Brief Report—Endocrine Care

# A Pilot Study of the Duodenal-Jejunal Bypass Liner in Low Body Mass Index Type 2 Diabetes

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**Context:** The duodenal-jejunal bypass liner (DJBL) is a device that mimics the intestinal portion of gastric bypass surgery and has been shown to improve glucose metabolism rapidly in obese subjects with type 2 diabetes (T2DM).

**Objective:** To assess the safety of the DJBL and to evaluate its potential to affect glycemic control beneficially in subjects with T2DM who were not morbidly obese.

**Patients and Design:** Adult men and women with T2DM of  $\leq 10$  years' duration with hemoglobin A1c (HbA1c)  $\geq 7.5\%$  and  $\leq 10\%$  and having a body mass index  $\geq 26$  to  $\leq 50$  kg/m<sup>2</sup> were enrolled in this prospective, 52-week, single-center, open-label clinical study.

Main Outcome Measures: Adverse events and changes in body weight, fasting plasma glucose (FPG) levels, and HbA1c levels.

**Results:** Sixteen of 20 subjects implanted with the DJBL completed the 1-year study (mean body mass index =  $30.0 \pm 3.6$ , mean  $\pm$  SD). Gastrointestinal disorders were reported by 13 subjects, and metabolic or nutritional disorders occurred in 14 subjects. FPG levels dropped from  $207 \pm 61$  mg/dL at baseline to  $139 \pm 37$  mg/dL at 1 week and remained low throughout the study. Mean body weight also declined, but the change in body weight was not significantly associated with change in FPG at 52 weeks. HbA1c declined from  $8.7 \pm 0.9\%$  at baseline to  $7.5 \pm 1.6\%$  at week 52.

**Conclusions:** The improvements in glycemic status were observed at 1 year in moderately obese subjects with T2DM, suggesting that the DJBL may represent an effective adjuvant to standard medical therapy of T2DM in this population. (*J Clin Endocrinol Metab* 98: E279–E282, 2013)

The duodenal-jejunal bypass liner (DJBL) is an endoscopically placed device that prevents contact between partially digested nutrients and the proximal intestine (1, 2). In studies of morbidly obese patients with type 2 diabetes (T2DM), reductions in fasting plasma glucose (FPG) were seen within 1 week after implantation of the DJBL and were maintained through 24 and 52 weeks (3, 4), suggesting that the DJBL might be an effective treatment for T2DM. The pilot study reported here was performed to see if this antidiabetic response might occur

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doi: 10.1210/jc.2012-2814 Received July 18, 2012. Accepted November 27, 2012. First Published Online January 21, 2013 in subjects with T2DM and lower body mass index (BMI).

# **Materials and Methods**

## Study ethics

The study protocol was reviewed and approved by the Ethics Committee of the Hospital Alemão Oswaldo Cruz, São Paulo, Brasil. All subjects provided signed, informed consent

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Abbreviations: AE, Adverse events; BMI, body mass index; DJBL, duodenal-jejunal bypass liner; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; T2DM, type 2 diabetes.

before enrolling in the study. The study was registered with ClinicalTrials.gov (NCT00986349).

## Study subjects

Adult men and women between the ages of 18 and 55 years with T2DM of  $\leq 10$  years' duration being treated with oral glucose-lowering medications were eligible for enrollment. Other enrollment criteria included hemoglobin A1c (HbA1c) ≥7.5% and  $\leq 10\%$ , BMI  $\geq 26$  and  $\leq 50$  kg/m<sup>2</sup> (although the investigator's interest in T2DM in lower BMI subjects resulted in an effective upper BMI limit of 36 kg/m<sup>2</sup>). Eligible women were postmenopausal, surgically sterile, or on oral contraceptives and agreed to remain on oral contraceptives for the duration of the trial. Exclusion criteria included type 1 diabetes, requirement to use insulin, autoimmune disease, weight loss of >4.5 kg within 12 weeks of screening, previous gastrointestinal surgery that might affect the ability to place the device or the function of the implant, active Helicobacter pylori, subjects unable to discontinue nonsteroidal anti-inflammatory drugs, subjects on weight loss medication, and subjects with active, uncontrolled gastroesophageal reflux disease.

#### Duodenal-jejunal bypass liner

The DJBL was manufactured by GI Dynamics (Endobarrier; Lexington, Massachusetts). The DJBL is a 60-cm impermeable fluoropolymer liner that is open at both ends and has a Nitinol anchor that reversibly fixes the device to the wall of the duodenum (5). The DJBL was deployed endoscopically using general anesthesia. At the end of the study (or earlier if indicated by an adverse event [AE] or other reasons), the device was removed using general anesthesia, except for 1 case, in which the device was removed under conscious sedation.

