OBES SURG (2013) 23:1354–1360
DOI 10.1007/s11695-013-0921-3

ORIGINAL CONTRIBUTIONS

Endoscopic Duodenal–Jejunal Bypass Liner Rapidly Improves Type 2 Diabetes

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Published online: 23 March 2013

Abstract
Background Bariatric procedures excluding the proximal small intestine improve glycemic control in type 2 diabetes within days. To gain insight into the mediators involved, we investigated factors regulating glucose homeostasis in patients with type 2 diabetes treated with the novel endoscopic duodenal–jejunal bypass liner (DJBL).
Methods Seventeen obese patients (BMI 30–50 kg/m^2) with type 2 diabetes received the DJBL for 24 weeks. Body weight and type 2 diabetes parameters, including HbA_{1c} and plasma levels of glucose, insulin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon, were analyzed after a standard meal before, during, and 1 week after DJBL treatment.
Results At 24 weeks after implantation, patients had lost 12.7±1.3 kg ($p<0.01$), while HbA_{1c} had improved from 8.4±0.2 to 7.0±0.2 % ($p<0.01$). Both fasting glucose levels and the postprandial glucose response were decreased at 1 week after implantation and remained decreased at 24 weeks (baseline vs. week 1 vs. week 24: 11.6±0.5 vs. 9.0±0.5 vs. 8.6±0.5 mmol/L and 1,999±85 vs. 1,536±51 vs. 1,538±72 mmol/L/min, both $p<0.01$). In parallel, the glucagon response decreased (23,762±4,732 vs. 15,989±3,193 vs. 13,1207±1,946 pg/mL/min, $p<0.05$) and the GLP-1 response increased (4,440±249 vs. 6,407±480 vs. 6,008±429 pmol/L/min, $p<0.01$). The GIP response was decreased at week 24 (baseline—115,272±10,971 vs. week 24—88,499±10,971 pg/mL/min, $p<0.05$). Insulin levels did not change significantly. Glycemic control was still improved 1 week after explantation.
Conclusions The data indicate DJBL to be a promising treatment for obesity and type 2 diabetes, causing rapid improvement of glycemic control paralleled by changes in gut hormones.

Keywords Obesity · Type 2 diabetes · Gut hormones · GLP-1 · GIP · Glucagon

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Introduction

The rising prevalence of obesity is accompanied by an increasing number of people suffering from obesity-related comorbidities. Type 2 diabetes (T2DM) is an important comorbidity of obesity and a major cause of morbidity and mortality [1, 2]. For decades, bariatric surgery has been performed to treat obesity, with additional remarkable effects on T2DM [3, 4]. Rapid remission of T2DM occurs particularly after bariatric procedures involving a bypass of the proximal small intestine, such as the Roux-en-Y gastric bypass (RYGB) [5–7].

Two major mechanisms have been hypothesized to explain the rapid improvement of T2DM. Firstly, the foregut hypothesis suggests that improved glycemia after proximal intestinal exclusion results from reduced secretion of diabetogenic hormones/anti-incretin factors in response to the absence of nutrition in the proximal small intestine [8, 9]. For example, intestinal glucagon synthesis has been suggested to decrease after exclusion of the proximal intestine [9]. Secondly, the hindgut hypothesis attributes improved glycemic control to enhanced secretion of incretins, like glucagon-like peptide-1 (GLP-1), in response to undigested nutrients in the distal small intestine [6, 10]. These theories are not mutually exclusive and additional factors likely play a role in the rapid glycemic improvement after bariatric surgery. Particularly, glucose-dependent insulinotropic polypeptide (GIP), a gut hormone which stimulates glucagon secretion in response to a meal, may also be involved [11]. Furthermore, caloric intake is of importance in improvement of T2DM [12].

Recently, a non-surgical duodenal–jejunal bypass liner (DJBL; GI Dynamics, Lexington, MA, USA) has been developed to mimic RYGB-related proximal small intestinal exclusion. The DJBL is a 60-cm-long impermeable liner which is delivered and retrieved endoscopically. Previous studies have shown its safety and efficacy: like RYGB, the DJBL causes significant weight loss and improvement of glycemic control [13–18]. Unlike RYGB, the anatomy of the stomach and small intestine is not affected by DJBL treatment [19], enabling mechanistic studies focusing exclusively on the role of the proximal intestine in T2DM.

