NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes

In this procedure, a plastic liner is inserted through the mouth into the bowel, with the help of an endoscope (a thin flexible tube with a camera on the end), so that it lines the upper part of the bowel (duodenum and jejunum). The liner is intended to reduce food absorption by forming a barrier between food and the bowel. The aim is to help people lose weight and improve control of their diabetes. The liner is usually removed after a year.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in April 2014 (25-04-2014).

Procedure name

- Implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes

Specialist societies

- Association of British Clinical Diabetologists (ABCD)
- British Obesity and Metabolic Surgery Society
- British Society of Gastroenterology
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland.

Description

Indications and current treatment

Type 2 diabetes is caused by insulin resistance with or without inadequate pancreatic insulin secretion. It is most commonly seen in people with obesity or who are overweight. Presenting symptoms include polyuria, polydipsia, and fatigue. Type 2 diabetes is commonly associated with raised blood pressure, abnormal blood lipid levels and a tendency to atherosclerosis. This combination is often described as the 'metabolic syndrome', which is associated with fatty liver and abdominal adiposity (increased waist circumference).

Type 2 diabetes is managed by lifestyle and dietary changes, exercise or antidiabetic drugs (as recommended in NICE's guideline on type 2 diabetes). If blood glucose levels remain poorly controlled, subcutaneous insulin injections may be needed.

What the procedure involves

Endoscopic implantation of a duodenal–jejunal bypass liner (DJBL) is a procedure that aims to improve glycaemic control in people with obesity or who are overweight.

The procedure is done with the patient under general anaesthesia or sedation, using image guidance. The liner is positioned endoscopically (via the mouth). Using a delivery catheter, a capsule containing a single-use impermeable DJBL is positioned in the duodenal bulb just distal to the pylorus. It is secured there using an integral spring metal anchor. The liner is advanced distally into the jejunum with the aid of a tension wire that is part of the 'introducer' device. It extends about 60 cm down the small intestine and forms a barrier between food and the intestinal wall, so delaying the mixing of digestive enzymes with food.

After the procedure, patients are recommended a diet that typically involves progression from fluids to semi-solid foods and then to solid foods.

After a maximum of a year, the liner is removed with the patient under sedation, using image guidance and endoscopy. The anchor has a drawstring mechanism such that it can be collapsed and partly withdrawn into a plastic hood fitted to the endoscope before withdrawal.

Outcome assessment tools

HOMA score and Matsuda index

The homeostatic model assessment of insulin resistance (HOMA-IR) and the Matsuda index ($10{,}000/\sqrt{[(G_0 \times I_0) * (G_{mean} \times I_{mean})]}$, where G is glucose and I is insulin, are used to estimate insulin resistance and sensitivity.

Insulinogenic index

The insulinogenic index [$(Ins_{30}-Ins_0)/(Gluc_{30}-Gluc_0)$ or $\Delta Ins_{30}/\Delta Glu_{30}$], where Ins_{30} is insulin in 30 minutes and $Gluc_{30}$ is glucose in 30 minutes, was used to estimate the first phase of insulin release.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to Implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes. Searches were conducted of the following databases, covering the period from their commencement to 25-04-2014: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with type 2 diabetes.
Intervention/test	Implantation of a duodenal–jejunal bypass liner
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 186 patients from 1 randomised trial[1], 6 case series[2–7] and 1 case report[8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes

Study 1 Koehestanie P (2014)

Details

Study type	**RCT**
Country	Netherlands (multicentre)
Recruitment period	Not reported
Study population and number	Patients with type 2 diabetes and obesity n=**77 (38 DJBL group versus 39 control group – low calorie diet)**
Age and sex	DJBL arm mean 49.5 years, control arm 49 years DJBL arm 38% (13/34) female, sham arm 36% (14 /39) female Mean BMI: DJBL arm 34.6 kg/m^2, sham arm 36.8 kg/m^2; Mean HbA_{1c}: 8.3%
Patient selection criteria	Inclusion criteria: aged 18–65 years, BMI 30–50 kg/m^2, type 2 diabetes for less than10 years with an HbA_{1c} level 7.5–10%. Exclusion criteria: weight loss of >4.5 kg within 12 weeks before screening, pregnancy or intention to become pregnant, use of NSAIDs, anticoagulation therapy, corticosteroids, weight loss medication, or drugs known to affect GI motility, substance abuse, active *Helicobacter pylori* infection, probable insulin production failure (C-peptide level of <10 ng/ml), iron deficiency, GI abnormalities, or previous surgery in GI, symptomatic gall stones or kidney stones, infection, bleeding disorders, GORD, connective tissue disorders, severe liver or kidney failure.
Technique	DJBL arm: EndoBarrier implanted under general anaesthesia, fluoroscopy and endoscopy guidance. Dose of glucose-lowering medication (except metformin) was reduced by 50% and PPIs given. Liquid diet for the first week, pureed food during the second week and solids thereafter. Recommended intake 1200 calories per day for women and 1500 calories per day for men. Patients advised to increase physical activity. Follow-up every month, after 6 months DJBL was removed and patients were followed up for an additional 6 months. Low calorie diet alone: patients received only dietary intervention.
Follow-up	**12 months (including 6-month follow-up after device removal)**
Conflict of interest/source of funding	Study funded by manufacturer. 4 authors are consultants for GI Dynamics.

