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ORIGINAL ARTICLE

Comparative efficacy and safety of the duodenal-jejunal bypass liner in obese patients with type 2 diabetes mellitus: A case control study

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Aims: The duodenal-jejunal bypass liner (DJBL) is an endoscopic device mimicking surgical duodenal-jejunal bypass, and is indicated for the treatment of obesity-associated type 2 diabetes mellitus. This analysis was conducted to evaluate the efficacy and safety of the DJBL in comparison to lifestyle changes and antidiabetic drugs.

Materials and Methods: To determine the efficacy and long-term safety of the DJBL, data concerning 235 obese patients with type 2 diabetes mellitus from the German DJBL registry were analysed. For comparison with standard treatment, propensity-score-matching with patients from the German DPV registry, including the matching parameters sex, age, diabetes duration, baseline BMI and baseline HbA1c, was applied. The final matched cohort consisted of 111 patients in the DJBL group and 222 matched control DPV patients.

Results: Mean treatment time with the DJBL was 47.5 ± 12.2 weeks, mean BMI reduction was 5.0 kg/m^2 (P < .001) and mean HbA1c reduction was 1.3% (11.9 mmol/mol) (P < .001). Reduction of antidiabetic medications and improvements in other metabolic and cardiovascular risk parameters was observed. In comparison to the matched control group, mean reductions in HbA1c (−1.37% vs −0.51% [12.6 vs 3.2 mmol/mol]; P < .0001) and BMI (−3.02 kg/m^2 vs −0.39 kg/m^2; P < .0001) were significantly higher. Total cholesterol, LDL cholesterol and blood pressure were also significantly better.

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Conclusion: This study provides the largest, so far, hypothesis-generating evidence for a putative positive risk/benefit ratio for treatment of obese patients with type 2 diabetes mellitus with the DJBL as an alternative treatment option for this patient population.

KEYWORDS

glycaemic control, obesity therapy, type 2 diabetes, weight control

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an important comorbidity of obesity and leads to multiple micro- and macrovascular long-term complications.[1] Beyond weight loss and glycaemic control, aggressive multifactorial management of cardiovascular risk factors is essential to prolong the life of obese patients with T2DM, and is currently considered to be the mainstay of therapy.[2]

Bariatric surgery is a well-established method for the treatment of obesity, with remarkable effects on T2DM, cardiovascular risk factors, cardiovascular events and overall mortality in obese patients.[3–7] However, bariatric surgery is invasive, potentially irreversible and is associated with specific complications; it is therefore not suitable for all patients with T2DM.[8] Thus, less invasive and safer bariatric techniques for treating obesity and T2DM, preferably with equal efficacy, are warranted. A less invasive, non-surgical and fully reversible approach to bariatric treatment of obesity and T2DM is provided by the duodenal-jejunal bypass liner (DJBL) (EndoBarrier; GI Dynamics, Lexington, Massachusetts) consisting of a 60 cm-long impermeable fluoropolymer tube that is endoscopically placed during gastroscopy and anchored in the duodenal bulb with self-expanding barbs, thereby creating duodenal-jejunal exclusion of the mucosa as a resorptive surface, thus mimicking Roux-en-Y gastric bypass. Pancreatic and bile secretions mix with the undigested nutrients at the distal end of the DJBL. The device is approved for a maximum treatment period of 12 months and is indicated for obese patients with T2DM.[9,10]

Small prospective studies have demonstrated promising improvements in diabetes control and loss of body weight.[11–21] To obtain prospective data in a larger cohort of patients, the ENDO Trial, a multicentre, double-blind, randomized trial, was conducted to evaluate the safety and efficacy of the DJBL. However, in March 2015, the US FDA discontinued enrollment of patients because of complications in the form of 7 hepatic abscesses. Based on incalculable study duration and associated cost, the trial was preliminarily terminated by the manufacturer (GI-Dynamics, Lexington, Massachusetts) in July 2015. Thus, clinical efficacy and long-term safety have not been investigated in a sufficiently large cohort of patients. Collecting this evidence is the primary aim of the German DJBL registry.

It is not known whether the DJBL is as effective as standard treatment for obese patients with T2DM as recommended in current guidelines. Therefore, we conducted propensity-score matching, comparing patients from the German DJBL registry and patients from a nationwide patient database in Germany and Austria (DPV registry) as a control group.

2 | MATERIALS AND METHODS

2.1 | German DJBL registry

The nationwide German DJBL registry (ClinicalTrials.gov Identifier: NCT02731859) was established in 2013 for evaluation of the efficacy and long-term safety of the DJBL, and for quality control of DJBL therapy in a large cohort of patients. It is managed at the Department of Endocrinology and Diabetology, University Hospital Hamburg-Eppendorf, Germany and is supported by an independent grant from the manufacturer of GI-Dynamics. The German DJBL registry is approved by the local Ethics Committee, Hamburg, Germany and the Hamburg Authorities Data Protection Department. Data are collected in compliance with the hospital data protection agencies in all participating centres after informed consent. An electronic case report form (eCRF) was designed for documentation of pre-specified datasets to collect prospective follow-up data on weight, glycaemic control, blood pressure, lipids, procedural specificities, cardiovascular events, obesity-associated morbidities, vitamin and mineral status, and safety at baseline, post-implantation (3, 6 and 12 months) and post-explantation (6, 12 and 24 months), as well as extra visits because of adverse events or other reasons.

