Effect of the Duodenal-Jejunal Bypass Liner on Glycemic Control in Patients With Type 2 Diabetes With Obesity: A Meta-analysis With Secondary Analysis on Weight Loss and Hormonal Changes

OBJECTIVE
Duodenal-jejunal bypass liner (DJBL) is an endoscopic device that may mimic small bowel mechanisms of Roux-en-Y gastric bypass (RYGB). Previous studies have demonstrated the efficacy of DJBL at inducing weight loss. We assessed the effect of DJBL on glycemic control in patients with type 2 diabetes (T2D) with obesity.

RESEARCH DESIGN AND METHODS
Data sources included MEDLINE, EMBASE, and Web of Science through 1 July 2017. Included were published studies that assessed DJBL outcomes in obese T2D patients.

RESULTS
Primary outcomes were change in HbA1c and HOMA of insulin resistance (HOMA-IR). Secondary outcomes were change in weight and gut hormones glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and ghrelin. Seventeen studies were included. At explant, HbA1c decreased by 1.3% [95% CI 1.0, 1.6] and HOMA-IR decreased by 4.6 [2.9, 6.3]. Compared with control subjects, DJBL subjects had greater HbA1c reduction by 0.9% [0.5, 1.3]. Six months after explant, HbA1c remained lower than baseline by 0.9% [0.6, 1.2]. At explant, patients lost 11.3 kg [10.3, 12.2], corresponding to a BMI reduction of 4.1 kg/m² [3.4, 4.9], total weight loss of 18.9% [7.2, 30.6], and excess weight loss of 36.9% [29.2, 44.6]. The amount of weight loss remained significant at 1 year postexplantation. After DJBL, GIP decreased, whereas GLP-1, PYY, and ghrelin increased.

CONCLUSIONS
DJBL improves glycemic control and insulin resistance in T2D patients with obesity. DJBL also appears to induce significant weight loss in this population. Additionally, changes in gut hormones suggest mechanisms similar to RYGB. Study limitations included heterogeneity among studies.
Type 2 diabetes (T2D) is one of the major comorbidities associated with obesity. As the prevalence of obesity rises, the number of patients affected by these comorbidities will continue to increase (1). In 2015, 30.3 million Americans, or 9.4% of the U.S. population, had T2D, which resulted in a 245 billion U.S. dollar cost to the health care system (2).

Traditionally, T2D has been treated with oral and injectable medications. Nevertheless, despite maximal doses and a combination of medical therapy, a proportion of patients fail to achieve adequate glycemic control. More recently, it has been demonstrated that Roux-en-Y gastric bypass (RYGB) is effective at inducing T2D remission in ~84–90% of patients at 1 year and 29–50% at 5 years (3–7). Specifically, Mingrone et al. (8) demonstrated in a randomized controlled trial (RCT) that more patients who underwent RYGB were able to maintain T2D remission at 5 years than those who were medically managed (37% vs. 0%, respectively). Similarly, a more recent RCT (the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently [STAMPEDE] trial) demonstrated similar findings. At 5 years, more patients who underwent RYGB had hemoglobin A1c (HbA1c) of <6% compared with those who received intensive antiabetic medical therapy alone (29% vs. 5%, respectively) (9,10). In addition, the RYGB group had a greater reduction in HbA1c than those who received medical therapy alone (2.1% vs. 0.3%, respectively). As a result, a recent joint statement by international diabetes organizations has suggested that metabolic surgery be recommended to treat T2D in patients with class III obesity (BMI ≥40 kg/m²) regardless of glycemic control and class I obesity (BMI 35–39.9 kg/m²) when hyperglycemia is inadequately controlled with lifestyle and optimal medical therapy. Surgery may also be considered for patients with T2D and class I obesity (BMI 30–34.9 kg/m²) if hyperglycemia remains inadequately controlled despite optimal treatment with either oral or injectable medications (11,12).