#### Study design

The study was a 52-week, prospective, open-label, singlecenter clinical study intended to assess the safety and efficacy of the DJBL in subjects with T2DM with a baseline BMI  $\leq$  50 kg/ m<sup>2</sup>. Baseline assessments were made within 30 days before device implantation. Weight was measured and fasting blood panels were taken at baseline and every study visit. All study participants received nutritional counseling at the baseline visit and were instructed to take an over-the-counter proton pump inhibitor (eg, omeprazole 40 mg twice per day) starting 3 days before device implantation and continuing until 2 weeks after explantation. Subjects followed a liquid diet for the first week after device implantation and were encouraged to limit caloric intake to 1200 cal for women or 1500 cal for men throughout the study. Subjects taking a sulfonylurea had their dose reduced by 50% at the time of implant procedure to avoid hypoglycemic episodes. If a hypoglycemic episode was experienced, the sulfonylurea was reduced by 50% again or discontinued if the subject was on the lowest dose. Dosages of metformin and/or thiazolidinediones remained unchanged throughout the trial unless a subject's fasting blood glucose was documented to be under 70 mg/dL on 3 consecutive days. Under this circumstance, metformin dose was reduced by 50%. Safety was assessed continuously during the study by soliciting information about AEs and by monitoring laboratory values.

#### **Statistical analyses**

The main objectives of the study were to evaluate the potential of the DJBL to affect glycemic control beneficially in subjects with T2DM who were not morbidly obese and to assess the safety of the DJBL. Baseline values and change from baseline are expressed as mean  $\pm$  SD. Because this was a pilot study, no statistical analyses were planned. However, several unplanned analyses were conducted. Changes from baseline at week 52 for body weight, FPG, and HbA1c were evaluated with the Student *t* test. The correlation between change in body weight and change in FPG or HbA1c was assessed by ANOVA.

# Results

A total of 36 subjects were screened and 23 subjects were enrolled in the study. The DJBL was successfully implanted in 20 subjects. In the remaining 3 subjects, the implantation could not be performed because of unfavorable anatomy. The 20 subjects (13 men) implanted with the DJBL had an average age of 49.8  $\pm$  6.7 years and had an average duration of T2DM of 6.6  $\pm$  3.1 years. Other baseline characteristics are presented in Table 1.

Sixteen of the 20 implanted subjects (80%) completed the 12 months of treatment with the DJBL. The mean and

Table 1. Body Weight, Glucose Metabolism, and Plasma Lipids During Treatment With the DJBL								
	Baseline (n = 20)	Week 1 (n = 20)	Week 4 (n = 20)	Week 12 (n = 19)	Week 24 (n = 18)	Week 36 (n = 17)	Week 52 (n = 16)	<i>P</i> Value
Body weight, kg	84.0 ± 16.6	81.8 ± 16.2	80.5 ± 16.7	79.0 ± 16.8	77.2 ± 16.7	77.7 ± 17.3	$77.2 \pm 17.6^{a}$	<.0001
BMI, kg/m <sup>2</sup>	$30.0 \pm 3.6$	29.3 ± 3.5	28.8 ± 3.6	28.3 ± 3.7	27.9 ± 3.8	28.2 ± 3.6	$28.5 \pm 3.3^{a}$	<.0001
FPG, mg/dL	207 ± 61	139 ± 37	149 ± 56	132 ± 41	143 ± 34	142 ± 28	155 ± 52	.012
HbA1c, %	$8.7 \pm 0.9$	ND	ND	$7.0 \pm 0.9$	$7.2 \pm 0.9$	ND	$7.5 \pm 1.6$	.004
Total cholesterol, mg/dL	221 ± 50	219 ± 72	178 ± 41	167 ± 38	178 ± 36	187 ± 39	188 ± 32	
HDL, mg/dL	42 ± 11	41 ± 7	38 ± 8	39 ± 7	40 ± 10	39 ± 9	40 ± 10	
LDL, mg/dL	135 ± 40	137 ± 65	104 ± 38	95 ± 33	101 ± 32	107 ± 35.4	108 ± 31	
TG, mg/dL	299 ± 212	195 ± 109	203 ± 135	178 ± 113	210 ± 126	222 ± 141	219 ± 158	

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoproteins; LDL, low-density lipoproteins; ND, not determined; TG, triglycerides. Values are expressed as mean  $\pm$  SD. *P* values are for change from baseline in the completer population. *P* values for weeks 1 to 36 were not determined. No statistical tests were performed on plasma lipid values.

<sup>a</sup> n = 15 because 52-week body weight was not recorded for 1 subject.

median implant durations were 348 and 365 days. The device was removed early in 4 subjects. The device was explanted from 1 subject at week 10 at the request of the investigator because of subject noncompliance with study visits, and 1 subject requested removal at month 7 due to recurring abdominal pain. Two subjects had their devices explanted early due to device rotation and/or migration. Of these 2 subjects, 1 had their device removed at month 6 in the absence of symptoms, and the second subject had the device explanted at month 10 due to abdominal pain.

