Weight Loss and Metabolic Improvement in Morbidly Obese Subjects Implanted for 1 Year With an Endoscopic Duodenal-Jejunal Bypass Liner

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Objective: To evaluate safety, weight loss, and cardiometabolic changes in obese subjects implanted with the duodenal-jejunal bypass liner (DJBL) for 1 year.

Background: The DJBL is an endoscopic implant that mimics the duodenal-jejunal bypass component of the Roux-en-Y gastric bypass. Previous reports have shown significant weight loss and improvement in type 2 diabetes for up to 6 months.

Methods: Morbidly obese subjects were enrolled in a single arm, open label, prospective trial and implanted with the DJBL. Primary endpoints included safety and weight change from baseline to week 52. Secondary endpoints included changes in waist circumference, blood pressure, lipids, glycemic control, and metabolic syndrome.

Results: The DJBL was implanted endoscopically in 39 of 42 subjects (age: 36 ± 10 years; 80% female; weight: 109 ± 18 kg; BMI: 43.7 ± 5.9 kg/m^2); 24 completed 52 weeks of follow-up. Three subjects could not be implanted due to short duodenal bulb. Implantation time was 24 ± 2 minutes. There were no procedure-related complications and there were 15 early endoscopic removals. In the 52-week completer population, total body weight change from baseline was -22.1 ± 2.1 kg ($P < 0.0001$) corresponding to 19.9 ± 1.8% of total body weight and 47.0 ± 4.4% excess of weight loss. There were also significant improvements in waist circumference, blood pressure, total and low-density lipoprotein cholesterol, triglycerides, and fasting glucose.

Conclusions: The DJBL is safe when implanted for 1 year, and results in significant weight loss and improvements in cardiometabolic risk factors. These results suggest that this device may be suitable for the treatment of morbid obesity and its related comorbidities. This study was registered at www.clinicaltrials.gov (NCT00985491).

(*Ann Surg* 2012;255:1080–1085)

Obesity has become an epidemic health problem worldwide with a prevalence of 36% among adult women and 32% among adult men in the United States.[1] Medical treatment (diet, physical activity, behavioral modification, and pharmacotherapy) is the primary approach of management of obesity with an average of 5% to 10% of initial weight loss with these therapies at 6 months.[2]

Bariatric surgery has demonstrated long-term sustained weight loss, resolution or improvement of associated co-morbidities, and improvement of overall survival.[3–7] Although bariatric surgery is associated with a low rate of postoperative complications and mortality in high volume centers,[8–10] the risk of postoperative complications and mortality raise concerns among physicians and patients. As has been reported among Medicare beneficiaries, hospitals with less experience and low volume of patients can have 30- and 90-day postoperative mortality rates as high as 2.0% and 2.8%, respectively.[11] Postoperative mortality and long-term complications may partially explain why many morbidly obese patients do not often consider bariatric surgery as an alternative of treatment. In a recent survey of 77 morbidly obese patients, 57% were not interested in a surgical procedure for weight management, 45% were concerned about the risk of death and postoperative complications, 30% said their physician did not recommend it, and 8% had never heard of bariatric surgery.[12] These data support the need for safer and less invasive treatments of morbid obesity.

The duodenal-jejunal bypass liner (DJBL; EndoBarrier Gastrointestinal Liner: GI Dynamics, Inc, Lexington, MA; Fig. 1) has undergone short-term (up to 6 months) clinical trials for the treatment of morbid obesity and type 2 diabetes (T2DM).[13–18] The DJBL is an endoscopically placed and removable device specifically designed to mimic the duodenal-jejunal exclusion created with gastric bypass. The DJBL prevents nutrient contact with the proximal intestinal mucosa. Bile and pancreatic secretions pass along the outer wall of the impermeable 60-cm liner and mix with the chyme as it exits distal to the liner in the jejunum. Initial reports confirmed that the DJBL was capable of producing significant weight loss with up to 24% excess weight loss (EWL) over implant durations of 3 and 6 months as an alternate method of weight loss before bariatric surgery.[16] In obese T2DM patients, addition of the device to standard medical therapy was associated with clinically meaningful improvements in HbA_{1c} and T2DM, albeit in a small number of patients treated.[14] The aim of this study was to evaluate the safety and efficacy of the DJBL in morbidly obese subjects for 1 year.