It has been hypothesized that some of the metabolic effect of RYGB appears to be independent of weight loss. In the foregut hypothesis, it is thought that RYGB excludes the proximal small intestine from being in contact with ingested nutrients. This may lead to a decrease in the secretion of unidentified duodenal factors that usually promote insulin resistance and T2D (13). Alternatively, the hindgut hypothesis proposes that RYGB leads to early delivery of nutrients to the distal small bowel, which then stimulates L cells in the terminal ileum and proximal colon to secrete more glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and other hormones (14). These ultimately lead to enhanced insulin secretion by pancreatic β-cells and decreased insulin resistance (15,16).

Given a known impact of RYGB on glycemic control, an endoscopic bariatric and metabolic device called the duodenal-jejunal bypass liner (DJBL) was developed to mimic some of the proposed small bowel mechanisms of RYGB. Specifically, DJBL is a 60-cm fluoropolymer liner that is anchored at the duodenal bulb and ends at the jejunum. It is placed and removed endoscopically and allows nutrients to pass directly from the stomach into the jejunum. Similar to the foregut hypothesis, the duodenum and proximal jejunum are excluded from direct contact with chyme, potentially downregulating production of anti-incretins. At the same time, undigested nutrients and bile reach the distal small intestine before mixing, potentially triggering hindgut mechanisms including upregulation of incretin production.

A recent meta-analysis has demonstrated the efficacy of the DJBL on inducing weight loss in patients with obesity regardless of diabetes status (17). However, the study did not find significant metabolic effects in the secondary analysis. We therefore aimed to conduct a systematic review and meta-analysis with a primary focus on assessing the effect of the DJBL on glycemic control in patients with obesity and concomitant T2D. In addition, a meta-regression was performed to assess predictors of response.

**RESEARCH DESIGN AND METHODS**

**Data Sources and Searches**

The search strategy, study eligibility criteria, selection process, data collection process, primary and secondary outcomes, and analyses were defined a priori and are described below.

We searched three databases—MEDLINE, EMBASE, and Web of Science—from inception to 1 July 2017 without language or study design restriction. An extensive search strategy was employed to find articles that relate to changes in HbA1c or weight or gut hormones after DJBL. Specifically, the following were searched by text words in the title and abstract: Endobarrier, duodenal sleeve*, jejunal sleeve*, gastrointestinal liner*, bypass liner*, duodenal jejunal bypass sleeve*, Gl dynamics sleeve*, GI dynamic*.

Duplicates were removed. Two of the authors (P.J. and A.V.H.) then independently reviewed titles and abstracts produced by the search. Studies deemed potentially relevant were reviewed in full to determine eligibility. Disagreements regarding final study inclusion were resolved by discussion with the senior author (C.C.T.).

**Study Selection**

**Study Design and Population**

RCTs, observational cohort studies, and case series that were published and peer reviewed were included. Reviews, editorials, case-control studies, case reports, conference abstracts, and studies using nonhuman subjects were excluded, as were articles without full text availability or English translation. Only one study from the same research group was selected to preserve independence of observations. Studies were included if there were adult subjects (defined as age >18 years) with obesity (defined as BMI ≥30 kg/m²) and T2D (defined as HbA1c ≥6.5%, or 48 mmol/mol, who underwent DJBL implantation. Studies that assessed changes in HbA1c as either a primary or secondary outcome were included. If a study included patients with obesity with and without T2D, only those with T2D were included in the analysis. Studies that did not contain a variance parameter were excluded. Corresponding authors were contacted for additional information if needed.

**Outcomes**

The primary outcomes were the change in HbA1c and HOMA of insulin resistance (HOMA-IR) at time of DJBL explantation compared with the levels at time of implantation.

Secondary outcomes were the change in HbA1c postexplantation and the changes in weight and gut hormones at time of explantation. In this study, the gut hormones of interest included ghrelin, glucose-dependent insulinoetric peptide (GIP), GLP-1, and PYY. If a study included both fasting and postprandial values, fasting ghrelin, postprandial GIP, postprandial GLP-1, and postprandial PYY levels were used for our analysis. Additionally,
pooled serious adverse events (SAEs) were reported. In this study, SAEs were defined as severe abdominal pain, dehydration, ulceration, gastrointestinal bleeding, acute pancreatitis, liver abscess, obstruction, and perforation. Weight changes were reported using absolute weight loss in kilograms (kg), percent total weight loss (TWL), and percent excess weight loss (EWL).

