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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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Abstract:

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 efficacy and safety of the DJBL in comparison to lifestyle changes and antidiabetic drugs.

Materials and Methods: For efficacy and long-term safety of the DJBL, data from 235 obese patients with type 2 diabetes mellitus from the German-DJBL-registry were analyzed. 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 5.0kg/m^2 ($p < 0.001$) and mean HbA1c reduction 1.3% [11.9mmol/mol] ($p < 0.001$). Reduction of antidiabetic medications and improvements of 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. 3.2mmol/mol], $p < 0.0001$), and BMI (-3.02kg/m^2 vs. -0.39kg/m^2 ; $p < 0.0001$) were significantly higher. Total cholesterol, LDL cholesterol and blood pressure were also significantly better.

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

Introduction:

Type 2 diabetes mellitus (T2DM) is an important comorbidity of obesity and leads to multiple micro- and macrovascular long-term complications¹. 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 therapy².

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 subjects³⁻⁷. However, bariatric surgery is invasive, potentially irreversible and associated with specific complications, and is therefore not suitable for all patients with T2DM⁸. Thus, less invasive and safer bariatric techniques to treat obesity and T2DM preferably with equal efficacy are warranted. A less invasive, non-surgical and fully reversible approach for bariatric treatment of obesity and T2DM is provided by the duodenal-jejunal bypass liner (DJBL; EndoBarrier®) consisting of a 60cm long impermeable fluoropolymer tube that is endoscopically delivered during gastroscopy, and anchored in the duodenal bulb with self-expanding barbs, thereby creating duodeno-jejunal exclusion of the mucosa as resorptive surface, and 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 in obese patients with T2DM^{9,10}.

Small prospective studies have demonstrated promising improvements of diabetes control and loss of bodyweight¹¹⁻²¹. To obtain prospective data in a larger cohort of patients, the “ENDO Trial”, a multi-center, double-blind, randomized trial was conducted to evaluate the safety and efficacy of the DJBL, but in March 2015, the

FDA stopped further enrollment of patients due to complications of 7 hepatic abscesses. Based on incalculable study duration and associated cost, the trial was preliminarily terminated by the manufacturer (GI-Dynamics) 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.

Currently it is not known, whether the DJBL is as effective as standard treatment of 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 control group.

Materials and Methods:

The German DJBL registry

The nationwide German-DJBL-registry (ClinicalTrials.gov Identifier: NCT02731859) was established in 2013 for evaluation of efficacy and long-term safety and for quality control of DJBL therapy in a large cohort of patients. It is run at the Department of Endocrinology and Diabetology, University Hospital Hamburg-Eppendorf, Germany, and supported by an independent grant from the manufacturer GI-Dynamics (Lexington, MA, USA). 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 centers 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, glycemic 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 6, 12 and 24 months after explantation, as well as extra visits due to e.g. adverse events.

Patients and data collection:

At the time of analysis, 255 patients from 14 German centres that implant the DJBL had been 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 two 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 three 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, called 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, diabetes departments of University Hospitals and community hospitals in Germany and Austria regularly document diabetes patients, and transmit anonymized data twice a year to Ulm, Germany, for central analyses and benchmarking as described

elsewhere²². 436096 DPV patients with T2DM, age ≥ 25 years with a BMI $\geq 27\text{kg/m}^2$ 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 9-15 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, 11701 patients from 116 centres fulfilling 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 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-registry²³. Patient selection from the German-DJBL registry for inclusion in this analysis is shown in Figure 1.

Statistical analysis

For evaluation of the German-DJBL-registry all patients with a complete im- and explantation dataset were included into statistical analysis. Therefore, also patients who had an early removal of the DJBL were evaluated (last observation carried forward/intention to treat analysis). Analysis was carried out by 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, Sign test instead of T-test was applied.

For the 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, NC, 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 Kruskal-Wallis-test (continuous variables) or Chi-Square-test (proportions). P-values were adjusted by 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 $\geq 1\%$, BMI-reduction by 5kg/m^2 , cholesterol reduction by $\geq 20\text{mg/dl}$, LDL-cholesterol-reduction $\geq 10\text{mg/dl}$ and HDL-cholesterol increase $\geq 5\text{mg/dl}$, triglyceride-reduction by $\geq 20\text{mg/dl}$ and reduction of systolic/diastolic blood pressure by $\geq 5\text{mmHg}$.