METHODS

Study Population

Morbidly obese subjects were enrolled in a single arm, open label, prospective trial of the DJBL (Fig. 2). A total of 42 subjects were enrolled at one center and 39 were implanted with the device. This study was conducted in Chile at the Pontificia Universidad Católica de Chile from March 2009 to October 2010. The trial was conducted according to the principles of good clinical practice and in compliance with the Medical Device Regulations for Chile, and it included approval from the Ethics Committee of the Faculty of Medicine. It

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Disclosure: This study was funded by GI Dynamics Inc, 1 Maguire Road, Lexington, MA 02421. Alex Escalona and Keith Gersin disclose the following financial relationships relevant to this publication. Keith Gersin is the chief medical officer, consultant, and shareholder in GI Dynamics. Alex Escalona is a consultant and research grant recipient. All other authors have no financial relationships with a commercial entity producing health-care related products and/or services to disclose relevant to this article.

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ISSN: 0003-4932/12/25506-1080
DOI: 10.1097/SLA.0b013e31825498c4

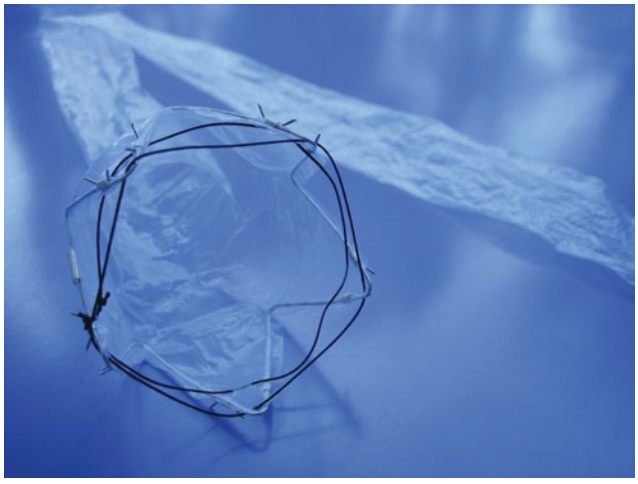

FIGURE 1. The duodenal-jejunal bypass liner.

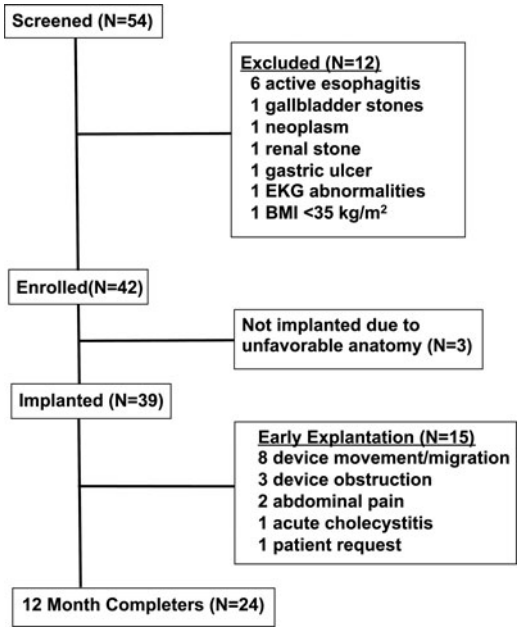

FIGURE 2. Participants flow chart.

was performed in accordance with the principles of the Declaration of Helsinki. All study participants provided written informed consent. This study was registered at www.clinicaltrials.gov (NCT00985491).