Significant decreases in body weight and BMI were demonstrated during the study (Table 1). At week 52, mean body weight had decreased by  $6.5 \pm 4.1$  kg. Mean FPG declined from 207  $\pm$  61 mg/dL at baseline to 139  $\pm$ 37 mg/dL 1 week after DJBL implantation (Table 1). At week 52, FPG was  $155 \pm 52$  mg/dL in the 16 subjects who completed the study, representing a mean change from baseline of  $-45.8 \pm 63.9 \text{ mg/dL}$  (P = .012). The distribution of HbA1c levels during the study is shown in Figure 1. Mean HbA1c declined from  $8.9 \pm 1.2\%$  (n = 20) at baseline to  $7.0 \pm 0.9\%$  (n = 19) at 3 months. At week 52, mean HbA1c was  $7.5 \pm 1.6\%$  (n = 16), representing a mean change from baseline of  $-1.16 \pm 1.36\%$  (*P* = .004). Ten of 16 subjects (62.5%) who completed the study demonstrated HbA1c levels  $\leq 7\%$  at week 52. Four of the 5 subjects with baseline HbA1c  $\geq 9\%$  in the completer population failed to demonstrate a reduction in HbA1c during the study. During the study, 7 subjects decreased and 4 subjects increased either the number of drugs or the doses of antidiabetic medications. No significant correlation between change in body weight and change in FPG or HbA1c was observed (data not shown).

The effect of treatment with the DJBL on plasma lipids is shown in Table 1. Low-density lipoproteins and triglycerides demonstrated substantial decrease by week 4 and remained low through the end of the study. No change in high-density lipoprotein cholesterol level was evident.



**Figure 1.** The distribution of HbA1c levels before and during treatment with the DJBL. DJBL, duodenal-jejunal bypass liner; HbA1c, hemoglobin A1c.

## Safety

Twenty-two of the 23 subjects who enrolled in the study experienced at least 1 AE. All AEs were mild or moderate in severity. Gastrointestinal disorders, including abdominal pain, nausea, and vomiting; and metabolism and nutrition disorders, including hypoglycemia and iron deficiency, were the most common device- or procedurerelated AEs and were experienced by 13 and 14 subjects, respectively.

# Discussion

Previous studies of the DJBL in patients with T2DM have shown beneficial effects on glucose metabolism in patients with mean baseline BMI of 38.9 (4) and 44.8 kg/m<sup>2</sup> (3). The results of this pilot study extend these observations to a nonmorbidly obese population with mean baseline BMI of 30.0 kg/m<sup>2</sup>. This lower BMI patient population is important because most people with diabetes have a BMI <30 kg/m<sup>2</sup> (6).

Gastrointestinal surgery has emerged as a treatment for T2DM in obese subjects (7–11). Although current guidelines indicate that bariatric surgery should be restricted to patients with BMI  $\geq$ 35 kg/m<sup>2</sup> (12), a number of studies have reported results in T2DM subjects with BMI <35 kg/m<sup>2</sup> (13). A recent review of 29 published studies of bariatric surgery in patients with T2DM with BMI <35 kg/m<sup>2</sup> concluded that these procedures resulted in statistically significant reductions in BMI, FPG, and HbA1c (13). Based on the results of the present study, the DJBL appears to mimic metabolic surgery in its ability to reduce FPG rapidly and may represent a nonsurgical approach to stopping or reversing progression of T2DM in patients with BMI <35 kg/m<sup>2</sup>, as well as in morbidly obese subjects.

People with T2DM are at 2 to 4 times higher risk for coronary heart disease compared with the general population (14, 15). Controlling the individual risk factors in patients with T2DM, for example, lowering blood lipid levels with statins, has been shown to reduce the incidence of major coronary events significantly in this population (16). Although the present study was not designed to measure the effect of treatment on the incidence of coronary events, the change in risk profile due to changes in diabetes status (i.e., HbA1c levels and plasma lipids (17) of individual study subjects) can be estimated using The UK Prospective Diabetes Study Risk Engine (18). In the 16 subjects who completed 1 year of treatment, the average 10year risk of coronary heart disease declined from 13.4% to 12.2%. Several unanswered questions remain to be addressed. For example, the durability of the response following removal of the DJBL is not known, and, although modest reductions in BMI were observed, the association between loss of body weight and the improvement in glycemic metabolism has not been elucidated in this population. The biologic mechanisms responsible for the rapid onset of improvement in glucose metabolism with the DJBL have not been determined. In addition, the contributions of changes in lifestyle, including changes in diet, to the overall response have not been evaluated. Finally, the roles of the DJBL as an adjuvant to conventional medical therapy or emerging treatments in T2DM or as a reversible alternative to bariatric surgery have not been established.

#### **Study limitations**

The small size of this study and the fact that it was open-label limit the strength of the observations. Because of the small number of patients in the study, the statistical analyses presented here should be considered as hypothesis-generating rather than providing strong inferences.

# Conclusions

The results of this study suggest that the DJBL may improve glycemic status and blood lipid levels in moderately obese subjects with T2DM. Based on these observations, the DJBL may represent an effective adjunct to pharmacologic treatment of diabetes in this population.

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