Results:

Patient Characteristics:

Baseline clinical characteristics of the German-DJBL-registry (table 1

Supplementary Appendix): 235 obese patients with T2DM were included in this analysis (62.0% female). Mean age at time of implantation of the DJBL was 51.6 ± 10.4 years, mean body weight $125.5 \pm 23.7\text{kg}$, mean BMI $43.1 \pm 6.9\text{kg/m}^2$, mean excess weight $52.5 \pm 20.5\text{kg}$ and mean HbA1c $8.4 \pm 1.8\%$ [$68 \pm 17.3\text{mmol/mol}$]. 86.3% had oral antidiabetic medication and/or GLP-1 receptor agonists, 22.8% GLP-

1 receptor agonists only. 64.0% were treated with insulin alone or in combination with oral antidiabetics and/or GLP-1 receptor agonist. Patients on insulin received a mean total insulin dose of 70.2 ± 53.1 U./day. Baseline systolic blood pressure was 136.6 ± 17.2 mmHg, and diastolic blood pressure 80.7 ± 10.8 mmHg.

Baseline clinical characteristics of matched patients from the German-DJBL-registry and the DPV-registry (table 1):

Due to the matching strategy, age, diabetes duration, HbA1c and BMI were comparable. There were no significant differences between the two groups for lipids, systolic and diastolic blood pressure. 36.9% in the German-DJBL-registry and 18.5% in the DPV-registry were treated with lipid lowering drugs, a significant difference. Antihypertensive and antidiabetic treatment was significantly more frequent in the German-DJBL-registry than in matched DPV-patients. In the German-DJBL-registry oral antidiabetics, GLP-1 analogues and, insulin therapy were applied significantly more frequent, but no difference in insulin dose was observed.

Efficacy of the DJBL in the German-DJBL-registry (table 2):

Mean treatment time with the DJBL was 47.5 ± 12.2 weeks.

Anthropometric parameters:

Mean weight reduction was 14.7 ± 9.0 kg, corresponding to a reduction in BMI of 5.0 ± 3.1 kg/m², an excess weight loss of 28.53 ± 9.0 % and reduction of waist circumference of 9.5 ± 9.7 cm ($p < 0.0001$ for all parameters).

Laboratory parameters:

HbA1c was reduced on average by $1.3 \pm 1.5\%$ [11.9 mmol/mol] ($p < 0.001$). For patients with no change of antidiabetic medication during the DJBL implantation period, the effect on HbA1c reduction was even higher ($1.5 \pm 1.6\%$ [14 mmol/mol]). In addition, on average total and LDL-cholesterol levels were reduced by 26.9 ± 42.7 and $21.8 \pm 34.7 \text{ mg/dl}$ respectively ($p < 0.001$). This effect was also seen for patients on stable therapy with lipid lowering agents. A slight but not significant reduction was seen for systolic blood pressure ($6.1 \pm 22.3 \text{ mmHg}$) and a significant reduction of diastolic blood pressure was observed ($3.6 \pm 13.6 \text{ mmHg}$, $p < 0.05$). Analysis of liver enzymes revealed a highly significant reduction of AST and ALT.

Change in medication:

51.0% of patients were able to reduce 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 time of implantation was 1.7/day, and was significantly reduced to 0.3 at time of explantation. Insulin dose (l.U./kg/day) was 0.7 l.U. at baseline and was reduced to 0.3 l.U. at time of explantation ($p < 0.0001$). Antihypertensive and lipid lowering drugs could be reduced in 15.32% and 21.05% of the patients, respectively.

Safety parameters:

Adverse events in the 235 patients were primarily gastrointestinal symptoms. 61 patients (26.0%) had mild to moderate and 4 patients (1.7%) severe abdominal pain. Nausea (12 patients-5.1%) and vomiting (12 patients-5.1%), diarrhoea (6 patients-2.6%), constipation (three patients-1.3%) and flatulence (two patients-0.9%) were also observed. Gastrointestinal symptoms were observed predominantly after

implantation and recovered by symptomatic treatment. One patient had severe dehydration with acidosis due to diarrhoea and vomiting. Serious-adverse events included dislocation/migration in 6 patients (2.6%), liver abscess in 4 patients (1.7%), GI bleeding in one patient (0.4%) (who took aspirin which is contraindicated), sleeve obstruction in two patients (0.9%), duodenal ulcer with perforation in one patient (0.4%), biliary colic without cholecystitis or cholangitis in one patient (0.4%), and oesophageal lesion without perforation in one patient (0.4%). Three liver abscesses appeared at month 12, one at month 6. All liver abscesses were drained and treated by antibiotics and cured without sequela. We recorded four adverse events (1.7%) not related to the DJBL (cardiac decompensation, newly diagnosed atrial fibrillation, newly peripheral arterial disease and stroke).