Participants were recruited from candidates eligible for bariatric surgery in the program of Bariatric Surgery at the Pontificia Universidad Católica de Chile. Eligible subjects were 18 years or older and 55 years or younger with a body mass index (BMI) greater than 35 kg/m^2 if presenting with comorbidities such as hypertension, diabetes, and/or dyslipidemia; otherwise with a BMI greater than 40 kg/m^2 and less than 60 kg/m^2. Exclusion criteria included pregnancy/intent to become pregnant, iron deficiency and/or iron deficiency anemia, unresolved alcohol or drug addiction, use of weight loss medication, anticoagulant use, severe coagulopathy, inability to discontinue nonsteroidal anti-inflammatory drugs, inflammatory bowel disease, symptomatic kidney stones, symptomatic gallstones, known bacterial infection at time of implant, anomalies or previous surgery of the gastrointestinal tract that could affect the ability to place the device, severe gastroesophageal reflux disease, or nontreated Helicobacter pylori.

Study Design

At baseline visit, subjects were instructed by a dietitian to consume a liquid diet the first week after implantation, a pureed diet during the second week, and a normal diet (1200–1500 kcal/d) combined with moderate physical activity (eg, brisk walking) for the remainder of the study duration. There were no other interventions, diet or exercise monitoring, throughout the study. Subjects were discharged the day after the implant, if they were able to tolerate the liquid diet. Participants were also instructed to take a provided proton pump inhibitor (40 mg BID omeprazole; Lomex, Saval, Santiago, Chile) starting 3 days before the implant through 2 weeks after explant. Daily multivitamin (Centrum, Wyeth, Santiago, Chile) and iron supplements (Folifer, Santiago, Chile) were provided and recommended for use during the 52 weeks of the implant duration. Helicobacter pylori was eradicated in all subjects with a positive urease test before DJBL implantation.

Postimplantation, all participants were evaluated at week 1 and then every 4 weeks until week 52 or time of device explantation. Visits included assessments of safety, weight, waist and hip circumference, and blood pressure. Surveillance endoscopies were performed at 12, 24, and 36 weeks. Per the protocol, device migration of 2 cm or more mandated explantation whether the subject was symptomatic or not. Baseline and postimplantation assessment included anthropometric measurements, fasting glucose, serum insulin, HbA_{1c}, lipid profile, hematocrit, hemoglobin, iron, calcium, and vitamin D. All blood samples were collected after an overnight fast and were analyzed at the laboratory of Pontificia Universidad Católica de Chile. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as $(\text{insulin}_{\text{fasting}} - \text{glucose}_{\text{fasting}})/22.5$. Metabolic syndrome was defined according to the Adult Treatment Panel III criteria.[19] All subjects were assessed at baseline with chest radiography, abdominal ultrasonography, electrocardiography, upper gastrointestinal endoscopy, and urease testing (He-Py Test: Bios-Chile, Santiago, Chile). Postexplantation, all participants were evaluated at months 1, 3, and 6. All these visits included assessments of safety, weight, waist, and hip circumference and blood pressure. An upper gastrointestinal endoscopy was performed at month 1.

Endpoints

Safety was evaluated in all subjects enrolled in this study. All adverse events were categorized using the MedDRA coding dictionary, version 10. Efficacy was evaluated per protocol analysis on the completer population implanted with the DJBL, defined as all subjects who completed the study through 52 weeks. The percentage of EWL was calculated as the amount of weight in kg that exceeded a BMI of 25 kg/m^2.[20]

The primary efficacy endpoints were changes in body weight, BMI, and EWL from baseline to week 52. Secondary efficacy endpoints included change from baseline to week 52 of waist circumference, blood pressure, lipids, glycemic variables (fasting glucose, insulin, HOMA-IR, HbA_{1c}), and metabolic syndrome.