2.2 | Patients and data collection

At the time of analysis, 255 patients from 14 German centres that implant the DJBL were included. Among those, 235 patients with T2DM had adequate datasets for the analysis of efficacy and long-term safety. General advice for clinical care of patients receiving DJBL treatment included 2 weeks of non-hypocaloric liquid nutrition after implantation, proton-pump inhibitors once or twice daily for the duration of implantation and 2 weeks after explantation, as well as nutrition counselling and clinical and laboratory evaluations during follow-up visits every 3 months. However, actual clinical care for DJBL patients was provided at the discretion of the physicians at the reporting centres.

For comparison of DJBL therapy with routine care (lifestyle changes, glucose-lowering drugs) in obese patients with T2DM in a matched control design, pseudonymous data for the routine care (control) group were extracted from a large multicentre diabetes patient registry, the Diabetes Prospective Follow-up Initiative (Diabetes-Patienten-Verlaufsdokumentation [DPV]; www.d-p-v.eu). In the DPV registry, 447 specialized primary care physician practices and diabetes departments of university and community hospitals in Germany and

Austria regularly document diabetes patients and transmit anonymized data twice yearly to Ulm, Germany, for central analysis and benchmarking as described elsewhere.[22] A total of 436 096 DPV patients with T2DM, aged ≥25 years, with a BMI ≥ 27 kg/m^2 and without prior bariatric surgery were included in this analysis. We analysed the most recent treatment year between 2011 and 2015. For each patient, data between 9 and 15 months, and 4 months prior to the most recent visit, were aggregated, corresponding to either implantation or explantation in the DJBL group, respectively. From the DPV registry, 11 701 patients from 116 centres who fulfilled the inclusion criteria were available. The initial study population of the German DJBL registry for this comparative analysis comprised 175 patients from 13 German centres. Because of missing parameters at baseline (n = 45) and at the end (n = 17) of the DJBL therapy, 113 patients from the German DJBL registry were available for analysis. A 2:1 (DPV registry:German DJBL registry) propensity-score matching (score-diff 0.01, based on an SAS Macro), with the following matching parameters, was performed: sex, age, diabetes duration, baseline BMI and baseline HbA1c. The final matched groups consisted of 111 patients in the German DJBL group and 222 matched patients from the DPV registry.[23] Patient selection from the German DJBL registry for inclusion in this analysis is shown in Figure 1.

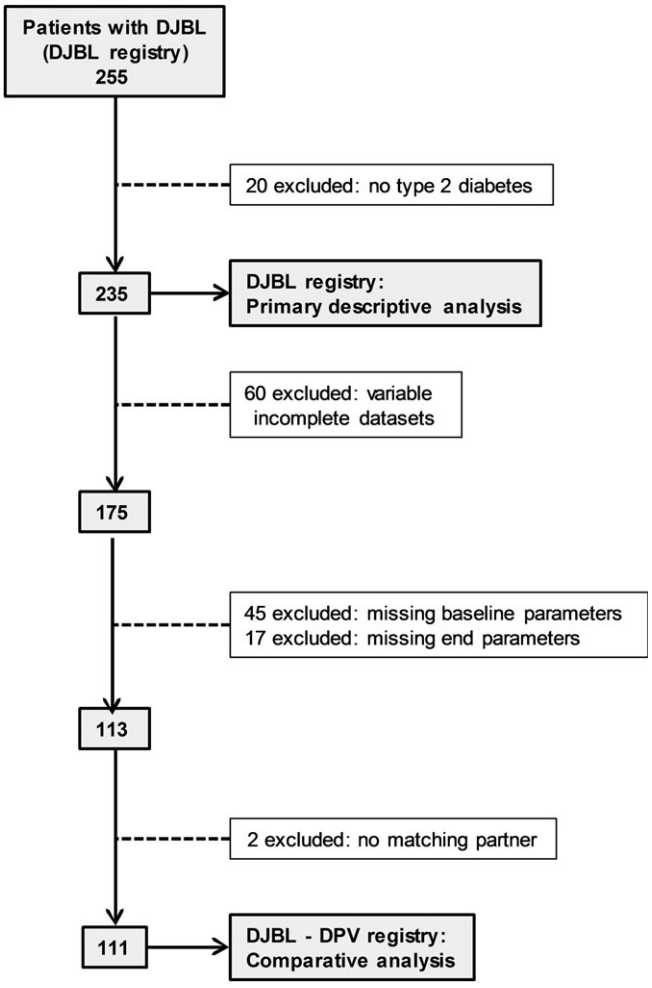

FIGURE 1 Patient disposition. Flow diagram depicting patient findings and selection in the German DJBL registry for inclusion in the primary descriptive analysis of the German DJBL registry and the comparative analysis of the DJBL vs standard of care (DPV registry) in patients with obesity and type 2 diabetes

2.3 | Statistical analysis

For evaluation of the German DJBL registry, all patients with a complete implantation and explantation dataset were included in the statistical analysis. Therefore, patients who had an early removal of the DJBL were also evaluated (last observation carried forward/intention-to-treat analysis). Analysis was carried out by the Sign test or T-test, which were preceded by the Shapiro Wilks test for the alpha-niveau of 5%. If a Gaussian distribution was refused by the Shapiro Wilks test, the Sign test rather than the T-test was applied. For comparison of the DJBL with routine care, data were analysed using the SAS statistical software package, version 9.4 (SAS for Windows; SAS Institute, Cary, North Carolina, USA).