Of 235 patients, in 143 patients the complete im- and explantation datasets were available. 35 patients (24.48%) had an early explantation before week 48. Twenty early explantations were due to adverse events caused by the DJBL, and 3 not related to the DJBL. In 11 early explantation patients, “no complication” was documented in the eCRF (table 3, Supplementary Appendix).

Comparative efficacy of the DJBL versus standard of care control group (DPV-registry):

Glycaemic control:

At the end of treatment, mean HbA1c was significantly lower in the DJBL group than in the control group ($-1.37 \pm 1.54\%$ vs. $-0.51 \pm 1.83\%$; [12.6 vs. 3.2mmol/mol] $p < 0.0001$) (figure 2A). The odds ratio of experiencing an HbA1c reduction of more than 1% [8.6mmol/mol] was 3.37 for the DJBL group (95% confidence interval [CI], 2.09 to 5.40) as compared to the control group (figure 3).

Weight loss:

DJBL therapy caused greater reductions in excess weight ($-33.57\% \pm 22.44\%$) than standard care ($-0.88\% \pm 18.61\%$) ($p < 0.0001$). Correspondingly, the DJBL group had a significantly greater reduction in BMI over time than did the control group ($-5.31 \pm 3.02 \text{ kg/m}^2$ vs. $-0.39 \pm 3.00 \text{ kg/m}^2$; $p < 0.0001$) (figures 2B and 2C). The odds ratio of BMI reduction of more than 5 kg/m^2 was 17.59 for the DJBL group (95% CI, 8.98 to 34.36) as compared to the control group (figure 3).

Cardiovascular risk parameters:

Reductions in total cholesterol were significantly higher with DJBL treatment ($-28.62 \pm 42.86 \text{ mg/dl}$) than with medical therapy ($-9.64 \pm 49.90 \text{ mg/dl}$; $p = 0.002$). For LDL cholesterol, there was also a significantly larger reduction in DJBL-patients ($-20.76 \pm 30.54 \text{ mg/dl}$) than in the control group ($-0.14 \pm 37.84 \text{ mg/dl}$; $p = 0.00068$) (figures 2D and 2E). Triglycerides and HDL cholesterol did not differ significantly between the two groups (figure 2F). The odds ratio for reduction of total cholesterol by more than 20 mg/dl was 2.17 (95% CI, 1.02 to 4.02), of LDL cholesterol of more than 10 mg/dl : 3.37 (95% CI, 1.83 to 6.18), and of triglycerides by more than 20 mg/dl : 1.34 (95% CI, 0.73 to 2.44; n.s.) in the DJBL group. For the increase of HDL cholesterol by more than 5 mg/dl the odds ratio was 1.35 (95% CI, 0.67 to 2.71; n.s.) (figure 3).

Patients in the DJBL group had a significantly greater reduction in systolic blood pressure ($-7.83 \pm 21.58 \text{ mmHg}$ vs. $-0.53 \pm 20.34 \text{ mmHg}$; $p = 0.0073$) and diastolic blood pressure ($-4.17 \pm 13.39 \text{ mmHg}$ vs. $-0.02 \pm 11.47 \text{ mmHg}$; $p = 0.0035$) than those in the control group (figures 2G and 2H). The odds ratio for reduction of more than 5 mmHg

of systolic blood pressure was 0.79 (95% CI, 0.48 to 1.30), for diastolic blood pressure 1.10 (95% CI, 0.66 to 1.84) (figure 3).

Change in medication:

Patients receiving DJBL displayed a greater reduction in antidiabetic medication (-10.8%) than patients receiving standard of care (-2.2%; $p < 0.0001$) (table 2, Supplementary Appendix). 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 of insulin therapy of 15.4% and 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/day). Use of lipid lowering drugs was stable in the DJBL group and tended to increase in the control group (table 4). Antihypertensive therapy and average numbers of antihypertensive agents was reduced in the DJBL group in contrast to the control group (table 2 Supplementary Appendix).