DJBL Implantation and Explantation

Subjects were admitted to the hospital in the morning of device implantation after 12 hours of fasting. Implantation was performed under general anesthesia with endotracheal intubation with endoscopic and fluoroscopic guidance as described.[16]

Subjects underwent DJBL removal after 12 hours of fasting. Explantation was similarly performed under general anesthesia with

endotracheal intubation with endoscopic visualization and fluoroscopic guidance as was previously described.[16] Subjects were discharged the same or following day.

Statistical Analysis

Student t test and χ^2 test for proportions were used in the analysis, as appropriate. Data were analyzed with the use of STATA software (version 11.0: StataCorp LP, College Station, TX) or SAS, version 9.2 or later (SAS Institute Inc, Cary, NC). Results are given as mean ± SEM unless otherwise specified.

RESULTS

Study Population

Forty-two of 54 screened subjects met inclusion/exclusion study criteria and 39 of them were implanted (Fig. 2). Three subjects were not implanted due to an unfavorable anatomy of the duodenal bulb (short duodenal bulb) that made it difficult to achieve adequate positioning of the DJBL. A summary of baseline characteristics and subject demographics is shown in Table 1. Total implantation time was 24 ± 2 minutes (mean ± SEM) and total fluoroscopic time was 8 ± 1 minutes. Among the 39 implanted subjects, 24 (64%) completed 52 weeks of follow-up. Endoscopic explantation of the DJBL was successful in all subjects. Total explantation time was 16 ± 3 minutes and total fluoroscopic time was 1 ± 0.3 minute.

Weight Loss, Cardiovascular, and Metabolic Parameters

Key weight change parameters over the 52 weeks postimplant are shown in Figure 3. Total body weight change from baseline was −22.1 ± 2.1 kg (range −38 kg to −2.1 kg) corresponding to a 19.9 ± 1.8% reduction (Fig. 3). BMI change from baseline was −9.1 ± 0.9 kg/m^2 and EWL was 47.0 ± 4.4% ($P < 0.0001$). Total body weight changes from baseline at 1, 3, and 6 months postexplant were −23.1 kg ($P < 0.0001$), −20.5 kg ($P < 0.0001$), and −17.7 kg ($P < 0.0001$), respectively (Fig. 4).

Secondary variables evaluated at 52 weeks (Table 2) demonstrated statistically significant reductions in waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and fasting glucose. In addition, the prevalence of metabolic syndrome was reduced from 83.3% to 41.6% of subjects ($P = 0.012$).

Among all implanted subjects, 6 were obese with T2DM. In these 6 subjects, body weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, and HbA_{1c} were all significantly reduced from baseline (Table 3). At week 52, the 18 obese subjects without T2DM had statistically significant reductions in body weight, BMI, waist circumference, diastolic blood pressure, total cholesterol, LDL-C, triglycerides, fasting glucose, fasting insulin, and insulin resistance (Table 3).

TABLE 1. Baseline Demographics and Subject Characteristics for the Implanted Population

	Subjects (N = 39)
Age, mean ± SD, y	35.6 ± 10.4
Gender, n (%)	
Female	31 (79.5)
Male	8 (20.5)
Race: caucasian, n (%)	39 (100)
Weight, mean ± SD, kg	108.9 ± 17.6
Waist circumference, mean ± SD, cm	115.0 ± 12.4
BMI, mean ± SD, kg/m^2	43.7 ± 5.9
Comorbidities, n (%)	
Type 2 diabetes	6 (15.4)
Insulin resistant	31 (79.5)
Hypertension	14 (35.9)
Dyslipidemia	5 (12.8)
Metabolic syndrome	26 (66.7)
Fatty liver disease	24 (61.5)