For BMI, HbA1c, excess weight, cholesterol, HDL, triglycerides, blood pressure, insulin treatment and daily insulin dose, differences between DJBL implantation and explantation, or the respective time-periods in the control group, were analysed. For the matched pair analysis, groups were compared by the Kruskall-Wallis test (continuous variables) or chi-squared test (proportions). *P* values were adjusted by the false discovery rate (FDR) for multiple comparisons. Subsequently, odds ratios with 95% Wald confidence intervals were generated by a logistic regression model, with maximum likelihood estimation for the following success criteria: HbA1c reduction by ≥1%, BMI reduction by 5 kg/m^2, cholesterol reduction by ≥20 mg/dL, LDL cholesterol reduction ≥10 mg/dL and HDL cholesterol increase ≥5 mg/dL, triglyceride reduction by ≥20 mg/dL and reduction in systolic/diastolic blood pressure by ≥5 mm Hg.

3 | RESULTS

3.1 | Patient characteristics

A total of 235 obese patients with T2DM (62.0% female) were included in this analysis of baseline clinical characteristics of individuals in the German DJBL registry (Table S1). Mean age at time of implantation of the DJBL was 51.6 ± 10.4 years, mean body weight was 125.5 ± 23.7 kg, mean BMI was 43.1 ± 6.9 kg/m^2, mean excess weight was 52.5 ± 20.5 kg and mean HbA1c was 8.4 ± 1.8% (68 ± 17.3 mmol/mol). Among these, 86.3% were using oral antidiabetic medication and/or GLP-1 receptor agonists, 22.8% were using GLP-1 receptor agonists only, and 64.0% were treated with insulin alone or in combination with oral antidiabetics and/or GLP-1 receptor agonists. Patients using insulin received a mean total dose of 70.2 ± 53.1 I.U./d. Baseline systolic blood pressure was 136.6 ± 17.2 mmHg and diastolic blood pressure was 80.7 ± 10.8 mmHg.

3.2 | Baseline clinical characteristics of matched patients from the German DJBL registry and the DPV registry

Because of the matching strategy, age, diabetes duration, HbA1c and BMI were comparable (Table 1). There were no significant differences

TABLE 1 Baseline clinical characteristics of the 2 matched study populations

Characteristics	German DJBL registry n = 111	DPV registry n = 222	*P* value
Female sex (%)	60.4	58.1	.7
Age (years) Mean ± SD	51.9 ± 9.0	52.5 ± 16.2	
Diabetes duration (years) Mean ± SD	9.5 ± 6.6	8.9 ± 7.7	
HbA1c (%) (mmol/mol) Mean ± SD	8.5 (69) ± 1.8	8.3 (67) ± 2.3	.2
BMI (kg/m^2) Mean ± SD	42.6 ± 6.8	41.9 ± 8.6	.6
Body weight (kg) Mean ± SD	124.7 ± 23.8	120.6 ± 27.8	
Cholesterol (mg/dL) Mean ± SD	(n = 58) 194.5 ± 43.1	(n = 123) 199.6 ± 50.8	.7
LDL cholesterol (mg/dL) Mean ± SD	(n = 59) 121.0 ± 31.5	(n = 105) 119.5 ± 37.8	.7
HDL cholesterol (mg/dL) Mean ± SD	(n = 60) 410 ± 8.4	(n = 109) 43.1 ± 11.4	.4
Triglycerides (mg/dL) Mean ± SD	(n = 60) 219.4 ± 158.9	(n = 118) 237.9 ± 215.9	.7
Treatment with lipid-lowering drugs (%)	36.9	18.5	.00078
Systolic blood pressure (mm Hg) Mean ± SD	(n = 76) 134.8 ± 18.3	(n = 212) 135.1 ± 19.8	.9
Diastolic blood pressure (mm Hg), Mean ± SD	(n = 76) 79.0 ± 11.0	(n = 212) 81.5 ± 12.0	.2
Treatment with antihypertensives (%)	82.9	34.7	<.0001
Treatment with antidiabetics (%)	99.1	63.5	.0001
Treatment with oral antidiabetics (%)	87.4	63.1	.0002
Treatment with GLP1-analogues (%)	28.8	13.1	.00136
Insulin therapy (%)	64.0	48.2	.013
Insulin dose (IE)/d Mean ± SD	(n = 65) 77.5 ± 59.8	(n = 107) 80.7 ± 49.2	.446

Data are given as n (%), mean with standard deviation (SD). *P* values are given for comparison between patients from the German DJBL registry and the DPV registry.

between the 2 groups in lipids or systolic and diastolic blood pressure. There was a significant difference concerning lipid-lowering drugs: 36.9% in the German DJBL registry and 18.5% in the DPV registry. Antihypertensive and antidiabetic treatment was significantly more frequent in patients in the German DJBL registry than in the matched DPV patients. In the German DJBL registry, oral antidiabetics, GLP-1 analogues and insulin therapy were applied significantly more frequently, but no difference in insulin dose was observed.