Analysis

Follow-up issues: In the device arm (n=34) 2 patients were lost to follow-up (at 191 and 272 days) and 1 withdrew consent (at day 10 due to abdominal pain); in the diet arm (n=39) 1 patient was lost to follow-up (at day 267) and 4 withdrew consent (at week 1, 3 months, day 273 and 315).

Study design issues: The method of randomisation was not reported. There was no allocation concealment. There was no significant difference between groups at baseline with respect to age, sex, BMI and comorbidities.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **38 DJBL versus 39 low-calorie diet alone**

Procedural outcomes in DJBL arm % (n)

Implantation success	89.4 (34/38)
Implantation failure	7.8 (3/38)
Withdrawal	2.6 (1/38)

Change in body weight (mean)

Mean body weight %	**DJBL arm (n=38)**	**Diet arm (n=39)**	**p value**
Baseline	105.4	110.8	0.29
6 months	94.8	105.5	<0.05
12 months	98.6	106.8	0.07

Excess weight loss was more in the DJBL group than in control group at 12-month follow-up (19.8% versus 11.7%, p<0.05).

Change in glycaemic control measured by HbA1c (mean)

Mean HbA_{1c} %	**DJBL arm (n=38)**	**Diet arm (n=39)**	**p value**
Baseline	8.3	8.3	0.82
6 months	7.0	7.9	<0.05
12 months	7.3	8.0	0.95

Change in fasting glucose (mean)

Mean fasting glucose mmol/litre	**DJBL arm (n=38)**	**Diet arm (n=39)**	**p value**
Baseline	11.0	11.0	0.87
6 months	8.5	10.0	0.10
12 months	9.0	9.7	0.41

Change in fasting insulin (mean)

Mean fasting insulin mU/litre	**DJBL arm (n=38)**	**Diet arm (n=39)**	**p value**
Baseline	15.0	17.0	0.11
6 months	11.1	14.0	0.40
12 months	15.0	15.7	0.73

85% of patients in DJBL arm showed decreased postprandial glucose excursions versus 48.7% of control patients (p<0.05).

Changes in oral glucose lowering medication

At 12-month follow-up, the daily insulin dose and use of sulfonylureas decreased or discontinued more in the DJBL group than in control group (p<0.05).

Change in cardiovascular parameters

The RCT of 77 patients reported that at 12-month follow-up, blood pressure decreased from 147/92 mmHg to 130/82 mmHg in the DJBL group and from 152/90 mmHg to 140/85 mmHg in the control group (p=0.31 for systolic pressure and p=0.38 for diastolic pressure). The total cholesterol levels were comparable with baseline, 4.4 versus 4.4 mmol/litre, DJBL versus control group, respectively (p=0.79).

Safety

Adverse events	**DJBL arm % (n)**	**Diet arm % (n)**
At least 1 adverse event	76.5 (29/38)	59.0 (23/39)
Minor GI symptoms, abdominal pain or discomfort	63.2 (25/38)	28.2 (11/39)
Nausea or vomiting	23.7 (9/38)	17.9 (7/39)
Mild to moderate hypoglycaemia	23.7 (9/38)	25.6 (10/39)
Adverse events requiring hospitalisation	8 (***5/8 device related:*** 1 melena and pain in epigastric area; 1 abdominal pain and dehydration both managed conservatively; 1 device blocked with food, removed device early; 1 symptomatic gallstones treated with cholecystectomy ***1 procedure related:*** oesophageal perforation during device removal at 6 months(caused by one of the barbs on the anchor not being covered by the removal hood), treated by endoscopic stenting and feeding tube, after 3 weeks resolved without sequelae)	8 (5 resolved without sequelae ; other needed treatment)

Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; GI, gastrointestinal; GORD, gastro-oesophageal reflux disease; HbA_{1c}, glycated haemoglobin; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; RCT, randomised controlled trial

Study 2 Rodriguez L (2009)

Details

Study type	**RCT**
Country	Chile (single centre)
Recruitment period	2007–8
Study population and number	Patients with type 2 diabetes and obesity n=**18 (12 DJBL versus 6 sham endoscopy)**
Age and sex	DJBL arm 45 years, sham arm 51 years DJBL arm 67% female, sham arm 50% female Mean BMI: DJBL arm 38.9 kg/m^2, sham arm 39.0 kg/m^2 Mean HbA_{1c}: 9.1%
Patient selection criteria	Aged 18–55 years with type 2 diabetes for more than 10 years and an HbA_{1c} 7–10%, fasting plasma glucose under 240 mg/dl and BMI 30–50 kg/m^2.
Technique	DJBL (EndoBarrier) procedures used fluoroscopy and endoscopy. Endoscopy 3 days and 4 weeks after explantation. Sham procedure: upper gastrointestinal endoscopy. Liquid diet for the first week, pureed food during the second week and solids thereafter. Recommended intake 1200 calories per day for women and 1500 calories per day for men.
Follow-up	**24 weeks**
Conflict of interest/source of funding	Study funded by manufacturer. Authors are consultants/ shareholder for GI Dynamics.

Analysis

Follow-up issues: 42% (5/12) of patients in the device arm (with explanted devices) and 24% (2/6) of patients in the sham ITT arm were lost to follow-up at 12 weeks.

Study design issues: The method of randomisation was not reported. There was no allocation concealment.

There was no significant difference between the groups at baseline.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **12 DJBL versus 6 sham endoscopy**

Change in glycaemic control measured by HbA_{1c} (ITT population) (mean±SD)

Mean HbA_{1c} %	DJBL arm (n=12)	Sham arm (n=6)	p value
Baseline	9.2	9.0	NS
12 weeks	−1.3±0.9	−0.8±0.3	NS
24 weeks	−2.4±0.7	−0.8±0.4	NS

HbA_{1c} change in population completing treatment is more than 0.05 at all time points between both arms.

Change in FPG concentration (ITT population) (mean±SD)

Mean FPG mg/dl	DJBL arm (n=12)	Sham arm (n=6)	p value
Baseline	193±24	140±38	<0.05
Week 1	−50±18	+25±29	0.042
Week 12	−45±26	−8±35	NS
Week 24	−83±39	+16±42	NS

Both arms had equivalent baseline FPG concentrations.

Oral antidiabetic medication use

	Follow-up	DJBL arm %	Sham arm %
Ceased drug use (ITT group)*	Week 12	42	17
Ceased drug use (group who completed treatment)**	Week 12	50	25
Ceased drug use (remaining patients)***	Week 24	40	25

*All treated patients. **All patients who completed at least 24 weeks. ***Patients remaining on the study.

Postprandial 7-point blood glucose profile

Mean postprandial plasma glucose AUC*	DJBL arm (n=12)	Sham arm (n=6)	p value
Baseline mg/dl	31,226± 11,570	27,558±11, 480	NS
Week 1	22% decrease	16% increase	0.016

* There was no change in postprandial insulin concentrations in either arm.

Weight loss: At 12 weeks mean weight loss was comparable (p>0.05) for both treatment arms (both ITT and completer groups).

Safety

Explants during 12 weeks' follow-up % (n)

Anchor migration (1 turned or migrated) 3 had symptoms: moderate pain (n=1), nausea and moderate vomiting (n=1) and mild abdominal pain and vomiting (n=1) 2 had no symptoms: noted at removal (n=1) and at scheduled endoscopy (n=1).	42 (5/12)

Adverse events (total 64)

Adverse events	DJBL % (n=episodes)
Upper abdominal pain (in 12 patients)	30.8 (20)
Vomiting (in 4 patients)	10.8 (7)
Abdominal pain	4.6 (3)
Nausea	7.7 (5)
Symptoms of hypoglycaemia (but blood glucose more than 100 mg/dl in all cases)	7.7 (5)
Decreased blood iron	6.2 (4)
Flatulence	4.6 (3)
Procedural vomiting	4.6 (3)
Increased blood cholesterol	3.1 (2)
Erosive duodenitis	1.5 (1)
Constipation	1.5 (1)
Diarrhoea	1.5 (1)
Gastritis	1.5 (1)
Headache	1.5 (1)
Decreased HDL cholesterol	1.5 (1)
Esophagitis	1.5 (1)
Pain	1.5 (1)

All events were mild or moderate.