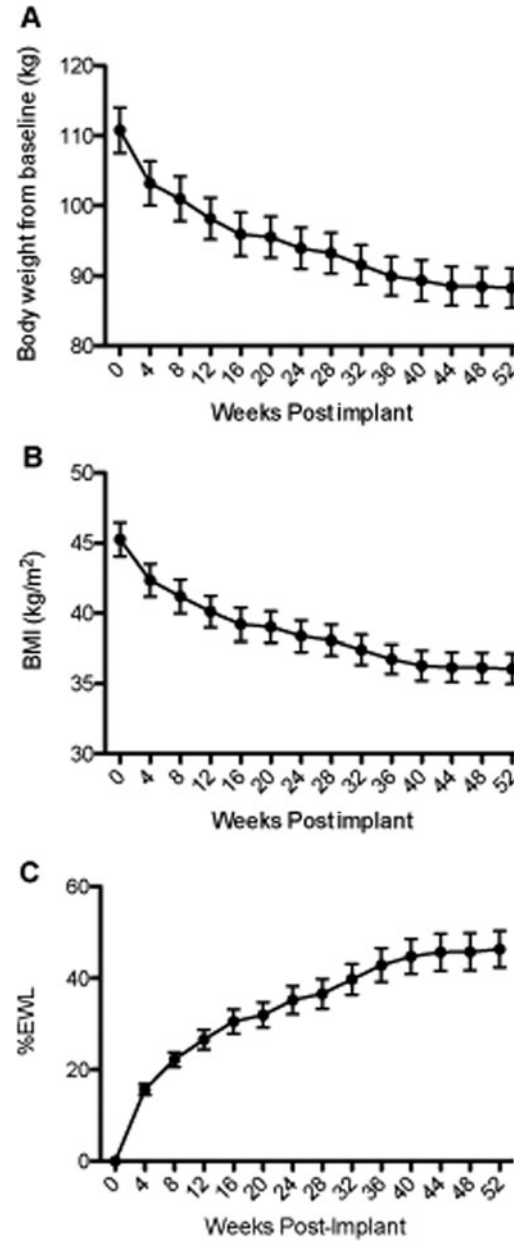

FIGURE 3. Effect of the DJBL on body weight over 52 weeks in the completer population, per protocol analysis (n = 24). A, Body weight from baseline over the observation period. B, BMI from baseline over the observation period. C, Percentage of EWL from baseline over the observation period. Mean ± SEM.

Safety and Tolerability

In the safety analysis population (N = 42), there were no procedure (implant/explant) related complications and no severe postprocedure adverse events. Among the 39 implanted subjects, 15 were explanted before 52 weeks and 24 completed 52 weeks of follow-up. The most frequent mild-to-moderate adverse events were gastrointestinal in nature: upper abdominal pain (81%), nausea (41%), vomiting (33%), and gastroenteritis (4.8%). Eight subjects were explanted because of device migration. No device migrated more than 5 cm. Reasons for endoscopic removal of the DJBL are shown in Table 4.

DISCUSSION

This is the first report of DJBL use for an implant period of 1 year. All treated subjects met the NIH (National Institute of Health) guidelines criteria for bariatric surgery candidates.[21] Mean baseline weight and BMI were 109 kg/m^2 and 44 kg/m^2, respectively. Over the course of the study, subjects who completed 52 weeks lost a mean of 22 kg (20%) and 47% EWL. The observed results of the 1-year weight loss is superior to the weight loss commonly observed after medical therapy at 1 year of follow-up and is similar to the 1-year weight loss observed after some bariatric procedures, for example, gastric banding.[22] Associated with the DJBL weight change was significant improvements in many cardiovascular risk factors.

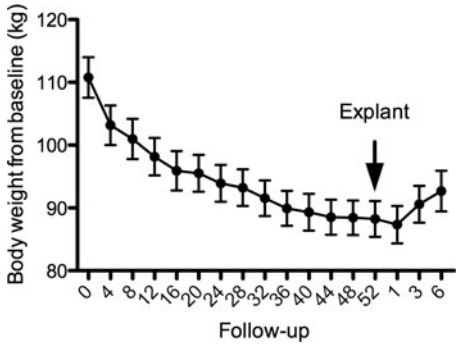

FIGURE 4: Effect of the DJBL on body weight over 52 weeks of implantation and 6 months postexplant in the completer population, per protocol analysis (n = 24). Follow-up is expressed in weeks from baseline to explant and in months after explant. Mean ± SEM.