Data Synthesis and Analysis

Our primary analysis was the change in percentage HbA1c, at time of DJBL explantation compared with the level at time of implantation. Traditional forest plots with two-sided 95% CIs were constructed. Subgroup analysis of the RCT studies was also performed.

Secondary analyses were defined a priori and were performed to assess the change in percentage HbA1c postexplantation compared with the level at time of implantation. Additionally, the effect of DJBL on weight loss was assessed and reported using absolute weight loss, TWL, or EWL. Gut hormonal change at time of explantation compared with baseline was reported using Hedges' g. Additionally, pooled SAEs were summarized.

Meta-regression analyses were performed to assess the influence of predefined clinical characteristics on the primary outcome. Significant predictors from the univariable regression analysis were included in the multivariable meta-regression analysis.

For studies that only provided CIs or interquartile ranges and those for which we were unable to obtain SD or SEM from the authors, a normal distribution was assumed in order to calculate SD and SEM. Heterogeneity was assessed for the individual meta-analyses using the $\chi^2$ test and the $I^2$ statistic. Significant heterogeneity was defined as $P < 0.05$ using the $\chi^2$ or $I^2 > 50\%$. A random-effects model was used except when statistical heterogeneity was not significant. Differences in subgroups were assessed using a $\chi^2$ test for interaction with a $P < 0.05$ defined as statistically significant. To assess for publication bias, a funnel plot was created and visually inspected for asymmetry. The trim and fill method was used to correct for funnel plot asymmetry and provide an adjusted effect. The classic fail-safe test was also applied to assess risk of bias across studies. Analyses were performed using Comprehensive Meta-Analysis, version 3.0 (Englewood, NJ).

RESULTS

Search Results

A total of 1,064 studies were identified, 147 of which were duplicates. After abstract review, 741 studies were excluded, leaving 176 articles for full manuscript review. Full article review resulted in 17 studies that satisfied all criteria and therefore were included in the systematic review and meta-analysis (Fig. 1) (18–34).

Out of 17 studies, 14 reported the effect of DJBL on glycemic control in patients with obesity and T2D; therefore, they were included in the primary meta-analysis (Table 1). None of the 14 studies that evaluated the glycemic effect of DJBL used a treat-to-target protocol. The remaining three studies reported the effect of DJBL on at least one of the following secondary outcomes: postexplantation glycemic control, weight loss, or changes in gut hormones. These studies were included in the secondary analyses. Out of the 14 studies included in the primary meta-analysis, 9 were observational studies and 5 were RCTs, with 2 comparing DJBL to a sham procedure and 3 comparing DJBL to lifestyle modification. Only the DJBL arm of the RCTs was included in the primary analysis, while both the DJBL and control arms of the RCTs were included in a subgroup analysis of the RCTs.

Primary Outcome

Effect of DJBL on HbA1c at Time of Explantation

A total of 14 included studies yielded a total of 412 obese subjects with diabetes who underwent attempted DJBL implantation. Of these, 388 underwent successful placement of DJBL (technical success rate of 94.2%). Reasons for unsuccessful implantation included abnormalities of the small intestine (such as polyps, sharp angulations, or short duodenal bulbs) and anesthetic side reaction. Mean age of the subjects ranged from 36 to 54 years old. Mean BMI and HbA1c at the time of DJBL implantation ranged from 30.0 to 48.9 kg/m² and from 6.7 to 9.2% (50 to 77 mmol/mol), respectively. On average, duration of T2D at the time of device implant ranged from 3.0 to 14.8 years. The majority (75–100%) of the subjects were on metformin at the time of implantation, while 0–63% were on insulin. Baseline diabetes medication usage is shown in Supplementary Table 1. On average, the device was implanted for 8.4 ± 4.0 months. At the time of DJBL explantation, HbA1c decreased by 1.3% [95% CI 1.0, 1.6] ($P < 0.0001$) (Fig. 2A), which corresponded to 13.3 mmol/mol [8.1, 18.5] ($P < 0.0001$). Heterogeneity across studies was high, with an $I^2$ of 62 ($P = 0.001$) and a Q-value of 34. Similarly, HOMA-IR significantly decreased by 4.6 [2.9, 6.3] ($P < 0.0001$) (five studies with 91 patients; average time of 9.6 ± 3.5 months from implantation). Fasting insulin decreased by 4.8 μU/L [2.7, 6.8] ($P < 0.0001$) (six studies with 122 patients; average time of 9.1 ± 3.4 months), and fasting glucose decreased by 44.6 mg/dL [31.2, 57.9] ($P < 0.0001$) (nine studies with 164 patients; average time of 8.2 ± 3.5 months).