Abbreviations used: AUC, area under the curve; BMI, body mass index; DJBL, duodenal–jejunal bypass liner; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; ITT, intention to treat; NS, not significant; SD, standard deviation,.

Study 3 de Moura (2011)

Details

Study type	**Case series**
Country	Brazil
Recruitment period	Not reported
Study population and number	Morbidly obese and type 2 diabetes patients n=**81**
Age and sex	Mean 50.8 years; 4.4% female Mean BMI: 43.8 kg/m^2
Patient selection criteria	Aged 18–65 years with a BMI over 35 kg/m^2, type 2 diabetes with or without comorbidities, TG/HDL ratio ≥3.5
Technique	DJBL (EndoBarrier) procedures used fluoroscopy and endoscopy. PPI used in entire study. Liquid diet initially, solid diet in third week.
Follow-up	**6 months**
Conflict of interest/source of funding	2 authors independent consultants of GI Dynamics.

Analysis

Follow-up issues: 38/54 patients completed the study (26 completed 24 weeks, 12 completed 20 weeks).

Study design issues: 70% (54/77) of the patients had an initial TG/HDL ratio greater than or equal to 3.5 indicating insulin resistance and metabolic syndrome.

Study population issues: Comorbidities: 86% had hypertension, 36.7% had hyperlipidaemia.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **54**

Procedural outcomes % (n)

Implantation success	96 (78/81)
Implantation failure (due to short duodenal bulb)	4 (3/81)

Control of diabetes (HbA_{1c} improvement) at 6 months

All patients implanted with the device achieved statistically significant reductions in HbA_{1c} ($p<0.005$). More than 70% of patients had HbA_{1c} levels of less than 7%.

Improvement in insulin resistance and metabolic syndrome at 6 months

	Number of patients *	**Initial average TG/HDL ratio**	**Final average TG/HDL ratio**	**p value**
Controlled TG/HDL	23	5.15	2.85	<0.001
Not controlled TG/HDL ratio	31	6.2	5.47	0.1641
Total	54	5.75	4.36	<0.001

*Patients presented with insulin resistance and metabolic syndrome. 42.6% of the patients presented a TG/HDL ratio lower than 3.5 at 6-month follow-up.

Weight loss

Average weight loss of 12.6% of their initial weight.

Relationship between TG/HDL ratio control and weight loss

Comparing the patients who lost weight with the patients who controlled their TG/HDL ratio, an association can be observed between a weight loss greater than 10% of initial weight and control of TG/HDL ratio ($p<0.01$) with an odds ratio of 5.06.

Safety

Early explantations

Total explants	**16**
Migration	9
Observation of a free device anchor during endoscopy	4
Bleeding without migration	1
Patient request	1
Investigator decision	1

12 devices were removed at 16 weeks, 2 at 12 weeks and 2 at 4 weeks.

Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; HbA_{1c}, glycated haemoglobin; PPI, proton pump inhibitor; TG/HDL ratio, triglyceride high density lipoprotein cholesterol ratio;

Study 4 de Moura (2012)

Details

Study type	**Case series**
Country	Brazil
Recruitment period	Not reported
Study population and number	Obese patients with type 2 diabetes n=**22**
Age and sex	Mean 46.2 years; 86.4% female Mean BMI: 44.8 kg/m^2
Patient selection criteria	Patients with type 2 diabetes, between 18 and 65 years with a BMI over 40 kg/m^2 and below 60 kg/m^2.
Technique	DJBL (EndoBarrier) was implanted and explanted after 52 weeks using fluoroscopy and endoscopy. PPIs were used until 2 weeks after explantation. Follow-up examinations were done at 1, 3 and 6 months after explantation. Patients were given 30 minutes' nutritional counselling (on diet, lifestyle and behaviour) at baseline and monthly follow-up visits. Liquid diet for 2 weeks. Daily vitamin and iron supplements were recommended.
Follow-up	**52 weeks**
Conflict of interest/source of funding	Study sponsored by GI Dynamics (manufacturer).

Analysis

Follow-up issues: 82% (18/22) patients completed 24 weeks of follow-up. Only 59% (13/22) patients completed 52 weeks of follow-up.

Study design issues: The drug treatment for type 2 diabetes was not specified or standardised.

Study population issues: 77% (17/22) of patients took drugs for diabetes.