In this pilot study, we investigated mechanisms by which proximal small intestinal exclusion by DJBL improves glycemic control in patients with T2DM. Glucose, insulin, GLP-1, GIP, and glucagon responses after a standard meal were studied before, during, and after DJBL treatment.

Materials and Methods

Subjects

Seventeen patients with T2DM and obesity were included at Maastricht University Medical Center and Atrium Medical Center Parkstad. Inclusion criteria were age 18–65 years, duration of T2DM <10 years, HbA_{1c} 7.5–10.0 %, and BMI 30–50 kg/m^2. Main exclusion criteria were blood glucose-lowering medication other than sulfonylurea derivates, metformin, or insulin; requiring >150 IU of insulin daily; type 1 diabetes; fasting c-peptide <1 ng/mL; >4.5 kg weight loss within 12 weeks prior to screening; use of weight loss medication or anti-inflammatory drugs; known infection, and exclusion criteria regarding safety of and compatibility with DJBL treatment. The study was approved by the Medical Ethics Committee and conducted according to the revised version of the Declaration of Helsinki. Written informed consent was obtained from every patient.

DJBL Procedure

The DJBL was delivered and retrieved as previously described (Fig. 1a, b) [16]. In brief, a gastroduodenal endoscopy was performed. A guide wire was placed into the duodenum over which the encapsulated DJBL was passed into the duodenal bulb. The DJBL was advanced into the small intestine, followed by deployment of the anchor. Correct positioning and patency were verified under fluoroscopy.

Patients were provided a standard of care nutritional counseling program, which suggested a regular diet with a maximum of 1,200 kcal for women and 1,500 kcal for men and was liquid for the first week after DJBL placement. Nutritional and T2DM counseling was performed regularly. After 24 weeks, the DJBL was explanted by a custom retrieval system [16].

Study Design

Subjects were studied on four occasions: (1) within 1 month prior to implantation, (2) within 1 week after implantation, (3) within 1 week prior to explantation, and (4) within 1 week after explantation in a subset of eight subjects (Fig. 1c). At each time point, weight was determined and a standardized meal tolerance test was performed (Fig. 1d): blood samples were drawn after an overnight fast; thereafter, a standard liquid meal (Ensure Plus®, Abbott Laboratories, IL, USA; 333 mL, 500 kcal, 20.8 g protein, 67.3 g carbohydrates, and 16.4 g fat) was consumed, followed by collection of blood samples in EDTA with aprotinin at 10, 30,

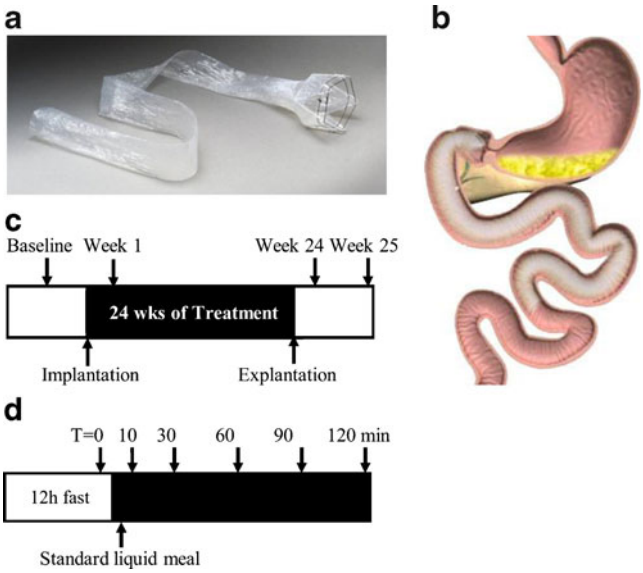

Fig. 1 The DJBL, the design of the study, and the meal tolerance test. **a** Depiction of DJBL, **b** implanted DJBL, **c** schematic overview of the study design, **d** design of the meal tolerance test

60, 90, and 120 min. Samples were immediately cooled, centrifuged, and stored at −80 °C until further analysis.

Plasma Parameters

Total GLP-1 was measured by a radioimmunoassay as previously described [20]. Glucagon and total GIP was assessed with the human diabetes bio-plex pro assay (Bio-Rad Laboratories BV, Veenendaal, The Netherlands) using Luminex xMAP® technology as per the manufacturer's instructions. Glucose, insulin, and HbA_{1c} were determined routinely at the Department of Clinical Chemistry.