In studies with baseline HbA1c ≥8%, or 64 mmol/mol, there was a greater reduction in HbA1c and fasting glucose compared with studies with lower initial HbA1c (change in HbA1c −1.4% [−1.7, −1.0] vs. −0.5% [−1.3, 0.2] or −15.3 mmol/mol [−18.6, −10.9] vs. −5.5 mmol/mol [−14.2, 2.2], $P$ for the difference = 0.03) (change in fasting glucose −49.2 mg/dL [−56.8, −41.5] vs. −5.4 mg/dL [−39.5, 28.7], $P$ for the difference = 0.01). There were no significant differences in the amount of change in HOMA-IR and fasting insulin in studies with higher versus lower baseline HbA1c. For the observational studies, the NOS scores were 8 in five studies and 7 in four studies. The major shortcoming was lack of blinding of outcome assessors in all studies. For the RCTs, the Jadad scores were 3 in two studies and 2 in three studies. None of the RCT studies were double-blind.

Risk of bias across studies was assessed using a funnel plot. Visual inspection demonstrated that smaller and statistically significant studies appeared to be
missing. The Duval and Tweedie trim and fill method resulted in a greater decrease in HbA1c at the time of explantation compared with baseline (1.4% [1.0, 1.7] vs. 1.3% [1.0, 1.6]) (15.3 mmol/mol [10.9, 18.6] vs. 14.2 mmol/mol [10.9, 17.5]). The classic fail-safe method suggested that 598 studies would be required to show no change in HbA1c at the time of DJBL explantation.

**Subgroup Analysis of RCTs**

One of the five RCT studies had only one obese patient with diabetes in the control arm and therefore was excluded from the subgroup analysis of the RCTs (33). The remaining four RCT studies included a total of 116 patients with obesity and concomitant T2D (63 DJBL subjects vs. 53 control subjects). Of these, two intended to treat T2D with DJBL with HbA1c being a primary or coprimary outcome, while the remaining two intended to treat obesity with DJBL with changes in HbA1c being one of the secondary outcomes. On average, the device was implanted for 4.5 ± 1.7 months. At the time of DJBL explantation, the DJBL group had a greater decrease in HbA1c by 0.9% [0.5, 1.3] (P < 0.0001) (Fig. 2B), or 9.7 mmol/mol [4.8, 14.7], compared with the control group (P < 0.0001). Heterogeneity across studies was low with an I² of 0 (P = 0.848) and a Q-value of 0.8. The remove-one analysis showed consistent results with a greater decrease in HbA1c in the DJBL arm compared with the control arm by 0.9% [0.5, 1.3], or 9.7 mmol/mol [4.8, 14.7].

**Secondary Outcomes**

**Effect of DJBL on HbA1c Postexplantation**

Six studies reported follow-up HbA1c after DJBL explantation. Of these, two, four, and two studies assessed HbA1c levels at 3, 6, and 12 months postexplantation, respectively. Of note, some studies reported postexplantation HbA1c at more than one time point. Supplementary Table 2 demonstrates T2D medication usage throughout the study period, including at the time of postexplantation follow-ups.