3.3 | Efficacy of the DJBL in the German DJBL registry

Mean treatment time with the DJBL was 47.5 ± 12.2 weeks (Table 2).

3.3.1 | Anthropometric parameters

Mean weight reduction was 14.7 ± 9.0 kg, corresponding to a reduction in BMI of 5.0 ± 3.1 kg/m^2, an excess weight loss of 28.53 ± 9.0% and a reduction in waist circumference of 9.5 ± 9.7 cm ($P < .0001$ for all parameters).

3.3.2 | Laboratory parameters

HbA1c was reduced, on average, by 1.3 ± 1.5% (11.9 mmol/mol) ($P < .001$). For patients with no change in antidiabetic medication during the DJBL implantation period, the effect on HbA1c reduction was even higher (1.5 ± 1.6% [14 mmol/mol]). In addition, on average, total and LDL cholesterol levels were reduced by 26.9 ± 42.7 and 21.8 ± 34.7 mg/dL, respectively ($P < .001$). This effect was also seen in patients receiving stable therapy with lipid-lowering agents. A slight but not significant reduction was seen in systolic blood pressure (6.1 ± 22.3 mm Hg) and a significant reduction in diastolic blood pressure was observed (3.6 ± 13.6 mmHg) ($P < .05$). Analysis of liver enzymes revealed a highly significant reduction in AST and ALT.

3.3.3 | Change in medication

A total of 51.0% of patients were able to reduce use of oral antidiabetic drugs and/or GLP-1 receptor agonists, and 78.0% of patients reduced doses of GLP-1 receptor agonists. Mean numbers of oral antidiabetic medications and/or GLP-1 receptor agonists at the time of implantation was 1.7/d, and was significantly reduced to 0.3 at the time of explantation. Insulin dose (I.U./kg/d) was 0.7I.U. at baseline and was reduced to 0.3I.U. at the time of explantation ($P < .0001$). Use of antihypertensive and lipid-lowering drugs was reduced in 15.32% and 21.05% of the patients, respectively.

3.3.4 | Safety parameters

Adverse events in the 235 patients were primarily gastrointestinal symptoms; 61 patients (26.0%) experienced mild to moderate abdominal pain and 4 patients (1.7%) experienced severe abdominal pain. Nausea (12 patients; 5.1%) and vomiting (12 patients; 5.1%), diarrhoea (6 patients; 2.6%), constipation (3 patients; 1.3%) and flatulence (2 patients; 0.9%) were also observed. Gastrointestinal symptoms were observed predominantly after implantation and recovered with symptomatic treatment. One patient had severe dehydration with acidosis as the result of diarrhoea and vomiting. Serious adverse events included dislocation/migration in 6 patients (2.6%), liver abscess in 4 patients (1.7%), GI bleeding in 1 patient (0.4%) who took aspirin which is contraindicated, sleeve obstruction in 2 patients (0.9%), duodenal ulcer with perforation in 1 patient (0.4%), biliary colic without

TABLE 2 Changes in anthropometric parameters, cardiovascular risk factors and medication in the whole German-DJBL registry before and after implantation of DJBL

Characteristics	Implantation	Explantation	Difference	*P* value
HbA1c (%) (mmol/mol) Mean ± SD n = 117	8.5 (69) ± 1.8	7.2 (55) ± 1.2	−1.3	<.0001
HbA1c (%)[a] (mmol/mol) Mean ± SD n = 42	8.6 (70) ± 1.8	7.1 (54) ± 1.0	−1.5	<.0001
BMI (kg/m^2) Mean ± SD n = 150	42.8 ± 7.0	37.8 ± 6.7	−5.0	<.0001
Body weight (kg) Mean ± SD n = 150	124.7 ± 22.6	110.0 ± 21.7	−14.7	<.0001
Excess weight (kg), Mean ± SD n = 150	51.7 ± 19.6	37.0 ± 19.4	−14.7	<.0001
Waist circumference (cm) Mean ± SD n = 33	113.1 ± 15.6	103.6 ± 14.7	−9.5	<.0001
Cholesterol (mg/dL) Mean ± SD n = 56	191.0 ± 50.6	164.1 ± 37.2	−26.9	.0002
Cholesterol (mg/dL)[a] Mean ± SD n = 40	191.6 ± 46.3	169.2 ± 31.3	−22.4	.0005
LDL-cholesterol (mg/dL) Mean ± SD n = 55	120.5 ± 34.0	98.7 ± 32.2	−21.8	.0002
LDL cholesterol (mg/dL)[a] Mean ± SD n = 39	126.7 ± 30.1	102.8 ± 28.5	−23.9	.0001
HDL cholesterol (mg/dL) Mean ± SD n = 56	41.3 ± 8.4	42.7 ± 19.0	1.4	.6835
HDL cholesterol (mg/dL)[a] Mean ± SD n = 40	41.9 ± 7.9	43.8 ± 21.8	1.9	.8714
Triglycerides (mg/dL) Mean ± SD n = 54	210.7 ± 158.4	175.0 ± 98.4	−35.7	.2203
Triglycerides (mg/dL)[a] Mean ± SD n = 39	193.2 ± 98.2	180.7 ± 92.6	−12.7	.5224
ALT (U/L) Mean ± SD n = 76	38.6 ± 23.3	25.2 ± 15.5	−13.4	<.0001
AST (U/L) Mean ± SD n = 62	34.4 ± 17.4	27.5 ± 18.9	−6.9	.013
Systolic blood pressure (mm Hg) Mean ± SD n = 78	134.5 ± 18.4	128.4 ± 16.5	−6.1	.0912
Systolic blood pressure (mm Hg)[a] Mean ± SD n = 32	133.5 ± 21.4	127.9 ± 15.7	−5.6	.1433
Diastolic blood pressure (mm Hg) Mean ± SD n = 78	80.0 ± 11.3	76.4 ± 10.6	−3.6	.0013
Diastolic blood pressure (mm Hg)[a] Mean ± SD n = 32	77.6 ± 13.0	75.0 ± 12.1	−2.6	.1892
	1.7	1.4	−0.3	<.0001