Other issues: 1 patient needed general anaesthesia for explantation. Authors suggest that changes in antidiabetic drug treatment regimens may have influenced the results.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **22**

Implantation success: 100%

Changes in metabolic parameters and lipid levels (mean±SD values)

	Base-line (n=22)	**24 weeks (n=16)**	**52 weeks (n=13)**	**LOCF* (n=22)**
Fasting glucose mg/dl	179.4± 68.8	−33.4± 9.2 (p<0.01)	−37.1±11.8 (p<0.01)	−30.3± 10.2 (p<0.01)
HbA_{1c} %	8.9± 1.7	−1.5±0.4 (p<0.001)	−2.3±0.3 (p<0.0001)	−2.1±0.3 (p<0.0001)
Fasting insulin U/ml	19.5± 14.7	−5.2±2.8	−10.1±4.2 (p<0.05)	−7.3±2.6 (p<0.05)
Total cholesterol mg/dl	201± 37	−16.7±6.9 (p<0.05)	−28.1±5.6 (p<0.01)	−19.7±5.9 (p<0.01)
Triglycerides mg/dl	213± 89	−56.8±25 (p=0.05)	−62.4±18.3 (p=0.01)	−44.8± 17.4 (p<0.05)
Diastolic blood pressure (mmHg)	79±10			−1.6±3.5 (p=0.65)

*last observation carried forward in all patients analysed on or just before explantation

Improvement in glycaemic control

At the end of the study 73% (16/22) of patients had an HbA_{1c} under 7% compared with 4.5% (1/22) at baseline.

Glycaemic control after device removal (at 6 months)

HbA_{1c} response continued for up to 6 months after device removal in 11 patients (mean change from baseline [8.9±1.7] was −1.7±0.7%).

Weight loss (mean±SD values)

Mean % EWL at 52 weeks (n=13)	39.0±3.9 (p<0.0001)
Mean % of EWL (LOCF, n=22)	35.5±3.1 (p<0.0001)
Decrease in mean BMI (kg/m^2) (LOCF, n=22)	−6.7±0.7
Mean reduction in waist circumference (cm) (LOCF, n=22)	−13.0±1.7

Safety

Early device explantations % (n)

Total explantations	**40 (9/22)**
Device related (median 31 weeks)	**27 (6/22)**
Device migration or rotation (48 weeks after implant)	14 (3/22)
Gastrointestinal bleeding (4 weeks after implant)	4 (1/22)
Abdominal pain (24 and 30 weeks after implant)	9 (2/22)
Non-device related 1 unrelated malignancy (at 17 weeks due to metastatic ovarian cancer) 2 at investigator request (at weeks 20 and 32 due to 'patients' non-compliance with follow-up')	**14 (3/22)**

Adverse events that occurred in more than 10% of patients

Adverse event	**% (n)**	**Device or procedure related (n)**
Gastrointestinal disorders	95 (21/22)	12
Upper abdominal pain	91 (20/22)	11
Nausea	50 (11/22)	7
Vomiting	63 (14/22)	7
Diarrhoea	13 (3/22)	1
Procedural and other complications		
Procedural nausea	45 (10/22)	4
Procedural vomiting	32 (7/22)	3
Back pain	59 (13/22)	5

All events were mild or moderate, except 1 severe event caused by an unrelated malignancy.

Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; EWL, excess weight loss; HbA_{1c}, glycated haemoglobin; LCOF, last observation carried forward; PPI, proton pump inhibitors; SD, standard deviation.

Study 5 Cohen RV (2013)

Details

Study type	**Case series**
Country	Brazil (single centre)
Recruitment period	Not reported
Study population and number	Patients with lower BMI and type 2 diabetes n=**23**
Age and sex	Mean 49.8 years; 58.3% female Mean BMI: 30 kg/m^2, type 2 diabetes duration: 6.6 years
Patient selection criteria	Aged 18 and 55 years with T2DM of <10 years, with oral glucose lowering medications, HbA_{1c} 7.5–10%, BMI 26–50 kg/m^2
Technique	EndoBarrier deployed and removed under general anaesthesia. Nutritional counselling, PPI before implantation and 2 weeks after explantation. Liquid diet in first week and 1200–1500 calories intake thereafter.
Follow-up	**52 weeks**
Conflict of interest/source of funding	Study funded by GI Dynamics (manufacturer).

Analysis

Follow-up issues: 16 patients completed 1-year treatment.

Study design issues: Patients with type 1 diabetes, insulin use, autoimmune disease, weight loss of >4.5 kg within 12 weeks, previous gastrointestinal surgeries, active *Helicobacter pylori* infection, on non-inflammatory drugs, weight loss medication, uncontrolled reflux disease were excluded.