At 3 months after device removal (two studies with 46 patients; average total time of 12.3 months from implantation), HbA1c remained significantly lower than the baseline level by 2.2% [1.6, 2.7] (P < 0.0001), or 19.1 mmol/mol [8.0, 30.2] (P = 0.001). Heterogeneity across studies was low with an I² of 42 (P = 0.189) and a Q-value of 1.7.

At 6 months after device removal (four studies with 120 patients; average total time of 15.1 months from implantation), HbA1c remained significantly lower than the baseline level by 0.9% [0.6, 1.2] (P < 0.0001), or 10.0 mmol/mol [7.0, 13.1] (P < 0.0001). Heterogeneity across studies was low with an I² of 47 (P = 0.129) and a Q-value of 5.7.
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<th>Table 1—Characteristics of studies included in the primary meta-analysis</th>
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<td>Stratmann 2016** Germany</td>
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<td><strong>RCTs</strong></td>
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<td>Tarnoff 2009** Chile</td>
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Data are presented as means, means ± SD, median [range], or range unless otherwise indicated. *Number of patients who successfully underwent DJBL implantation. **No weight data on the diabetes subgroup.
At 12 months after device removal (two studies with 80 patients; average time of 23.0 months from implantation), there was no statistically significant difference in HbA1c compared with the baseline level ($P = 0.865$). Heterogeneity across studies was high with an $I^2$ of 68 ($P = 0.078$) and a $Q$-value of 3.1.

**Effect of DJBL on Weight Loss in Patients With Obesity and Concomitant T2D**

Ten studies with a total of 352 patients assessed the effect of DJBL on the amount of weight loss in patients with obesity and concomitant T2D. At the time of explantation (9.2 ± 3.1 months from device implantation), patients lost 11.3 kg [10.3, 12.2] ($P = 0.0001$) (Fig. 3). Heterogeneity across studies was low with an $I^2$ of 25 ($P = 0.209$) and a $Q$-value of 3.1. This corresponded to a decrease in BMI of 4.1 kg/m$^2$ [3.4, 4.9] ($P < 0.0001$) (nine studies with 340 subjects), TWL of 18.9% [7.2, 30.6] ($P = 0.002$) (four studies with 305 subjects), and EWL of 36.9% [29.2, 44.6] ($P < 0.0001$) (four studies with 301 subjects). Six studies reported follow-up weights after DJBL explantation. Of these, one, three, and two studies assessed follow-up weights at 3, 6, and 12 months postexplantation, respectively.

At 6 months after device removal (three studies with 104 subjects; average time of 15.3 months from implantation), patient weights remained significantly lower than the baseline weights by 7.1 kg [5.2, 9.0] ($P < 0.0001$). This corresponded to a decrease in BMI of 2.1 kg/m$^2$ [1.1, 3.1] ($P < 0.0001$) (three studies with 104 subjects), TWL of 8.0% [5.9, 10.2] ($P < 0.0001$) (two studies with 131 subjects), and EWL of 25.5% [13.5, 37.4] ($P < 0.0001$) (two studies with 131 subjects).

Similarly, at 12 months after device removal (two studies with 80 subjects; average time of 23.0 months from implantation), patient weights remained significantly lower than the baseline weights by 10.7 kg [5.0, 16.4] ($P < 0.0001$). This corresponded to a decrease in BMI of 3.9 kg/m$^2$ [1.4, 6.3] ($P = 0.002$) (two studies with 80 subjects), TWL of 7.2% [5.5, 8.9] ($P < 0.0001$) (two studies with 80 subjects), and EWL of 27.7% (one study with 59 subjects).