TABLE 2 (Continued)

Characteristics	Implantation	Explantation	Difference	*P* value
Average number of daily antidiabetic drugs (OAD and GLP1-ReceptorAgonist) Mean ± SD n = 132	± 0.71	± 0.9		
Insulin dose (IE/kg bodyweight/d) n = 132	0.7 ± 0.44	0.4 ± 0.2	−0.3	<.0001

Data are given as n (%), mean with standard deviation (SD). *P* values are given for comparison between implantation and explantation.

[a] Subgroup of patients with stable interfering medication.

cholecystitis or cholangitis in 1 patient (0.4%) and oesophageal lesion without perforation in 1 patient (0.4%). Three liver abscesses appeared at month 12 and 1 at month 6; all were drained and treated with antibiotics and were cured without sequelae. We recorded 4 adverse events (1.7%) not related to the DJBL: cardiac decompensation, newly diagnosed atrial fibrillation, newly diagnosed peripheral arterial disease and stroke. Of 235 patients, complete implantation and explantation datasets were available for 143. Among these, 35 patients (24.48%) underwent early explantation before week 48, 20 of which were necessary because of adverse events caused by the DJBL, and 3 were not related to the DJBL. In 11 patients who underwent early explantation, "no complication" was documented in the eCRF (Table S3).

3.4 | Comparative efficacy of the DJBL vs the standard-of-care control group (DPV registry)

3.4.1 | Glycaemic control

At the end of treatment, mean HbA1c was significantly lower in the DJBL group than in the control group (−1.37 ± 1.54% vs −0.51 ± 1.83% [12.6 vs. 3.2 mmol/mol]) (*P* < .0001) (Figure 2A). The odds ratio for experiencing an HbA1c reduction of more than 1% (8.6 mmol/mol) was 3.37 for the DJBL group (95% confidence interval [CI], 2.09-5.40) as compared to the control group (Figure 3).

3.4.2 | Weight loss

DJBL therapy brought about greater reductions in excess weight (−33.57% ± 22.44%) than did standard care (−0.88% ± 18.61%) (*P* < .0001). Correspondingly, the DJBL group had a significantly greater reduction in BMI over time than did the control group (−5.31 ± 3.02 kg/m^2 vs −0.39 ± 3.00 kg/m^2) (*P* < .0001) (Figure 2B, C). The odds ratio for BMI reduction of more than 5 kg/m^2 was 17.59 for the DJBL group (95% CI, 8.98-34.36) as compared to the control group (Figure 3).

3.4.3 | Cardiovascular risk parameters

Reductions in total cholesterol were significantly higher with DJBL treatment (−28.62 ± 42.86 mg/dL) than with medical therapy (−9.64 ± 49.90 mg/dL) (*P* = .002). For LDL cholesterol, there was also a significantly larger reduction in DJBL patients (−20.76 ± 30.54 mg/dL) than in the control group (−0.14 ± 37.84 mg/dL) (*P* = .00068) (Figure 2D,E). Triglycerides and HDL cholesterol did not differ significantly between the 2 groups (Figure 2F). The odds ratio for reduction of total cholesterol by more than 20 mg/dL was 2.17 (95% CI, 1.02-4.02), for reduction of LDL cholesterol of more than 10 mg/dL was 3.37 (95% CI, 1.83-6.18), and for reduction of triglycerides by more than 20 mg/dL was 1.34 (95% CI, 0.73-2.44; n.s.) in the DJBL group. For the increase in HDL cholesterol by more than 5 mg/dL, the odds ratio was 1.35 (95% CI, 0.67-2.71; n.s.) (Figure 3). Patients in the DJBL group had a significantly greater reduction in systolic blood pressure (−7.83 ± 21.58 mm Hg vs −0.53 ± 20.34 mm Hg) (*P* = .0073) and in diastolic blood pressure (−4.17 ± 13.39 mm Hg vs −0.02 ± 11.47 mmHg) (*P* = .0035) than those in the control group (Figure 2G,H). The odds ratio for reduction of more than 5 mm Hg in systolic blood pressure was 0.79 (95% CI, 0.48-1.30) and in diastolic blood pressure was 1.10 (95% CI, 0.66-1.84) (Figure 3).