Women either postmenopausal, sterile or on oral contraceptives were included.

Sulfonylurea dosage reduced to avoid hypoglycaemic events.

Key efficacy and safety findings

Efficacy

Number of patients analysed: 23

Procedural outcomes % (n)

Implantation success	87 (20/23)
Implantation failure (due to unfavourable anatomy)	13 (3/23)
Mean implantation duration	348 days

Body weight glucose metabolism and plasma lipids during treatment with DJBL

	Baseline (n=20)	**Week 12 (n=19)**	**Week 52 (n=16)**	**p value**
FPG (mg/dl)	207±61	132±41	155±52	0.012
HbA_{1c} (%)	8.7±0.9	7.0±0.9	7.5±1.6	0.004
Total cholesterol (mg/dl)	221±50	167±38	188±32	NR
Low density lipoprotein (mg/dl)	135±40	95±33	108±31	NR
HDL (mg/dl)	42±11	39±7	40±10	NR
Body weight (kg)	84.0±16.6	79.0±16.8	77.2±17.6	<0.0001
BMI (kg/m^2)	30.0±3.6	28.3±3.7	28.5±3.3	<0.0001

62.5% (10/16) patients who completed the study had HbA_{1c} levels <7% at week 52. 4/5 patients with HbA_{1c} >9% at baseline did not show any reduction in HbA_{1c}.

Diabetic medications: 7 patients decreased and 4 increased the number of drugs or the doses of antidiabetic drugs.

No significant correlation between change in body weight and change in FPG or HbA_{1c} was observed (data not reported in paper).

Safety

	% (n)
At least 1 adverse event (mild or moderate)	96% (22/23)
Most common device- or procedure-related adverse events	
Gastrointestinal disorders (including abdominal pain, nausea and vomiting)	56 (13/23)
Metabolic and nutritional disorders, including hypoglycaemia and iron deficiency	61 (14/23)
Early device removals (1 patient at 10 weeks due to noncompliance with follow-up, 1 at 7 months due to recurring abdominal pain, in 2 due to device rotation and/or migration at 6 and 10 months)	**20% (4/20)**

Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; HDL, high density lipoprotein; PPI, proton pump inhibitors; T2DM, type 2 diabetes mellitus.

Study 6 Cohen RV (2013)

Details

Study type	**Case series**
Country	Brazil (single centre)
Recruitment period	Not reported
Study population and number	Patients with type 2 diabetes and BMI≤ 36kg/m^2 n=**16**
Age and sex	Mean 49.8 years; 37.5% (6/16) female Mean BMI: 30 kg/m^2, Mean HbA_{1c} %: 8.6
Patient selection criteria	Patients with oral glucose lowering medications, no insulin,
Technique	EndoBarrier deployed and removed under GA after 52 weeks. Regular antidiabetic medications were continued during implantation period. They were kept constant and additional medication given by physician only if baseline HbA_{1c} levels were exceeded. Consistent diet, exercise and lifestyle advice throughout. Before each follow-up (1, 12, 24 and 52 weeks), all diabetic medications were stopped for 24 hours and patients fasted overnight and a standard 525 calories meal given.
Follow-up	**52 weeks after implantation and 26 weeks after explantation**
Conflict of interest/source of funding	Study funded by GI Dynamics (manufacturer).

Analysis

Follow-up issues: All 16 patients completed 1-year treatment.

Study design issues: Combined therapies (DJBL and regular antidiabetic medical therapy) used in the study; results may be confounded by the inclusion of diabetic medications. Four patients had higher HbA_{1c} levels before implantation.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **16**

Body weight, glucose metabolism during and after treatment with DJBL (n=16)