Discussion:

This analysis includes the largest population of obese patients with T2DM treated by the DJBL under real life conditions. DJBL therapy caused significant and clinically relevant improvements in glycaemic control, weight reduction and reduction in antidiabetic medication. These results support those reported by Betzel et al.²⁴ in a small monocenter cohort . However, we observed higher weight reduction (14.7kg vs. 12.8kg) and improvement of HbA1c (1.07% vs. 0.76% [-9.3 vs. -6mmol/mol]), which

may be due to the slightly higher baseline BMI, weight, HbA1c and the longer mean implantation time in our cohort. Of note, the applied method of last observation carried forward/intention to treat analysis may have somewhat overestimated the effect size due to inclusion of early removals.

One meta-analysis²⁵ and one review²⁶ report, that DJBL treatment is associated with a significant weight reduction but no significant improvement of glycaemic control in obese patients with T2DM. We propose, however, that the lack of effect on glycaemic control in these analyses may be due to 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 of medication, including antidiabetic (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 medications, antihypertensive drugs and lipid-lowering therapies. It may be speculated that this baseline imbalance in medications represents a bias that could act in either over- or underestimation of the DJBL effect. If the assumption would be true that the intensive medications use in this group had an impact on beta cell survival and function that allow a greater reversibility in the beta cell dysfunction,

the DJBL effect was overestimated. If the more intense medication in the DJBL group would be considered to represent a surrogate of more advanced metabolic disease, it may be implied that the true impact of the DJBL treatment was underestimated, 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 13kg/m²²⁸. The study from Schauer et al. showed a BMI reduction of 10.40kg/m² for gastric bypass and 9.0kg/m² for sleeve gastrectomy and a significant improvement of glycaemic control (HbA1c-reduction of up to 2.9% [9mmol/mol]) with less antidiabetic medication after 12 months in comparison to intensive medical care²⁷. Of note, in this analysis the observed improvements of BMI and HbA1c by 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 by 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 missing.

In the analysis of the German-DJBL-registry, more than 26% had transient mild to moderate adverse primarily gastrointestinal symptoms. These adverse events occurred predominantly after implantation, were probably caused by the intervention and recovered by symptomatic treatment. Some patients had serious adverse events, but these were rare and nonfatal. The safety profile reported here is comparable, and in some instances better than the published DJBL safety profile²⁸.

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) risks included increased frequency of pancreatitis and hepatic abscess. As liver abscesses are currently one of the major concerns, strategies for reduction of this complication are discussed including antibiotic prophylaxis, reduction of proton-pump-inhibitors and shortage of the treatment phase, because of occurrence of liver abscesses typically during 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 underreporting of data to the registries may have introduced a bias into the trial. Furthermore, we cannot be sure, 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 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 the DJBL patients that cannot exactly be quantified, and still a limited overall number of DJBL patients within the analysis. Also, patient related outcomes were not sufficiently addressed in this trial. In the lack 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 of glycaemic control, reduced need of antidiabetic medication, significant weight loss and improvement of 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 AE's, but also rare serious events, which must be considered in clinical judgement for choosing this therapy for a patient with T2DM. This study so far provides the largest evidence for a positive risk-benefit-ratio for treatment of patients with T2DM with the DJBL. Of note, at this point the results of this study are only pertinent to T2DM patients with substantially elevated BMI (mean 43.1kg/m²; table 1 supplementary appendix), and generalisability of the findings to patient groups with lower BMIs is restricted. Nevertheless, more efficacy and safety studies, especially RCT's comparing DJBL with optimal medical treatment or gastric bypass are needed to further evaluate the efficacy 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 also by the German DJBL registry. These studies will more broadly evaluate, whether the DJBL represents an efficacious and safe nonsurgical option for the treatment of obese patients with T2DM in routine clinical care.