Statistical Analyses

GraphPad Prism 5.0 and Statistical Package for Social Sciences 17.0 were used. Total area under the curve (AUC) of the different hormones was calculated using trapezoidal method. Longitudinal changes were tested with linear mixed models. A p-value of <0.05 was considered as statistically significant. Data are presented as statistical model estimated means and standard error of the mean (SEM).

Results

Proximal Small Intestinal Exclusion Results in Significant Weight Loss and Rapid Glycemic Control

Baseline characteristics of study subjects are shown in Table 1. Patients had a mean BMI of 37.0±1.3 kg/m^2 with an average weight of 116.0±5.8 kg and a mean HbA_{1c} of 8.4±0.2 %. After 24 weeks, at the time of device explantation, mean weight loss was 12.7±1.3 kg, corresponding with an excess weight loss of 29.8±3.5 % and a BMI reduction of 4.1±0.4 kg/m^2 (all p<0.01). HbA_{1c} had decreased to 7.0±0.2 % (p<0.01). Importantly, this HbA_{1c} reduction occurred despite decreased glucose-lowering medication in 16/17 subjects.

Table 1 Baseline characteristics of the study population

	Number of patients, N=17
Age (years)	51±2
Sex (male)	14 (82.4)
Weight (kg)	116.0±5.8
BMI (kg/m^2)	37.0±1.3
HbA_{1c} (%)	8.4±0.2
Fasting glucose (mmol/L)	11.6±0.5
Fasting insulin (μU/mL)	25.5±7.8

Data are shown as mean ± SEM or number (%)

At baseline, patients had pathognomonic high glucose levels. At 1 week after DJBL placement, fasting glucose had markedly decreased from 11.6±0.5 to 9.0±0.5 mmol/L (p<0.01; Fig. 2a). The postprandial glucose curve was shifted downwards, resulting in a decreased AUC of the glucose response (baseline—1,999±85 vs. week 1—1,536±51 mmol/L/min, p<0.01; Fig. 2b). This initial glycemic improvement persisted throughout the study (fasting glucose at baseline—11.6±0.5 vs. week 24—8.6±0.5 mmol/L; AUC glucose at baseline—1,999±85 vs. week 24—1,538±72 mmol/L/min, both p<0.01).

In line with the high glucose levels, insulin levels were high at baseline. However, despite the decreased glucose levels, fasting insulin levels did not change significantly during DJBL treatment (baseline—25.5±7.8 vs. week 1—22.5±7.8 μU/mL and baseline—25.5±7.8 vs. week 24—15.1±3.1 μU/mL, p=0.23 and p=0.06, respectively; Fig. 2c). Moreover, also the insulin response to a meal, as reflected by the AUC of insulin, was unaffected by DJBL treatment (baseline—6,603±1,100 vs. week 1—6,688±1,164 μU/mL/min and baseline—6,603±1,100 vs. week 24—6,446±770 μU/mL/min, p=0.86 and p=0.84, respectively; Fig. 2d).

Consistent with the high glucose and insulin concentrations, HOMA-IR as an indicator of insulin sensitivity was high at baseline (14.6±5.8). At 1 week after DJBL implantation, HOMA-IR had improved in 11/17 patients. This improvement progressed, resulting in an improved HOMA-IR in 14/17 patients at week 24 (baseline—14.6±5.8 vs. week 1—9.2±3.5 and baseline—14.6±5.8 vs. week 24—6.3±1.8, both p=0.06; Fig. 2e).

Increased GLP-1 and Decreased GIP Response after DJBL Treatment

Next, we investigated the effect of DJBL treatment on gut hormones GLP-1 and GIP during a meal tolerance test.

At baseline, subjects showed a marginal increase of GLP-1 in response to a meal, indicating an aberrant postprandial GLP-1 response (Fig. 3a). Within 1 week after DJBL implantation, however, postprandial GLP-1 concentrations increased and a clear meal-related response appeared. This pattern remained throughout the treatment period. Whereas fasting GLP-1 levels were not affected by the DJBL (baseline—29.0±2.6 vs. week 1—32.5±2.7 pmol/L and baseline—29.0±2.6 vs. week 24—30.3±2.6 pmol/L, p=0.21 and p=0.70, respectively), the postprandial GLP-1 response increased significantly (baseline—4,440±249 vs. week 1—6,407±480 pmol/L/min and baseline—4,440±249 vs. week 24—6,008±429 pmol/L/min, both p<0.01; Fig. 3b).