**Effect of DJBL on Gut Hormones at Time of Explantation**

Seven studies with a total of 124 patients reported the changes in gut hormones after DJBL implantation. Of these, six, five, four, and three studies assessed changes in GLP-1, GIP, ghrelin, and PYY, respectively. **GLP-1.** Of the six studies, five assessed changes in postprandial GLP-1 (22, 26, 30,
while one evaluated changes in fasting GLP-1 after DJBL (28). Overall, GLP-1 level did not significantly change after DJBL (Hedges’ g of 0.33 [−0.09, 0.75], P = 0.13, I² = 77). However, when only studies that evaluated postprandial GLP-1 were included (the preferred method of analysis) (14), there was a significant increase in postprandial GLP-1 levels after DJBL (Hedges’ g of 0.46 [0.02, 0.90], P = 0.04, I² = 75). GIP. Of the five studies, four assessed changes in postprandial GIP (21,26,30,32), while one evaluated changes in fasting GIP after DJBL (28). GIP level was significantly lower than the baseline level (Hedges’ g of −0.36 [−0.57, −0.15], P < 0.001, I² = 26 when all five studies were included) (Hedges’ g of −0.33 [−0.56, −0.10], P = 0.006, I² = 37 when only four studies with postprandial GIP were included). Ghrelin. All four studies evaluated changes in fasting ghrelin (21,28,32,34). After DJBL, fasting ghrelin significantly increased (Hedges’ g of 1.45 [0.25, 2.65], P = 0.018, I² = 92). PYY. Of the three studies, two assessed changes in postprandial PYY (30,32), while one evaluated changes in fasting PYY (34). Overall, PYY significantly increased after DJBL (Hedges’ g of 0.57 [0.08, 1.05], P = 0.023, I² = 61 when all three studies were included), although this change became nonsignificant when only two studies with postprandial PYY were included in the analysis (Hedges’ g of 0.86 [−0.42, 2.13], P = 0.19, I² = 53).

SAEs
Nine studies reported adverse events in obese patients with diabetes who received DJBL treatment. Most common adverse events were abdominal pain, nausea, and vomiting, which occurred more commonly immediately after DJBL implantation. SAEs occurred in 55 out of 350 DJBL cases (15.7%). These included gastrointestinal bleeding (16), hypoglycemic events (8), acute pancreatitis (6), sleeve migration (5), severe abdominal pain (4), liver abscesses (4), anchor perforation next to the pylorus into the stomach (4), sleeve obstruction (3), esophageal perforation during explantation (2), acute cholecystitis and duodenal fistula (1), ulceration at the duodenal bulb (1), and dehydration (1). In the control group, 19 hypoglycemic events were reported in 47 patients. Supplementary Table 3 details each SAE and its corresponding management.

Meta-Regression Analysis
On a univariable meta-regression analysis, baseline HbA1c and the amount of weight loss were significant predictors of the amount of HbA1c decrease at the time of DJBL explantation (β = −0.78 [−1.28, −0.27], P = 0.002 for baseline HbA1c and β = −0.08 [−0.16, −0.01], P = 0.027 for amount of weight loss). Baseline BMI, duration of T2D, baseline insulin use, change in HOMA-IR, and duration of device implantation were not associated with the amount of HbA1c change (P > 0.05 for all). On a multivariable meta-regression analysis, baseline HbA1c had a trend toward being a significant predictor of the improvement in glycemic control after DJBL after controlling for amount of weight loss (β = −0.72 [−1.50, 0.05], P = 0.067) (Supplementary Fig. 1). The amount of weight loss no longer predicted the amount of HbA1c change once controlled for baseline HbA1c (P = 0.14).

CONCLUSIONS
This systematic review and meta-analysis is the first to focus on a patient population with obesity and concomitant T2D. Prior studies included subjects with obesity regardless of diabetes status encompassing different phenotypes that may respond differently to a specific therapy. Our study demonstrates that DJBL is associated with significant improvements in glycemic control and weight loss, an association also notable in the poorly controlled subgroup. These metabolic and weight-loss effects appear to last up to at least 6 months and 12 months after device removal, respectively. Additionally, DJBLs is associated with an increase in GLP-1 and PYY and a decrease in GIP, supporting a possible incretin mechanism. The safety profile of DJBL appears to be acceptable, with a 15.7% SAE rate and with <1% of patients requiring surgical intervention to address adverse events.