3.4.4 | Change in medication

Patients who received the DJBL displayed a greater reduction in use of antidiabetic medication (−10.8%) than did patients who received standard of care (−2.2%) (*P* < .0001) (Table S2). The average number of diabetes agents per patient per day decreased in the DJBL group from 2.24 to 1.94 and tended to increase in the control group from 2.48 to 2.65. There was a significant reduction in the requirement for insulin therapy of 15.4% and for insulin dose per day (−39.1 ± 52.7) in the DJBL group at the end of treatment in contrast to the control group (1.3% increase in insulin requirement and − 4.40 ± 38.8 reduction in insulin dose/d). Use of lipid-lowering drugs was stable in the DJBL group and tended to increase in the control group (Table S2). Antihypertensive therapy and average numbers of antihypertensive agents were reduced in the DJBL group in contrast to the control group (Table S2).

4 | DISCUSSION

This analysis includes the largest population of obese patients with T2DM treated with the DJBL under real life conditions. DJBL therapy caused significant and clinically relevant improvements in glycaemic control, weight reduction and reduction in use of antidiabetic medication. These results support those reported by Betzel et al[24] in a small monocentre cohort. However, we observed higher weight reduction (14.7 kg vs 12.8 kg) and improvement in HbA1c (1.07% vs 0.76% [−9.3 vs −6 mmol/mol]), which may be the result of the slightly higher baseline BMI, weight and HbA1c, and the longer mean time of implantation, in our cohort. Of note, the applied method of last observation carried forward/intention-to treat analysis may have somewhat overestimated the effect size as the result of inclusion of early removals.