In contrast, a postprandial rise in GIP levels was present before DJBL implantation (Fig. 3c). At 1 week after DJBL placement, postprandial GIP levels had not significantly

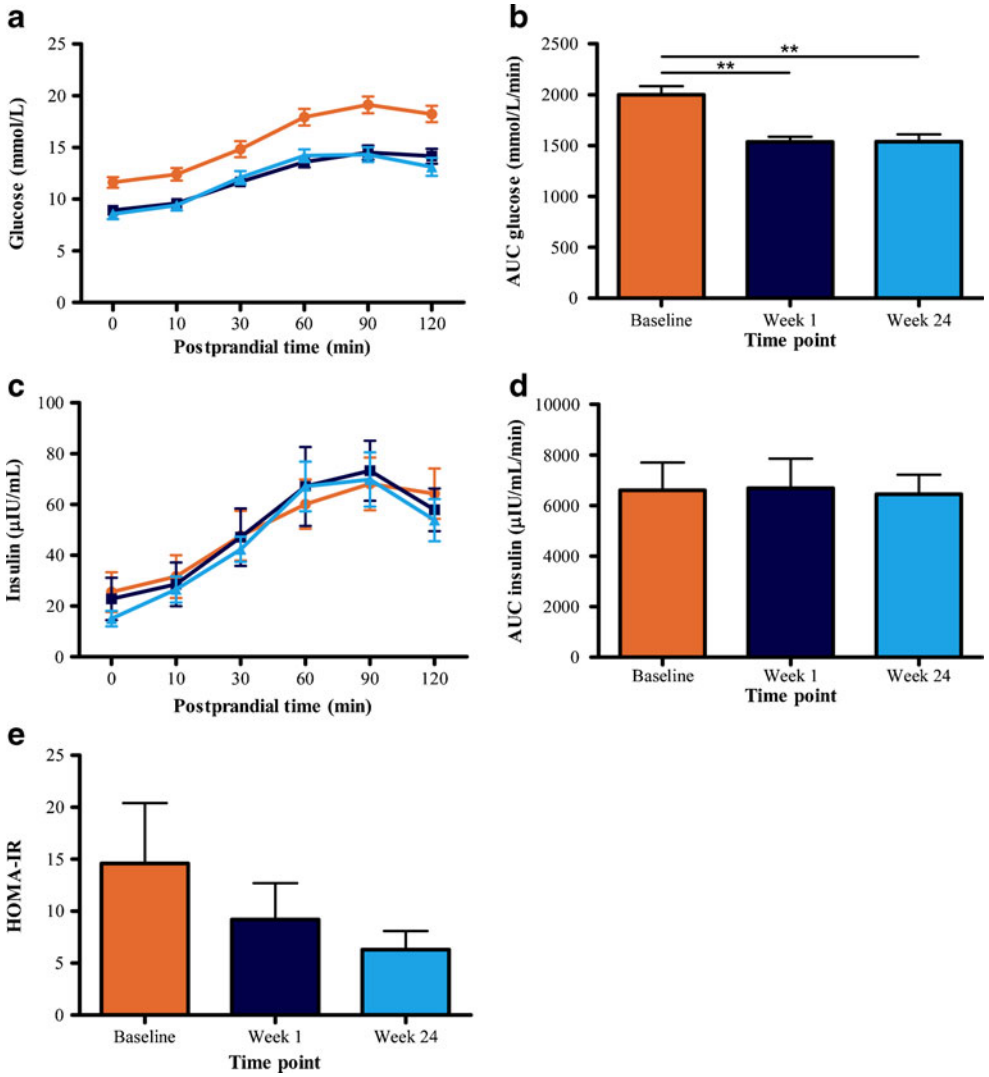

Fig. 2 Effects of DJBL treatment on fasting and postprandial glucose and insulin levels and on HOMA-IR. **a** Plasma glucose concentrations during the meal tolerance test at baseline, at 1 week after implantation of the DJBL, and just prior to DJBL explantation. **b** Area under the curve calculations for glucose. **c** Plasma insulin concentrations obtained during the meal tolerance tests and **d** area under the curve calculations for insulin. **e** HOMA-IR values. An *asterisk* indicates $p<0.05$; *two asterisks* indicate $p<0.01$

changed, although they tended to be lower (baseline—115,272±10,971 vs. week 1—99,388±11,073 pg/mL/min, $p=0.06$; Fig. 3d). During the study period, postprandial GIP levels further decreased, reaching statistical significance at week 24 (baseline—115,272±10,971 vs. week 24—88,499±10,971 pg/mL/min, $p=0.02$). DJBL treatment did not affect fasting GIP concentrations (baseline—145.9±23.3 vs. week 1—233.1±128.3 pg/mL and baseline—145.9±23.3 vs. week 24—155.1±29.8 pg/mL, $p=0.50$ and $p=0.79$, respectively).

