer population. At week 1, 80% of DJBL subjects and 25% of sham-treated subjects had a reduction in postprandial glucose

Table 2. All Incidents of Device-Related Adverse Events Among 12 Patients

Adverse event	*DJBL [% (n)]*
Upper abdominal pain	30.8 (20)
Vomiting	10.8 (7)
Abdominal pain	4.6 (3)
Nausea	7.7 (5)
Symptoms of hypoglycemia[a]	7.7 (5)
Blood iron decreased	6.2 (4)
Flatulence	4.6 (3)
Procedural nausea	4.6 (3)
Procedural vomiting	3.1 (2)
Blood cholesterol increased	3.1 (2)
Erosive duodenitis	3.1 (2)
Constipation	1.5 (1)
Diarrhea	1.5 (1)
Gastritis	1.5 (1)
Headache	1.5 (1)
HDL-C decreased	1.5 (1)
Esophagitis	1.5 (1)
Pain	1.5 (1)
Serum ferritin decreased	1.5 (1)

Percentages are based on the number of adverse events in the treatment arm. HDL-C, high-density lipoprotein cholesterol.
[a]In all five episodes, blood glucose values were >100 mg/dL.

excursions from baseline ($P = 0.10$ between arms). Postprandial plasma glucose area under the curve (AUC) was reduced from baseline by 22% in the DJBL arm compared with a 16% increase in the sham arm ($P = 0.016$ between arms; Fig. 4E). There was no change in postprandial insulin concentrations in either arm. In the ITT population at week 1, postprandial plasma glucose AUC was reduced from baseline by 19% in the DJBL arm compared with an 11% increase in the sham arm ($P = 0.014$ between arms).

Safety and tolerability

All adverse events were mild or moderate. Subject disposition throughout the study is shown in Figure 3, and device-related adverse events are summarized in Table 2. Although all 12 DJBL subjects had at least one episode of mild or moderate abdominal pain and four DJBL subjects had mild or moderate vomiting episodes, no subject requested the removal of the DJBL for these reasons. Three DJBL subjects were explanted in response to an adverse event related to device migration or turning including moderate abdominal pain (one), moderate nausea and moderate vomiting (one), and mild abdominal pain and mild vomiting (one). The remaining two DJBL migrations were observed at the time of removal (one) and scheduled endoscopy (one), at which time they were removed. These two subjects had no symptoms. Four-week postexplant endoscopies in the four subjects with anchor migrations showed no clinically significant findings.

Discussion

The endoscopic DJBL improved glycemic control in obese T2DM subjects in a randomized, sham-controlled pilot study. With weight loss maintained comparable in both arms, FPG concentrations decreased dramatically in the DJBL arm as early as 1 week after device implantation and normalized by week 24. In contrast, FPG remained elevated in T2DM subjects receiving sham treatment. Seven-point glucose profiles in the DJBL arm were consistently reduced at all postimplantation time points. In contrast, profiles for the sham group were more variable and had larger postmeal excursions. Reflecting these improvements in ambient glycemia, HbA_{1c} decreased substantially more in the device arm than in the sham arm, although this did not reach statistical significance. Postprandial glucose excursions during the meal tolerance test were also improved in DJBL, but not sham-treated T2DM subjects, again most interestingly at the 1 week time point.

This study was designed to minimize differences in weight loss between DJBL and sham subjects in the first few weeks. This matching permits the analysis of glycemic changes independent of weight loss. However, as the trial progressed, subjects with the DJBL began to lose more weight than the sham subjects. Because of the small number of subjects in the sham arm and because one of the three sham subjects lost a significant amount of weight, differences did not reach statistical significance.