TABLE 3. Effects of the DJBL on Metabolic Parameter Change From Baseline in the 52-Week Completer Population Stratified by T2DM or Non-T2DM

	Week 52 Change From Baseline	*P*
Obese subjects with type 2 diabetes (n = 6)		
Weight, kg	−17.1 ± 4.3	0.0109
BMI, kg/m^2	−7.3 ± 1.8	0.0105
Waist circumference, cm	−16.5 ± 3.0	0.0027
Systolic blood pressure, mm Hg	−17 ± 6	0.0405
Diastolic blood pressure, mm Hg	−16 ± 2	0.0003
HbA_{1c}, %	−1.4 ± 0.6	0.0525
Obese subjects without diabetes (n = 18)		
Weight, kg	−24.1 ± 2.4	<0.0001
BMI, kg/m^2	−9.8 ± 0.9	<0.0001
Waist circumference, cm	−22.0 ± 1.9	<0.0001
Diastolic blood pressure, mm Hg	−13 ± 2	<0.0001
Total cholesterol, mg/dL	−40 ± 7	<0.0001
LDL-C, mg/dL	−28 ± 5	<0.0001
Triglycerides, mg/dL	−49 ± 14	0.0031
Fasting glucose, mg/dL	−5.8 ± 1.3	0.0003
Fasting insulin, μU/mL	−7.0 ± 1.6	0.0006
HOMA-IR	−1.7 ± 0.4	0.0002

Values are expressed as Mean ± SEM unless otherwise indicated. P values were calculated from paired Student *t* tests.

TABLE 4. Reasons for Early Explantation of the DJBL

Reason	Subjects (N = 15)	Comments
Anchor Movement: n		
Weeks 12–24	1	
Weeks 24–36	2	
After week 36	5	
Total	8	
Device obstruction, n	3	Weeks 1, 8, and 10
Abdominal pain, n	2	Weeks 1 and 11
Acute cholecystitis, n	1	Week 12
Patient request, n	1	At week 24 had RYGB

RYGB indicates Roux-en-Y gastric bypass.

TABLE 2. Effects of the DJBL on Metabolic Parameters in the 52-Week Completer Population (N = 24)