Decreased Postprandial Glucagon after DJBL Treatment

Since both GLP-1 and GIP affect glucagon secretion, we next assessed the potential effect of DJBL treatment on glucagon levels in response to a meal.

At baseline, glucagon levels peaked following meal ingestion (Fig. 3e), which is typical for patients with T2DM [21]. This abnormal pattern was largely corrected 1 week after DJBL implantation. Furthermore, the AUC of the glucagon response was significantly decreased at this time point (baseline—23,762±4,732 vs. week 1—15,989±3,193 pg/mL/min, $p=0.02$; Fig. 3f). The improved glucagon response remained throughout the study, resulting in only a minor meal-related glucagon induction after 24 weeks (baseline—23,762±4,732 vs. week 24—13,207±1,946 pg/mL/min, $p=0.02$). Fasting glucagon levels did not change over time (baseline—105.9±14.9 vs. week 1—79.7±15.2 pg/mL and baseline—105.9±14.9 vs. week 24—78.7±14.9 pg/mL, $p=0.12$ and $p=0.16$, respectively).

Persistent Amelioration of Glycemic Control 1 Week after DJBL Explantation

To determine if the improved glucose homeostasis was maintained after removal of the DJBL, we studied a subset of patients 1 week after explantation. Importantly, the glucose response to a meal remained decreased (Table 2). No significant changes in the insulin response or HOMA-IR were observed. GLP-1 levels decreased from 6,342±557 just prior