Postprandial serum insulin concentrations did not differ between the DJBL and sham-treated arms during the MTT. This finding suggests an improvement in β-cell function and enhanced insulin secretion after DJBL. Several factors have been shown to play a major role in regulating the pancreatic β-cell's secretory response to glucose stimulation.[14–16] One factor is glucose sensitivity, a reflection of the ability of the β-cell to respond to changes in prevailing plasma glucose concentrations. A second factor is rate sensitivity, referring to the magnitude of the β-cell response to the rate of change in plasma glucose concentration. A third factor is potentiation, a factor related to the release of endogenous incretin hormones, neuronal inputs, and changes in incremental plasma glucose concentrations after ingestion of a meal, all of which increase the sensitivity of the β-cell insulin secretory response to subsequent plasma glucose concentrations. Thus, the stimulatory effect of glucose on insulin secretion is not constant during the course of a meal because the insulin response to a meal is dependent not only on ambient glucose concentrations, but also on incretins, neurotransmitters, and other nutrients. Compared to healthy subjects, T2DM patients exhibit a blunted rise in potentiation following glucose ingestion,[16] with a small or insignificant increment at 2 h post-glucose load. Therefore, data from the DJBL subjects suggest enhanced β-cell function.

The rapid improvement in glycemic control observed in morbidly obese T2DM patients after RYGB and BPD has been attributed to neurohormonal regulatory factors triggered by chyme (incompletely digested nutrients) diverted away from the proximal intestine and delivered directly to the distal intestine.[9,17–20] This diversion has been associated with reductions in circulating concentrations of peptide hormones derived from the proximal intestine, such as glucose-dependent insulinotropic polypeptide, and increases in hormones derived from the distal intestine, such as neurotensin, neuropeptide YY, and enteroglucagon (a surrogate marker for glicentin, oxyntomodulin, glucagon-like peptide-1, and glucagon-like peptide-2). Additional putative mediators of the rapid resolution of hyperglycemia after bariatric surgery include reduced ghrelin, reduced leptin, reduced insulin, and increased adiponectin. The DJBL can be considered analogous to the RYGB without gastric restriction and thus is expected

to produce similar changes in the regulation of intestinal hormones.

The importance of duodenal-jejunal bypass, without gastric restriction, in resolving hyperglycemia was demonstrated in Goto-Kakizaki rats, a spontanous, nonobese T2DM model.[9,17] Surgical exclusion of the proximal duodenum resulted in marked improvement in glucose tolerance as compared to controls. These data suggest that nutrient flux through the duodenum plays a significant role in the regulation of glucose homeostasis in T2DM. In humans, Rubino et al.[17] investigated the hormonal effects of RYGB prior to weight loss in 10 morbidly obese patients, six with T2DM using OADs. Three weeks postsurgery there were significant reductions in blood concentrations of glucose, insulin, insulin-like growth factor-1, and leptin, with trends towards decreased glucose-dependent insulinotropic polypeptide and increased enteroglucagon, corticosterone, glucagon-like peptide-1, and cholecystokinin. The six T2DM patients were euglycemic without OADs within 3 weeks postsurgery. T2DM patients had higher preoperative circulating glucose-dependent insulinotropic polypeptide than the normoglycemic patients, and their glucose-dependent insulinotropic polypeptide levels normalized after surgery.

The adverse event profile from this pilot study suggests acceptable safety and tolerability for the DJBL. The type and incidence of adverse events appear to be less clinically significant than those associated with bariatric surgery.

Limitations of this study include the small subject number and the necessity to remove three devices due to abdominal pain or anchor migration. The management of subjects' OAD medications also biases the results in favor of sham improvement. Subjects with the DJBL were taken off of metformin more than those receiving sham treatment, and yet the protocol did not specify this. Had DJBL subjects remained on metformin as they should have, further improvements in FPG and HBA_{1c} might have been attained.

The ability of the DJBL to rapidly normalize glycemic control in obese T2DM subjects represents a promising development in the search for novel therapies that provide relief to the clinical progression of this disease and are less invasive than bariatric surgery. The results of this diabetes-specific pilot study are encouraging and support further clinical investigations.

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Author Disclosure Statement

L.R., M.G., K.S.G., and C.S. are paid consultants for GI Dynamics. K.S.G. is also a shareholder and medical director of GI Dynamics. E.R., P.F., M.S.O., J.S., C.G.A., C.P., and A.R. have no disclosures.

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