	Baseline n = 24	Week 12 n = 24	Week 24 n = 24	Week 36 n = 24	Week 52 n = 24
Weight, kg	110.6 ± 3.4	98.2 ± 3.0 $P < 0.0001$	93.9 ± 2.9 $P < 0.0001$	89.9 ± 2.8 $P < 0.0001$	88.2 ± 2.8 $P < 0.0001$
BMI, kg/m^2	45.1 ± 1.3	40.1 ± 1.1 $P < 0.0001$	38.4 ± 1.1 $P < 0.0001$	36.7 ± 1.0 $P < 0.0001$	36.0 ± 1.1 $P < 0.0001$
Waist circumference, cm	120.5 ± 6.8	105.1 ± 2.2 $P = 0.0023$	100.1 ± 2.5 $P = 0.0122$	96.1 ± 2.5 $P = 0.0007$	96.0 ± 2.6 $P = 0.0012$
Systolic blood pressure, mm Hg	134 ± 3	135 ± 3 $P = 0.7287$	131 ± 4 $P = 0.5335$	125 ± 3 $P = 0.0078$	125 ± 2 $P = 0.0106$
Diastolic blood pressure, mm Hg	85 ± 1	80 ± 2 $P = 0.0530$	81 ± 3 $P = 0.1789$	80 ± 2 $P = 0.0401$	71 ± 2 $P < 0.0001$
Total cholesterol, mg/dL	197 ± 7	165 ± 8 $P < 0.0001$	164 ± 8 $P < 0.0001$	159 ± 7 $P < 0.0001$	161 ± 8 $P < 0.0001$
HDL-C, mg/dL	44 ± 2	39 ± 2 $P = 0.0026$	43 ± 2 $P = 0.4188$	42 ± 2 $P = 0.2260$	44 ± 2 $P = 0.7000$
LDL-C, mg/dL	121 ± 6	98 ± 7 $P < 0.0001$	95 ± 7 $P < 0.0001$	92 ± 5 $P < 0.0001$	95 ± 7 $P < 0.0001$
Triglycerides, mg/dL	160 ± 16	142 ± 13 $P = 0.1654$	133 ± 12 $P = 0.0749$	123 ± 11 $P = 0.0203$	115 ± 11 $P = 0.0025$
Fasting glucose, mg/dL	104 ± 6	95 ± 3 $P = 0.1520$	94 ± 3 $P = 0.0295$	95 ± 4 $P = 0.0894$	94 ± 6 $P = 0.0131$
Fasting insulin, μU/mL	21 ± 2	18 ± 3 $P = 0.2512$	14 ± 2 $P < 0.0001$	14 ± 2 $P = 0.0047$	16 ± 4 $P = 0.0923$
HOMA-IR	5.7 ± 0.9	4.3 ± 0.6 $P = 0.0275$	3.4 ± 0.4 $P = 0.0003$	3.5 ± 0.7 $P = 0.0064$	4.6 ± 1.8 $P = 0.4249$
HbA_{1c}, %	6.3 ± 0.3	5.8 ± 0.1 $P = 0.0377$	5.8 ± 0.1 $P = 0.0393$	5.9 ± 0.1 $P = 0.1607$	6.0 ± 0.2 $P = 0.0944$

Values are expressed as Mean ± SEM. *P* values are for change from baseline and were calculated from paired Student *t* test.

At 1-year of follow-up, these subjects had significant reductions in waist circumference, blood pressure, LDL-C, triglycerides, and fasting glucose. This explains the dramatic reduction in the prevalence of metabolic syndrome from 83% to 42% at the end of the year. In the 6 subjects with T2DM, HbA1c had a clinically significant mean reduction of 1.4%. Interestingly, the fasting insulin level and HOMA-IR value is significantly reduced at week 36 but not at week 52 (Table 2). Indeed, the mean insulin and HOMA-IR increased from week 36 to 52. The analysis per patient allowed us to identify 1 patient with a poor response to the treatment. From baseline to week 52, this patient presented a weight reduction of 2.1 kg with a fasting glucose and insulin of 205 mg/dL and 28.1 μU/mL at baseline (HOMA-IR = 14.2) and 213 mg/dL and 81 μU/mL at 52 weeks (HOMA-IR = 42.6). In a small sample of patients, this outlier affects significantly these results. The mean $\pm$ SEM HOMA-IR at 52 weeks, excluding this outlier (n = 23), is 2.8 $\pm$ 0.49 instead of 4.6 $\pm$ 1.8 (n = 24) with this subject.

Because the intent of this study was to evaluate the safety and efficacy of the DJBL without adjunct weight loss therapies, these were not added to subject regimens except for a general recommendation of diet and physical activity at baseline. It is well known that the combination of 2 or more therapies can achieve a greater reduction of weight than either therapy alone. In the Diabetes Prevention Program (DPP) the combination of lifestyle modification plus pharmacotherapy resulted in almost double the weight loss, with a mean of 12 kg at 1 year, compared with groups receiving either pharmacotherapy or sibutramine alone.[23] Papalazarou et al[24] recently reported greater weight reductions over 3 years in patients who underwent vertical banded gastroplasty combined with lifestyle interventions compared with patients undergoing standard postprocedure care. Therefore, addition of lifestyle intervention, pharmacotherapy, and/or supervised physical activity could improve the results of DJBL treatment even further in the context of a multidisciplinary approach.