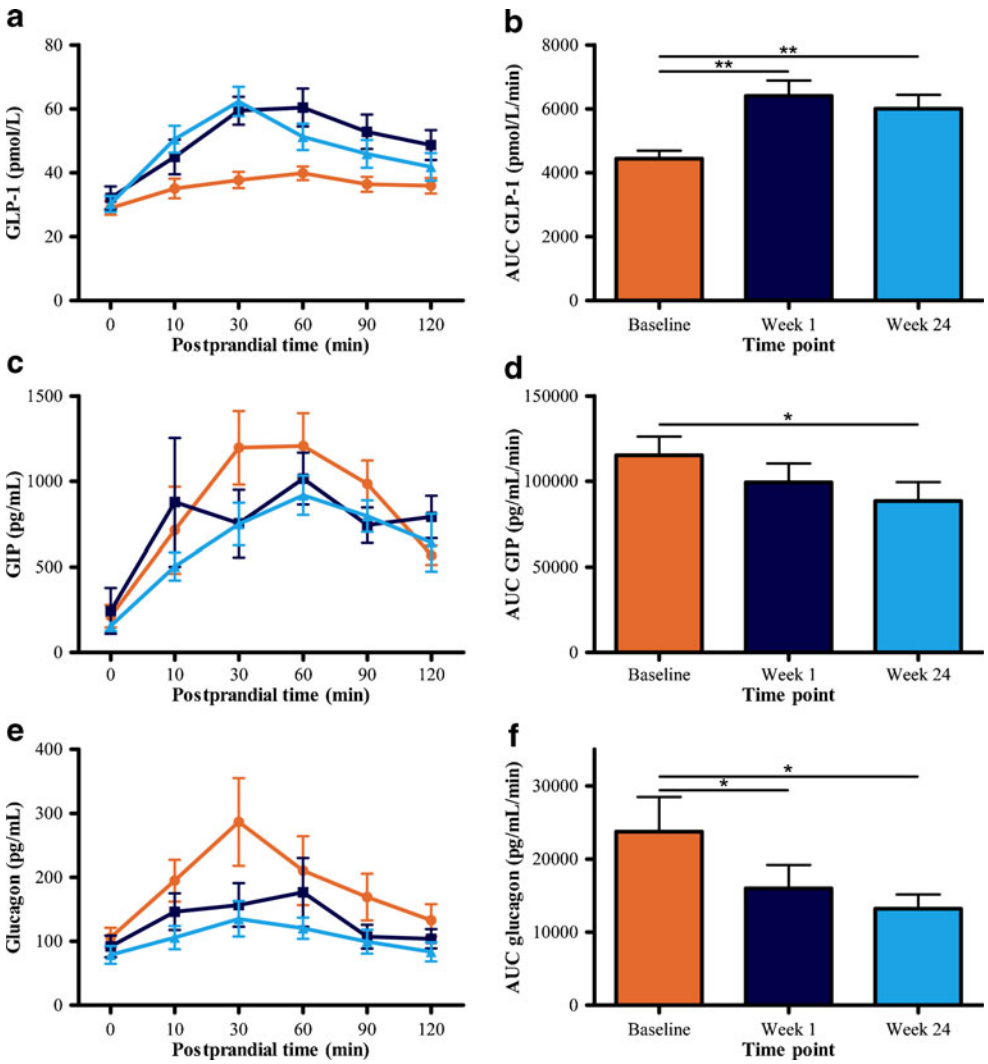

Fig. 3 Effects of DJBL treatment on fasting and postprandial GLP-1, GIP, and glucagon levels. **a** Plasma concentrations of GLP-1 during the meal tolerance test at baseline, at 1 week after implantation of the DJBL, and just prior to DJBL explantation. **b** Area under the curve calculations for GLP-1. **c** Plasma GIP concentrations during the meal tolerance tests and **d** area under the curve calculations for GIP. **e** Plasma glucagon levels during the meal tolerance tests. **f** Area under the curve calculations for glucagon. An *asterisk* indicates $p<0.05$; *two asterisks* indicate $p<0.01$

to explantation to 5,226±557 pmol/L/min at 1 week post-explantation ($p=0.03$). In contrast, the improved glucagon and GIP response remained at 1 week after device removal.

Conclusion

The mechanisms responsible for the improvement of T2DM after proximal intestinal exclusion are subject to debate. In the current pilot study, we investigated the effect of duodenal–jejunal exclusion by a novel device, the DJBL, on glycemic control and hormones involved in glucose homeostasis. Our results show that exclusion of the proximal small intestine by DJBL results in significant weight loss and rapid decrease of both fasting and postprandial glucose levels, whereas insulin levels do not change significantly. Hence, it is tempting to speculate that the rapid improvement of glucose homeostasis might result from increased insulin sensitivity and/or decreased hepatic glucose production.

Table 2 Changes in total glucose, insulin, GLP-1, GIP, and glucagon response after DJBL explantation

	Week 24, $N=8$	Week 25, $N=8$	p-value
AUC of glucose (mmol/L/min)	1,560±126	1,506±126	0.55
AUC of insulin (μU/mL/min)	7,520±937	6,183±1,068	0.06
AUC of GLP-1 (pmol/L/min)	6,342±557	5,226±557	$p<0.05$
AUC of GIP (pg/mL/min)	73,645±10,389	144,947±54,331	0.16
AUC of glucagon (pg/mL/min)	8,686±713	10,655±2,446	0.36
HOMA-IR	8.3±4.2	7.3±4.2	0.28

Data are shown as mean ± SEM

DJBL-induced changes in glucagon, GLP-1, and GIP suggest that these hormones are involved in the improvement of glycemic control.

Surgically bypassing the duodenum and jejunum has been shown effective in treating T2DM in both overweight and mildly obese subjects [22, 23]. Moreover, T2DM can resolve within 24 h after RYGB [5]. Previous studies indicated that the DJBL improves T2DM rapidly [13, 16]. The initial improvement of T2DM therefore seems to be weight loss-independent and may result from increased insulin sensitivity, mediated by increased GLP-1 levels [24, 25]. In line with this, we observed increased GLP-1 levels as early as 1 week after DJBL implantation. The improved HOMA-IR levels further indicate that DJBL treatment might increase insulin sensitivity.

Improved insulin sensitivity has also been reported following caloric restriction. In particular, very low calorie diets (<<1,000 kcal/day) have been shown to rapidly improve insulin sensitivity [12, 26]. In the present study, patients were advised a moderate diet with a maximum of 1,500 kcal/day for men and 1,200 kcal/day for women. Interestingly, Pournaras et al. compared RYGB, gastric banding, and a diet of ~1,000 kcal/day and found reduced insulin resistance only after RYGB [27]. In view of these data, we consider calorie restriction to be responsible only to a limited extent for the observed improved glycemic control. Unpublished data of a group of patients subjected to similar nutritional and type 2 diabetic counseling further support this; inferior improvement of type 2 diabetes was observed.