Given the rising number of patients with obesity and concomitant T2D, effective treatments for these diseases are urgently needed. While medications and lifestyle modification are effective, some patients still fail to respond and require more aggressive therapy. Bariatric surgeries have been shown to be effective at treating obesity and T2D, with recent recommendations suggesting their use as a treatment option for T2D in patients requiring more aggressive therapy.
with BMI $\geq 40$ kg/m$^2$ or $\geq 35$ kg/m$^2$ if T2D remains inadequately controlled despite optimal medical therapy. Nevertheless, despite its efficacy, only $\sim 1\%$ of patients who are eligible undergo surgery, leaving a majority of the patient population sub-optimally managed (35,36).

Endoscopic bariatric and metabolic therapies (EBMTs) have risen to fill the treatment gap between medical and surgical therapies. EBMTs may be further categorized into gastric and small bowel therapies (37). Previous meta-analysis studies have demonstrated a significant impact of gastric EBMTs on weight loss and obesity-related comorbidities. Specifically, a meta-analysis of 17 studies including 1,683 patients shows that the ORBERA intragastric balloon (IGB) (Apollo Endosurgery, Austin, TX) is associated with EWL of 25.44% and TWL of 11.27% at 12 months after implantation (36). Additionally, IGBs are demonstrated to be associated with a decrease in HbA1c by 0.6%, or 6.6 mmol/mol (12 observational studies; 470 subjects with mean baseline HbA1c of 6.1% [5.5, 6.6], or 43 mmol/mol [37, 49]) (38). From a small bowel therapy standpoint, DJBLs remain the most widely studied device worldwide. A recent meta-analysis shows that DJBLs are associated with weight loss of 5.1 kg (four RCTs; 151 subjects) and EWL of 12.6% (four RCTs; 166 subjects) in patients with obesity (with or without T2D) (17). In this meta-analysis, only two studies were included in the diabetes subgroup analysis and no improvement in glycemic indexes were identified. Furthermore, long-term efficacy data of these EBMT devices remain to be determined.

With the aim to assess the effect of DJBLs on T2D, our study includes only patients with obesity and concomitant T2D. Out of the 14 studies included in the primary analysis, 8 include only patients with obesity and diabetes. For the remaining six, four report glycemic outcomes in diabetes subgroups, and we were able to receive the diabetes subgroup data from the authors of the remaining two studies. In our meta-analysis, 1 year after device implantation, HbA1c decreases by 1.3% or 14.2 mmol/mol (nine observational studies and five RCTs; 412 subjects) compared with baseline, which is approximately twice the decrease seen in observational studies with IGBs, although baseline HbA1c was lower in these studies.

Additionally, our study also demonstrates that DJBL is associated with significant weight loss in patients with obesity and concomitant T2D. Specifically, at the time of device explantation, patients lose 11.3 kg (ten studies; 352 patients), which corresponds to a decrease in BMI of 4.1 kg/m$^2$ (nine studies; 340 subjects), TWL of 18.9% (four studies; 305 subjects), and EWL of 36.9% (four studies; 301 subjects). Interestingly, the amount of weight loss associated with DJBL appears to be greater in patients with obesity and concomitant diabetes compared with those with obesity alone. This observation suggests that these two patient populations may represent different phenotypes, which may cause them to have a different response to the procedure. Further studies to investigate this observation are warranted.

In our study, DJBL is also shown to be associated with changes in incretin hormones in a similar direction as those following RYGB, suggesting that it touches upon some analogous small bowel mechanisms of action. Specifically, postprandial GLP-1 and PYY increase after DJBL. GLP-1 and PYY are anorectic incretin hormones that are secreted postprandially in the distal ileum/proximal colon. In addition to inducing weight loss (via increasing satiety and delaying gastric motility), both hormones are thought to play a key role in improved glucose homeostasis by inducing a release of insulin from pancreatic cells following ingestion of oral glucose. Previous studies have shown that after RYGB, GLP-1 and PYY increase compared with the presurgical levels (39–41). Of note, in our study, a subgroup analysis of postprandial GLP-1 was statistically significant from the baseline pre-DJBL levels. For PYY, a subgroup analysis on the postprandial level yielded a non-significant result. This could be due to a lack of statistical power, with only two studies reporting postprandial PYY values. In our study, GIP decreased after DJBL. Literature on GIP levels after RYGB remain heterogeneous (42,43); therefore, no comparison of GIP changes between DJBL and RYGB can be made. Furthermore, unlike RYGB that affects both gastric and small bowel anatomy, DJBL only affects small bowel mechanisms. Therefore, as expected, the gastric gut hormone, i.e., ghrelin, which is secreted in the fundus of the stomach, does not decrease after DJBL (unlike RYGB). In fact, our study shows that ghrelin increases after DJBL, a finding similar to that seen after dieting and exercise, likely as a response to weight loss (44).