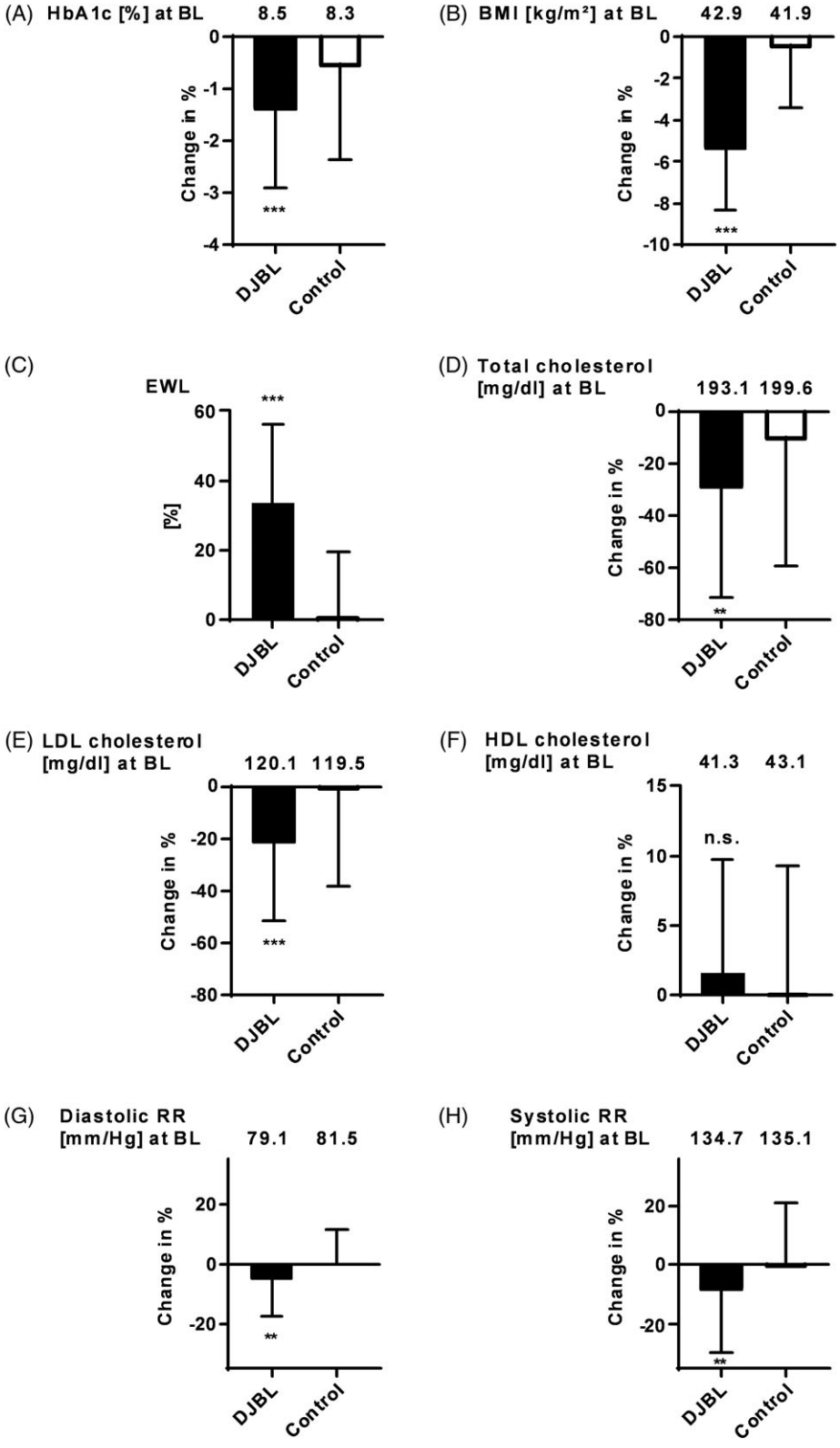

FIGURE 2 Comparative efficacy of the DJBL vs standard of care (DPV registry) in patients with obesity and type 2 diabetes. Differences between DJBL implantation (BL) and explantation or respective time-periods in the control group for A, Hb1Ac ***P < .001; B, BMI ***P < .001; C, EWL ***P < .001; D, total cholesterol **P < .01; E, LDL cholesterol ***P < .001; F, HDL cholesterol n.s.; G, diastolic blood pressure **P < .01; H, diastolic blood pressure **P < .01. Abbreviations: BL, baseline; EWL, excess weight loss

One meta-analysis[25] and 1 review[26] report that DJBL treatment is associated with significant weight reduction but no significant improvement in glycaemic control in obese patients with T2DM. We propose, however, that the lack of effect on glycaemic control in these analyses may be explained by the limited number of eligible studies.

The main strength of our study is the matched comparison of the DJBL with standard lifestyle changes and pharmacotherapy for the treatment of T2DM in a significant number of obese patients. Up to now there are only small observational studies and RCTs comparing DJBL with sham endoscopy, diet or lifestyle modification. The results of our analysis show that DJBL treatment, as compared with lifestyle changes and pharmacotherapy, is associated with significantly better glycaemic control, weight reduction and control of cardiovascular risk factors, with less requirement for medication, including antidiabetic

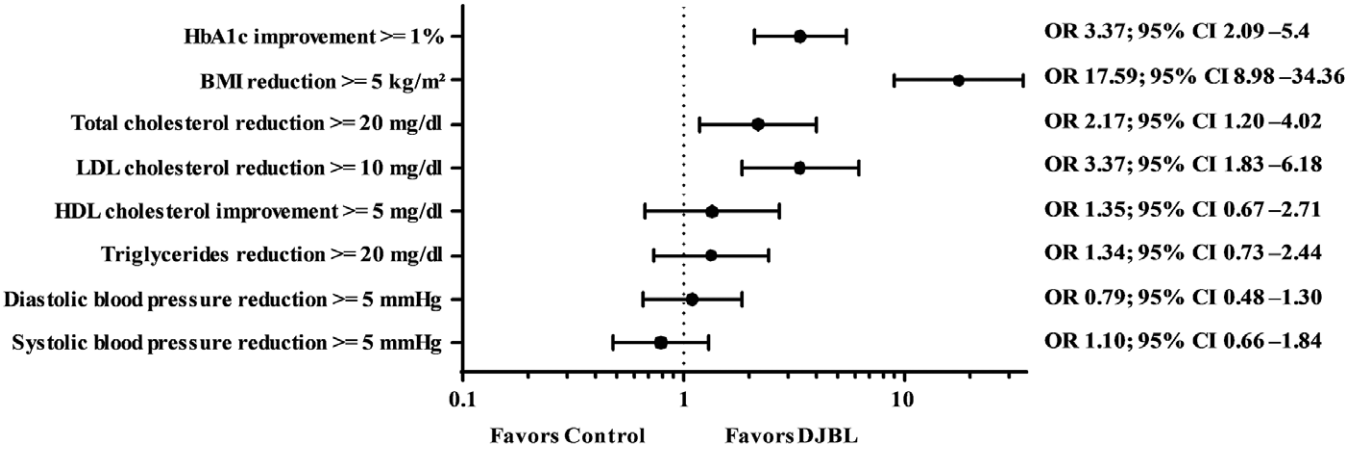

FIGURE 3 Forest plot evaluating comparative efficacy of the DJBL vs standard of care (DPV registry) in patients with obesity and T2DM. Odds ratios with 95% Wald confidence intervals are shown for HbA1c reduction by ≥1% (8.6 mmol/mol), BMI reduction by 5 kg/m^2, total cholesterol reduction by ≥20 mg/dL, LDL cholesterol reduction ≥10 mg/dL and HDL cholesterol increase ≥5 mg/dL, triglyceride reduction by ≥20 mg/dL and reduction of systolic or diastolic blood pressure by ≥5 mm Hg

(especially insulin), antihypertensive and lipid-lowering drugs. As the overall percentage of patients receiving lipid-lowering drugs was low, we cannot derive the magnitude of the DJBL effect on lipids in populations that would have had adequate lipid-lowering medications as per guidelines.

Of note, the patients in the German DJBL registry were treated to a higher extent with oral antidiabetic, antihypertensive and lipid-lowering therapies. It may be speculated that this baseline imbalance in medications represents a bias that could act in either over or under-estimation of the DJBL effect. If the assumption were true that the use of intensive medications in this group had an impact on beta cell survival and function which accounts for greater reversibility in beta cell dysfunction, the DJBL effect was over-estimated. If the more intense medication in the DJBL group were considered to represent a surrogate of more advanced metabolic disease, it may be implied that the true impact of DJBL treatment was under-estimated, because these patients achieved better HbA1c and concomitant metabolic parameters despite more advanced disease.