After intentional weight loss, weight regain is a major challenge. This is especially true for medical treatment but is also seen in bariatric surgery.[25,26] Less than 20% of patients can lose and maintain a 10% weight reduction with medical treatment during the first year.[27] In this series, subjects regained a mean of 4.4 kg after 6 months following the removal of the DJBL without any kind of maintenance program. This represents a weight change of -17.7 kg from baseline to 18 months in subjects who completed 52 weeks of implantation. Weight loss maintenance in the DPP helped 37% of patients maintain a weight loss of at least 7% after 3 years.[28,29] Using similar strategies, other studies show that patients can lose and preserve 3.2% of their original body weight for at least 2 years.[26,30] A multidisciplinary maintenance program may be helpful post DJBL removal to prevent weight regain in these patients and should be evaluated in future trials.

The safety and tolerability of the DJBL for 1 year was demonstrated. Fifteen out of 39 implanted subjects were explanted before week 52, primarily due to device migration or obstruction. In subjects with device obstructions or removal due to abdominal pain, episodes of overeating were identified. Detailed recommendations regarding eating behavior and diet composition may prevent or diminish this problem in the future. In these 15 subjects, the median duration of implant was 24 weeks. Considering that most of weight reduction (75% in 52 weeks completers) occurs during the first 6 months of implantation, most of these 15 subjects received a significant benefit from the implant.

Eight of 39 subjects were explanted earlier because of device migration. The long-term stability and safety profile of the DJBL has been improving with clinical experience and device modifications. In its initial experience, the rate of migration was 42% at 24 weeks,[14] significantly higher than the 3% at 24 weeks observed in this series with the new anchoring design. This dramatic improvement in stability together with the significant effect on weight loss and cardiovascular risk factors may permit considering the DJBL as a primary alternative for the treatment of morbid obesity.

The DJBL's endoscopic reversibility is advantageous, as long-term nutritional deficiencies and malnutrition problems inherent to bariatric surgery may be avoided. A potential disadvantage is the impact on long-term efficacy and weight maintenance. Ten-year follow-up of the DPP outcomes study showed that lifestyle group subjects regained weight over time, ultimately weighing only 2 kg less than at randomization.[29] Nevertheless, 10 years later, the cumulative incidence of diabetes remained lower in this group than in other treatment groups with less weight loss, underscoring the ability of even modest weight loss to prevent long-term comorbidities. In addition, the DJBL most likely will be able to be reimplanted. It is an interesting alternative that should be explored in that future and could provide continued long-term efficacy.

This study is the first report of the efficacy and safety of the DJBL for 1 year, which adds to what was previously reported in studies with shorter follow-up. However, this study has some limitations. The small sample size may limit the statistical power of the study and true associations could not be found for that reason. As a single arm open label study, there is no comparative group. Although the intent of this study was to evaluate the safety and efficacy of the DJBL without adjunct weight loss therapies, we cannot rule out some minor effect on weight loss due to the initial baseline recommendation of diet and physical activity. The 1-year efficacy was evaluated only in subjects who completed 52 weeks. Intention-to-treat analyses should be included in future randomized controlled trials to analyze at 1 year all implanted patients, including patients explanted before the 52 weeks.

CONCLUSIONS

The DJBL is safe when implanted for 1 year, and results in significant weight loss and improvements in cardiometabolic risk factors. These results suggest the DJBL may be considered as an alternative primary treatment of morbid obesity and supports the future conduct of long-term, randomized, controlled clinical trials.

ACKNOWLEDGMENTS

The authors thank Andy Levine and Ken Malomo for data analysis and assistance in the conduct of the study and Loretta L. Nielsen for revision of the written manuscript.

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