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Memmingen Internistische Praxis; Murnau am Staffelsee - diabetol. SPP; München
Diabetes-Zentrum Süd; Münster Clemens-Hospital Innere; Münster Herz Jesu

Innere; Neumarkt Innere; Neunkirchen Innere Medizin; Neuwied Marienhaus
Klinikum St. Elisabeth Innere; Nidda Bad Salzhausen Klinik Rabenstein/Innere-1
Reha; Oberhausen Innere; Oberndorf Gastroenterologische Praxis Schwerpunkt
Diabetologie; Offenbach/Main Innere Medizin; Ottobeuren Kreiskrankenhaus;
Pfullendorf Innere Medizin; Pirmasens Städtisches Krankenhaus Innere; Plauen
Vogtlandklinikum; Prenzlau Krankenhaus Innere; Rastatt Kreiskrankenhaus Innere;
Reutlingen Klinikum Steinenberg Innere; Rosenheim Innere Medizin; Rosenheim
Schwerpunktpraxis; Rostock Universität Innere Medizin; Saaldorf-Surheim
Diabetespraxis; Schwerin Innere Medizin; Spaichingen Innere; Stuttgart Bethesda
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Contribution statement:

KL, NR, RWH, JS and JA initiated and designed this study. NR, KF and RWH performed statistical analysis.

KL, NR, RWH, JS and JA interpreted the data, and revised the manuscript critically for important intellectual content. All authors were responsible for patient inclusion in

the registries and data acquirement. KL wrote the draft of the manuscript. All authors approved the final version of the manuscript. KL, NR, RWH, JS and JA are the guarantors of the work. They had full access to all the data and take responsibility for accuracy of the data analysis and interpretation.

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Table 1: Baseline clinical characteristics of the two matched study populations

Characteristics	German-DJBL-registry	DPV-registry	p – value
	n = 111	n = 222	
Female sex – [%]	60.4	58.1	p = 0.7
Age – [year], mean $\pm$ SD	51.9 $\pm$ 9.0	52.5 $\pm$ 16.2	
Diabetes duration – [year], mean $\pm$ SD	9.5 $\pm$ 6.6	8.9 $\pm$ 7.7	
HbA1c – [%], (mmol/mol) mean $\pm$ SD	8.5 (69) $\pm$ 1.8	8.3 (67) $\pm$ 2.3	p = 0.2
BMI – [kg/m ²], mean $\pm$ SD	42.6 $\pm$ 6.8	41.9 $\pm$ 8.6	p = 0.6
Body weight – [kg], mean $\pm$ SD	124.7 $\pm$ 23.8	120.6 $\pm$ 27.8	
Cholesterol – [mg/dl], mean $\pm$ SD	(n = 58) 194.5 $\pm$ 43.1	(n = 123) 199.6 $\pm$ 50.8	p = 0.7
LDL-Cholesterol – [mg/dl], mean $\pm$ SD	(n = 59) 121.0 $\pm$ 31.5	(n = 105) 119.5 $\pm$ 37.8	p = 0.7
HDL-Cholesterol – [mg/dl], mean $\pm$ SD	(n = 60) 410 $\pm$ 8.4	(n = 109) 43.1 $\pm$ 11.4	p = 0.4
Triglycerides – [mg/dl], mean $\pm$ SD	(n = 60) 219.4 $\pm$ 158.9	(n = 118) 237.9 $\pm$ 215.9	p = 0.7
Treatment with lipid lowering drugs – [%]	36.9	18.5	p = 0.00078
Systolic Blood pressure – [mmHg], mean $\pm$ SD	(n = 76) 134.8 $\pm$ 18.3	(n = 212) 135.1 $\pm$ 19.8	p = 0.9
Diastolic Blood pressure – [mmHg], mean $\pm$ SD	(n = 76) 79.0 $\pm$ 11.0	(n = 212) 81.5 $\pm$ 12.0	p = 0.2
Treatment with antihypertensive – [%]	82.9	34.7	p < 0.0001
Treatment with antidiabetics – [%]	99.1	63.5	p = 0.0001
Treatment with oral antidiabetics – [%]	87.4	63.1	p = 0.0002
Treatment with GLP1- Analogues – [%]	28.8	13.1	p = 0.00136
Insulin therapy – [%]	64.0	48.2	p = 0.013
Insulin dose – [IE]/d mean $\pm$ SD	(n = 65) 77.5 $\pm$ 59.8	(n = 107) 80.7 $\pm$ 49.2	p = 0.446