One year after bariatric surgery patients achieve an excess weight loss of 60% and a BMI reduction of 13 kg/m^2. The study from Schauer et al. showed a BMI reduction of 10.40 kg/m^2 with gastric bypass and of 9.0 kg/m^2 with sleeve gastrectomy and a significant improvement in glycaemic control (HbA1c reduction up to 2.9% [9 mmol/mol]), with less antidiabetic medication after 12 months, in comparison to intensive medical care.[27] Of note, in this analysis the observed improvements in BMI and HbA1c with the DJBL were not as effective as bariatric surgery. This may be a specific feature of the endoscopic intervention of the DJBL as compared to surgical alteration of GI anatomy with bariatric surgery, but heterogeneity in the trial populations cannot be excluded. It is also important to note that prospective head-to-head RCTs comparing DJBL with bariatric surgery are lacking.

In the analysis of the German DJBL registry, more than 26% of patients had transient mild-to-moderate adverse events, primarily gastrointestinal symptoms. These adverse events occurred predominantly after implantation, were probably caused by the intervention and were resolved with symptomatic treatment. Some patients had serious adverse events, but these were rare and non-fatal. The safety profile reported here is comparable to, and in some instances better than, the published DJBL safety profile.[28] In the ENDO Trial, device-related serious adverse events were gastrointestinal bleeding (2.8%), hepatic abscess (1.8%), liner obstruction (2.3%), intestinal perforation (0.5%), pancreatitis (0.9%) and intolerance (abdominal pain, vomiting and nausea [2.3%]). In this trial, short-term events consisted primarily of GI bleeding, liner obstruction and intolerance, whereas later (> 6 months) events included increased frequency of pancreatitis and hepatic abscess. As liver abscesses are currently 1 of the major concerns, strategies for reduction of this complication are discussed, including antibiotic prophylaxis, reduction of proton-pump inhibitors and shortening of the treatment phase because of the occurrence of liver abscesses, typically during the later part of the treatment phase after month 9.

Limitations of the study include the fact that the analyses were derived from registry data and not from a randomized controlled trial. While we have taken great care to optimize propensity-score matching, we cannot exclude that over- or under-reporting of data to the registries may have introduced a bias into the trial. Furthermore, we cannot be certain that the patients in the DPV registry received best care, including lifestyle intervention, homogenously. Nevertheless, we believe that the control group represents standard of care in real life in Germany. Further limitations include the restricted generalizability of the DJBL treatment results to T2DM patient populations with lower BMIs, certain imbalances in baseline medications, a putative "in-study" effect of the liquid nutrition and extra counselling in DJBL patients that cannot be quantified exactly, as well as the limited overall number of DJBL patients within the analysis. Also, patient-related outcomes were not sufficiently addressed in this trial. In the absence of larger randomized trials, however, we still believe that this observational trial provides the most comprehensive comparative information on the efficacy and safety of DJBL treatment to date.

In conclusion, the DJBL combines improvement in glycaemic control, reduced need of antidiabetic medication, significant weight loss

and improvement in other related metabolic and cardiovascular risk parameters in obese patients with T2DM. However, it is important to mention that DJBL treatment is associated with a substantial number of transient, mild AEs, but also with rare serious events, which must be taken into consideration in judging the appropriateness of this therapy for a patient with T2DM. This study provides hypothesis-generating evidence for a putative positive risk/benefit ratio for treatment of patients with T2DM using the DJBL. At this point, the results of this study are pertinent only to T2DM patients with substantially elevated BMI (mean 43.1 kg/m^2) (Table S1) and generalizability of the findings to patient groups with lower BMIs is restricted. More efficacy and safety studies, especially RCTs comparing DJBL with optimal medical treatment or gastric bypass, are urgently needed to evaluate in more detail the effect of the DJBL on T2DM, quality of life, weight loss, cardiovascular outcome and mortality. Furthermore, trials with long-term follow-up after DJBL explantation are of great interest. This question will be addressed by the German DJBL registry. These studies will more broadly evaluate whether the DJBL represents an efficacious and safe non-surgical option for the treatment of obese patients with T2DM in routine clinical care.

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Conflict of interest

J. S. has attended advisory board meetings and speaker's bureaus for GI-Dynamics, Lexington, Massachusetts. J. A. has attended advisory board meetings and speaker's bureaus for and has received research support from GI-Dynamics, Lexington, Massachusetts. K. L. has attended advisory board meetings and speaker's bureau for and has received research support from GI-Dynamics, Lexington, Massachusetts. N. R. has received travel support for an EndoBarrier registry meeting and has received a research grant for establishment of the DJBL registry from GI-Dynamics, Lexington, Massachusetts. F. D. has received travel support for an EndoBarrier registry meeting from

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Author contributions

K. L., N. R., R. W. H., J. S. and J. A. initiated and designed the study. N. R., K. F. and R. W. H. performed the statistical analysis. K. L., N. R., R. W. H., J. S. and J. A. interpreted the data, and revised the manuscript critically for important intellectual content. All authors were responsible for patient inclusion in the registries and for acquisition of data. K. L. wrote the draft of the manuscript. All authors approved the final version of the manuscript. K. L., N. R., R. W. H., J. S. and J. A. are the guarantors of the work. They had full access to all data and take responsibility for the accuracy of the data analysis and interpretation.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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