In addition, reduced hepatic glucose production may be responsible for the DJBL-induced improvement of T2DM. Hepatic glucose production was likely reduced due to the decreased glucagon response observed already early after DJBL treatment. This assumption finds support in the rapid decrease of fasting glucose levels since fasting glucose levels are primarily determined by hepatic glucose synthesis [28]. Decreased hepatic glucose production might also be related to the increase in GLP-1 and the decrease in GIP that occurred after DJBL implantation. GLP-1 inhibits glucagon secretion [29], whereas GIP tends to augment the glucagon response to a meal [30, 31].

Taken together, we propose that proximal intestinal exclusion by DJBL treatment affects insulin sensitivity and hepatic glucose production. However, to thoroughly assess the involvement of these mechanisms in the amelioration of glucose homeostasis, further investigations including hyperinsulinemic euglycemic clamping studies enhanced by glucose tracers are required.

Our data fit both proposed major hypotheses to explain the rapid improvement of T2DM after proximal small intestinal exclusion. In accordance with the foregut hypothesis, prevention of digestion and uptake of nutrients in the proximal intestine after DJBL treatment was associated with decreased secretion of glucagon, a diabetogenic factor, contributing to reduced glucose levels [8, 9]. The DJBL-induced decrease of GIP is also in line with this theory because GIP is secreted in the proximal intestine and affects glucagon secretion [9]. Additionally, our data are in agreement with the hindgut hypothesis because the observed GLP-1 increase is likely to be the result of undigested nutrients in the distal small intestine [6, 10].

Whereas the initial rapid improvement of T2DM after bariatric surgery is considered weight loss-independent, weight loss plays a role in longer-term improvement of T2DM [32, 33]. Given the observed weight loss after 24 weeks of DJBL treatment, these mechanisms may contribute to improvement of glucose homeostasis by DJBL treatment and its sustained amelioration at 1 week after explantation.

According to the recent position statement of the International Diabetes Federation, bariatric surgery should be incorporated in T2DM treatment algorithms [34]. In comparison to conventional bariatric procedures, the DJBL procedure is less invasive, reversible, and safe [13–18]. The majority of the device-related adverse events was minor, mainly consisting of abdominal discomfort. Three patients presented with an adverse event requiring hospitalization: one with obstipation, one with melena, and one patient with abdominal discomfort causing dehydration. All adverse events were managed conservatively; neither early explantation nor surgical intervention was required.

DJBL treatment appears to have similar effects on glycemic control as invasive bariatric techniques. We therefore propose it as a promising alternative for bariatric surgery in the treatment of T2DM. Further studies should be directed at investigating maximal treatment duration, longer-term impact on glucose homeostasis, and its effects on other obesity-related comorbidities. Additionally, the DJBL provides a unique human model enabling insight into mechanisms responsible for the beneficial effects of proximal small intestinal exclusion on body weight and T2DM.

In conclusion, our pilot study shows that DJBL treatment leads to rapid improvement of glycemic control which is paralleled by changes in the GLP-1, GIP, and glucagon response to food intake. Additional studies may provide further insight into the role of the proximal small intestine in T2DM.

Acknowledgments The authors would like to thank the patients contributing to this trial; the trial nurses, Y. Wils and R. Nelissen; the students who helped in conducting this research: G. Latten, N. Geubbels, M. de Wolf, T. van der Horst, R. Erbil, B. van der Putten, H. D'Agnolo, S. Peeters Weem, and M.A. Joosten; B. Winkens for statistical assistance; Dr. R.J. de Ridder, Dr. G.H. Koek, and Dr. C.M.

Bakker for their help with the DJBL procedures; Prof. Dr. A.A. Masclee, Dr. J. Maljaars, and Y. Slaats for their help regarding the study design; and I.C. Arts and E. Theunisz for the Luminex analyses.

Conflict of Interest N.D.B. received an open research grant from GI Dynamics. J.W.M.G. received an open research grant and support for travel to meetings for the study or other purposes from GI Dynamics. All other authors have no conflicts of interest relevant to this article.

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