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

Table 2: Changes of 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 $\pm$ SD n = 117	8.5 (69) $\pm$ 1.8	7.2 (55) $\pm$ 1.2	-1.3	p < 0.0001
HbA1c – [%]*, (mmol/mol) mean $\pm$ SD n = 42	8.6 (70) $\pm$ 1.8	7.1 (54) $\pm$ 1.0	-1.5	p < 0.0001
BMI – [kg/m ²], mean $\pm$ SD n = 150	42.8 $\pm$ 7.0	37.8 $\pm$ 6.7	-5.0	p < 0.0001
Body weight – [kg], mean $\pm$ SD n = 150	124.7 $\pm$ 22.6	110.0 $\pm$ 21.7	- 14.7	p < 0.0001
Excess weight – [kg], mean $\pm$ SD n = 150	51.7 $\pm$ 19.6	37.0 $\pm$ 19.4	-14.7	p < 0.0001
Waist circumference – [cm], mean $\pm$ SD n = 33	113.1 $\pm$ 15.6	103.6 $\pm$ 14.7	-9.5	p < 0.0001
Cholesterol – [mg/dl], mean $\pm$ SD n = 56	191.0 $\pm$ 50.6	164.1 $\pm$ 37.2	-26.9	p = 0.0002
Cholesterol – [mg/dl]*, mean $\pm$ SD n = 40	191.6 $\pm$ 46.3	169.2 $\pm$ 31.3	-22.4	p = 0.0005
LDL-Cholesterol – [mg/dl], mean $\pm$ SD n = 55	120.5 $\pm$ 34.0	98.7 $\pm$ 32.2	-21.8	p = 0.0002
LDL-Cholesterol – [mg/dl]*, mean $\pm$ SD n = 39	126.7 $\pm$ 30.1	102.8 $\pm$ 28.5	-23.9	p = 0.0001
HDL-Cholesterol – [mg/dl], mean $\pm$ SD n = 56	41.3 $\pm$ 8.4	42.7 $\pm$ 19.0	1.4	p = 0.6835
HDL-Cholesterol – [mg/dl]*, mean $\pm$ SD n = 40	41.9 $\pm$ 7.9	43.8 $\pm$ 21.8	1.9	p = 0.8714
Triglycerides – [mg/dl], mean $\pm$ SD n = 54	210.7 $\pm$ 158.4	175.0 $\pm$ 98.4	-35.7	p = 0.2203
Triglycerides – [mg/dl]*, mean $\pm$ SD n = 39	193.2 $\pm$ 98.2	180.7 $\pm$ 92.6	-12.7	p = 0.5224
ALT – [U/l], mean $\pm$ SD n = 76	38.6 $\pm$ 23.3	25.2 $\pm$ 15.5	-13.4	p < 0.0001
AST – [U/l], mean $\pm$ SD n = 62	34.4 $\pm$ 17.4	27.5 $\pm$ 18.9	-6.9	p = 0.013
Systolic blood pressure – [mmHg], mean $\pm$ SD n = 78	134.5 $\pm$ 18.4	128.4 $\pm$ 16.5	-6.1	p = 0.0912

Systolic blood pressure – [mmHg]*, mean $\pm$ SD n = 32	133.5 $\pm$ 21.4	127.9 $\pm$ 15.7	-5.6	p = 0.1433
Diastolic blood pressure – [mmHg], mean $\pm$ SD n = 78	80.0 $\pm$ 11.3	76.4 $\pm$ 10.6	-3.6	p = 0.0013
Diastolic blood pressure – [mmHg]*, mean $\pm$ SD n = 32	77.6 $\pm$ 13.0	75.0 $\pm$ 12.1	-2.6	p = 0.1892
Average number of daily antidiabetic drugs (OAD and GLP1-ReceptorAgonist) – mean $\pm$ SD n = 132	1.7 $\pm$ 0.71	1.4 $\pm$ 0.9	-0.3	p < 0.0001
Insulin dose – [IE/kg bodyweight/day] n = 132	0.7 $\pm$ 0.44	0.4 $\pm$ 0.2	-0.3	p < 0.0001

Data given as n (%), mean with standard deviation (SD). P-values are given for the comparison between im- and explantation. * Subgroup of patients with stable interfering medication.

Figure legends:

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 versus standard of care (DPV-registry) in patients with obesity and type 2 diabetes.