Treatment with DJBL is accompanied by adverse events, with some being serious. In our study, the pooled SAE rate was 15.7%, which is comparable to other EBMTs. Most common SAEs were GI bleeding, the majority of which were treated with supportive care. There were also four hepatic abscess cases, with none requiring surgical intervention. In the 17 included studies, no deaths were reported. Of note, the U.S. Safety and Efficacy of EndoBarrier in Subjects With Type 2 Diabetes Who Are Obese (ENDO) trial was stopped early due to a hepatic abscess rate of 3.5%, which was above the predetermined threshold. Similarly, none of these patients required intensive care unit stay or surgical intervention, and there were no deaths.

This study has several limitations. First, the primary outcome of the study, i.e., the change in HbA1c at time of DJBL explantation, does not take into account the changes in antidiabetes medications throughout the study period. Additionally, many studies were initiated prior to the availability of sodium–glucose cotransporter 2 inhibitors; therefore, they did not include patients who were on these agents. Similarly, patients on GLP-1 agonists were included only in the later studies. Therefore, not all patients had maximized the medical therapy for T2D. Nevertheless, most studies report a decrease in medication dosages and/or discontinuation of antidiabetes medication including insulin. Therefore, the change in HbA1c reported in this study is likely conservative and possibly underestimates the true effect on glucose homeostasis. Second, the majority of the included studies were observational studies. To account for this, a subgroup analysis of RCTs was performed. Moreover, none of the RCTs used a treat-to-target protocol, which may have affected the amount of HbA1c changes. Third, each of the included studies has varied loss–to–follow-up rates, which may have introduced a bias. If available, the outcome reported using an intention-to-treat analysis is used in the meta-analysis in order to minimize this loss–to–follow-up bias. Furthermore, due to a limited number of included studies, only three covariates are allowed in our meta-regression model. Therefore, these covariates are defined a priori using expert opinion with avoidance of collinearity. Last, heterogeneity among studies remains relatively high, especially for studies that evaluate the effect of DJBL.
on gut hormones. These differences are likely due to different methods, assays, and timing of measurement. To control for this, Hedges g is used to report the direction of changes in gut hormones. However, the interpretation of the magnitude of changes remains limited. Additionally, in order to address the heterogeneity of the included patient population among different studies, a subgroup analysis of studies with average baseline HbA1c of ≥8% vs. <8% is also conducted, confirming a significant effect for those subjects with poorly controlled diabetes.

In summary, this systematic review and meta-analysis suggests that DJBL is associated with significant improvement in glycemic indexes for patients with obesity and concomitant T2D. Additionally, substantial weight loss is experienced in this population, which persists for at least 1 year after device removal. Moving forward, small bowel EBMTs may have implications as an adjunct therapy to pharmacotherapy and lifestyle intervention for the care of patients with obesity and concomitant T2D.

Duality of Interest. C.C.T. has contracted research for Aspire Bariatrics, USGI Medical, Spatz, and Apollo Endosurgery; has served as a consultant for Boston Scientific, Covidien, USGI Medical, Olympus, and Fractyl; holds stock and royalties for GI Windows and EndoSilm; and has served as an expert reviewer for GI Dynamics. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.J. contributed to the study design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and final approval of the manuscript. A.V.H. contributed to the acquisition of data and final approval of the manuscript. C.C.T. contributed to the study design, critical review of the manuscript, and final approval of the manuscript.

Prior Presentation. Parts of this study were presented as an oral presentation at Digestive Disease Week (DDW) 2017, Chicago, IL, 6–9 May 2017.

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