Figure 2: Comparative efficacy of the DJBL versus standard of care (DPV-registry) in patients with obesity and type 2 diabetes. Differences between DJBL implantation (baseline; BL) and explantation or the respective time-periods in the control group for **A.** Hb1Ac. *** $p < 0.001$, **B.** BMI. *** $p < 0.001$, **C.** EWL (excess weight loss). *** $p < 0.001$, **D.** Total Cholesterol. ** $p < 0.01$, **E.** LDL cholesterol. *** $p < 0.001$, **F.** HDL cholesterol. N.s., **G.** Diastolic blood pressure, ** $p < 0.01$, **H.** Diastolic blood pressure, ** $p < 0.01$.

Figure 3: Forest plot evaluating the comparative efficacy of the DJBL versus standard of care (DPV-registry) in patients with obesity and T2DM. Odds ratios with their 95% Wald confidence intervals are shown for HbA1c-reduction by $\geq 1\%$ [8.6 mmol/mol], BMI-reduction by 5 kg/m², 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 mmHg.

Figure 1: Patient disposition

Figure 2: Comparative efficacy of the DJBL versus standard of care control group

Figure 3: Comparative efficacy of DJBL versus standard of care (control)

Supplementary Appendix

Table 1: Baseline clinical characteristics of all patients with type 2 diabetes mellitus included in the German DJBL registry

Characteristics	German DJBL registry	Number of patients with available data
Female sex – [%]	62.0	235
Age [year], mean $\pm$ SD	51.6 $\pm$ 10.4	234
HbA1c – [%], (mmol/mol) mean $\pm$ SD	8.4 (68) $\pm$ 1.8	214
BMI – [kg/m ²], mean $\pm$ SD	43.1 $\pm$ 6.9	235
Body weight – [kg], mean $\pm$ SD	125.5 $\pm$ 23.7	235
Excess weight – [kg], mean $\pm$ SD	52.5 $\pm$ 20.5	235
Waist circumference – [cm], mean $\pm$ SD	117.6 $\pm$ 16.4	62
Systolic Blood pressure – [mmHg], mean $\pm$ SD	136.6 $\pm$ 17.2	167
Diastolic Blood pressure – [mmHg], mean $\pm$ SD	80.7 $\pm$ 10.8	167
Treatment with lipid lowering drugs – [%]	36.2	229
Therapy with oral antidiabetics and/or GLP-1 receptor agonists – [%]	86.3	233
Therapy with GLP-1 receptor agonists only – [%]	22.8	233
Insulin therapy – [%]	64.0	233
Insulin dose – [IU]/d mean $\pm$ SD	70.2 $\pm$ 53.1	111

Data given as n (%), mean with standard deviation (SD).

Table 2: Changes in Medication

Characteristics	German DJBL Registry (GER) Implantation minus Explantation n = 111	DPV matched time period n = 222	p – value GER/DPV
Treatment with insulin – [%]	-15.4	+1.3	
Insulin dose [IE]/d	-39.1 ± 52.7	- 4.4 ± 38.8	p < 0.0001
Treatment with antidiabetics – [%]	-10.8	- 2.2	
Average number of antidiabetic drugs – [%]	-0.3	+0.17	
Treatment with antihypertensives – [%]	-2.7	+4.9	
Average number of antihypertensive drugs – [%]	-0.1	-0.05	
Treatment with lipid lowering drugs – [%]	0.0	+3.6	
Average number of lipid lowering drugs – [%]	0.0	-0.02	

Data given as mean. P-values are given for the comparison between patients from the German DJBL registry and the DPV – registry.

Table 3: Reasons and Time Points of Early Explantation

Reason for Explantation	n	Time points of explantation (weeks after implantation; individual patients)
Abdominal pain	11	3; 4; 4; 13.9; 13.9; 13.9; 19; 22; 29.1; 30; 38.6
“No complication” documented in the eCRF	11	23.4; 41.3; 42; 42.1; 43; 43; 44; 45.1; 46.1; 46.4; 47.0
Dislocation	3	26.9; 31; 44.3
Nausea and vomiting	2	28.4; 30.6
Bolusobstruction	2	10.1;34.3
Complication not defined	1	0
Inversion of the DJBL	1	1.7
Liver abscess	1	48
Atrial fibrillation and need for anticoagulation	1	22
Indication for NSAR use because of an Orthopedic intervention	1	37
Iron deficiency anaemia due to suspected malabsorption by the DJBL and diabetic foot syndrome with thrombotic occlusion of the arteria femoralis with indication for anticoagulation	1	42
TOTAL (n)		