	Baseline	**Week 1**	**Week 12**	**Week 52**	**Week 78***	**p value (all)**
HbA_{1c} (%)^	8.6	–	6.9	7.5	7.8	<0.001
Mean fasting glucose concentration (mg/dl)	203.3±13.5	138.3±8.2	130.8±10.8	155.1±13.1	150.2±10.06	<0.001
Median HOMA-IR score (IQR)	6.6 (4.2–13.4)	3.1 (1.7–4.8)	3.1 (1.9–4.3)	3.0 (2.2–4.7)	4.4 (2.0–6.1)	<0.001
Median Matsuda index score (IQR)	1.7 (1.2–2.3)	3.4 (2.2–6.1)	3.5 (1.9–4.9)	3.2 (2.2–4.6)	2.4 (1.8–4.4)	<0.001
Mean fasting insulin (microU min/ml)	16.3 (2.3)	10.7 (1.6)	13.4 (2.5)	11.0 (1.9)	13.2 (1.6)	0.051
Mean insulin AUC (microU min/ml)	5757±606.7	4399±701.3	5280±825.6	5068±713.7	5018±642.8	0.28
Median (IQR) insulogenic index score I30/G30	0.36 (0.2-0.7)	0.6 (0.3-0.8)	0.36 (0.15-0.69)	0.41 (0.23-0.68)	0.53 (0.16-0.73)	0.43
Mean fasting insulin secretion after meal rate (pmol/min/m^2)	128.4±12.8	114.1±14.9	120.4±14.4	128.7±16.8	124.8±15.9	0.51
Mean total insulin secretion rate after meal (nmol/min/m^2)	23.0±1.7	22.7±2.5	25.7±2.9	24.7±7	23.4±2.2	0.46
Mean C-peptide fasting (nanogram/ml)	3.8±0.4	3.1±0.3	3.2±0.4	3.1±0.4	3.2 ±0.4	0.024
Mean C-peptide AUC (nanogram/min/m)	743.3±50.3	689.1±69.5	773.2±75.0	763.3±0.5	744.8±65.9	0.46
Mean body weight (kg)	82.1±4.5	80.8±4.0	77.9±4.3	76.2±4.3	79.7±4.6	<0.001
Mean BMI (kg/m^2)	30.0±0.9	29.4±0.8	28.7±0.9	28.1±0.9	29.4±0.9	<0.001

*26 weeks after DJBL removal. ^4 patients did not show an improvement during the 52 weeks.

Safety

No device-related complications.

Mild, transient abdominal pain (self-limiting) after first week of implantation: 19% (3/16)

Abbreviations used: AUC, area under the curve; BMI, body mass index; DJBL, duodenal–jejunal bypass liner; GA, general anaesthesia; HbA_{1c}, glycated haemoglobin; HOMA-IR, homeostatic model of assessment of insulin resistance; IQR, interquartile range.

Study 7 Munoz R (2014)

Details

Study type	**Case series**
Country	Chile (single centre)
Recruitment period	2009–2011
Study population and number	Morbidly obese patients n=**79 (21 with type 2 diabetes)**
Age and sex	Mean 35.4 years; 72% (44/79) female Mean BMI: 43±5.6 kg/m^2
Patient selection criteria	Between 18 and 55 years with a BMI >35 kg/m^2 if presenting with comorbidities such as hypertension, diabetes, and/or dyslipidaemia; otherwise with a BMI 40–60 kg/m^2.
Technique	DJBL (EndoBarrier) was implanted and explanted using fluoroscopy and endoscopy. Patients were advised at baseline to take a liquid and pureed diet for 2 weeks, followed by normal diet and moderate physical therapy for the rest of the study period. Proton pump inhibitors, multivitamins and iron supplements were used during the study period. Surveillance endoscopies were performed at 12, 24 and 36 weeks.
Follow-up	**52 weeks**
Conflict of interest/source of funding	Study was funded by GI Dynamics (manufacturer). Two authors disclosed a financial relationship with the manufacturer.

Analysis

Follow-up issues: Only 77% (61/79) patients completed 52 weeks of follow-up

Other issues: Data on 39 patients were included in a previous publication

Key efficacy and safety findings

Efficacy

Number of patients analysed: **79 (21 with T2DM)**

Clinical factors associated with weight loss

Univariate analysis shows that fasting glycaemia (r^2=−0.303, p<0.013), insulin resistance determined by HOMA-IR (r^2=−0.457, p<0.019) and glycated haemoglobin HbA_{1c} (r^2=−0.471, p<0.001) were inversely associated with %EBWL at 52 weeks after DJBL implantation.

Multivariate analysis indicates that only baseline HbA_{1c} levels were associated inversely with %EBWL after 1 year of treatment (β adjusted coefficient −0.758, p<0.016).

No differences at 1 year in %EBWL were observed between patients with or without T2DM (%EBWL T2DM 46.7±20% versus non T2DM 46.8±18.6%, p=0.988).

Mean % EBWL

At 3 months: 33±12; at 1 year: 46±18

Safety

No complications related to implant and explant procedures.

	% (n)
Early device removal*	**26 (21/79)**
Device migration	8
Device obstruction	5
Abdominal pain	2
Liver abscess (medical treatment)	1
Upper gastrointestinal bleeding	1
Cholangitis	1
Ulcerative colitis	1
Acute cholecystitis	1
Patient request	1

*further information not reported in all cases.

Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; %EBWL, percentage of excess body weight loss; HbA_{1c}, glycated haemoglobin; HOMA-IR, homeostatic model of assessment of insulin resistance; T2DM, type 2 diabetes.

Study 8 De Jonge (2013)

Details

Study type	**Case series**
Country	Brazil (single centre)
Recruitment period	Not reported
Study population and number	Obese patients with type 2 diabetes n=**17**
Age and sex	Mean 51 years; 18% (3/17) female Mean BMI: 37 kg/m^2; HbA_{1c} 8.4%
Patient selection criteria	Aged 18 and 55 years with type 2 diabetes of <10 years, with oral glucose lowering medications, HbA_{1c} 7.5–10%, BMI 26–50 kg/m^2
Technique	DJBL (EndoBarrier) deployed and removed under GA after 24 weeks. Nutritional counselling and proton pump inhibitors given before implantation and 2 weeks after explantation. Liquid diet in first week and 1200–1500 calories intake thereafter. Glucose, insulin, GLP-1, GIP and glucagon responses after a standard meal were studied before, during and 1 week after DJBL treatment.
Follow-up	**24 weeks**
Conflict of interest/source of funding	Study funded by GI Dynamics (manufacturer).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **17**

Changes in diabetic parameters and gut hormones

	Baseline	**1 week**	**24 weeks**
HbA_{1c} (%)	8.4 ± 0.2	–	7.0 ± 0.2 (P<0.01)
Fasting glucose mmol/litre	11.6±0.5	9.0±0.5 (p<0.01)	8.6±0.5 (p<0.01)
Postprandial glucose AUC mmol/litre/min	1999±85	1536±51 (p<0.01)	1588±72 (p<0.01)
Fasting Insulin microU/ml	25.5±7.8	22.5±7.8 (p=0.23)	15.1±3.1 (p=0.06)
Insulin AUC microU/ml/min	6.603±1100	6688±1164 (p=0.86)	6446±770 (p=0.84)
HOMA-IR	14.6±5.8	9.2±3.5 (p=0.06)	6.3±1.8 (p=0.06)
Fasting GLP-1 pmol/litre	29.0±2.6	32.5±2.7 (p=0.21)	30.3±2.6 (p=0.70)
Postprandial GLP-1 pmol/litre/min	4440 ± 249	6407 ± 480 (p<0.01)	6008 ± 429 (p<0.01)
Fasting GIP pg/ml	145.9±23.3	233.1±128.3 (p=0.50)	155.1±29.8 (p=0.79)
GIP pg/ml/min	115,272 ± 10,971	99,388±11073	88,499 ± 10,971 (p<0.05)
Fasting glucagon pg/ml	105.9±14.9	79.7±15.2 (0.12)	78.7±14.9 (p=0.16)
Glucagon AUC pg/ml/min	23,762 ± 4,732	15,989 ± 3,193 (p=0.02)	13,1207 ± 1,946 (p=0.02)

1 week after device removal (at week 25) in a subset of 8 patients, glucose response to a meal remained decreased and no significant changes in insulin response or HOMA-IR were observed. GLP-1 levels decreased but the improved glucagon and GIP response remained the same.

Mean weight loss

At 24 weeks after implantation, patients lost 12.7±1.3 kg (p<0.01).

Safety

Not reported

Abbreviations used: AUC, area under the curve; BMI, body mass index; DJBL, duodenal–jejunal bypass liner; GIP, gastric inhibitory peptide; GLP-1, glucagon like peptide-1; HbA_{1c}, glycated haemoglobin; HOMA-IR, homeostatic model of assessment of insulin resistance.

Study 9 Koehestanie P (2014)

Details

Study type	**Case series**
Country	Netherlands
Recruitment period	Not reported
Study population and number	Obese patients with type 2 diabetes n=**12**
Age and sex	Mean 50.3 years; 40% (5/12) female Type 2 diabetes duration 7.4 years, BMI 33.5 kg/m^2
Patient selection criteria	Aged between 18 and 60 years, BMI 28–35 kg/m^2, T2DM with HbA_{1c} level above 7%. Patients were allowed to take metformin, sulfonylurea derivatives and/or insulin.
Technique	DJBL (EndoBarrier) deployed and removed under GA after 24 weeks. Nutritional counselling, liquid diet in first week and 1200–1500 calories intake thereafter.
Follow-up	**24 weeks**
Conflict of interest/source of funding	Four authors received consultancy fees from GI Dynamics (manufacturer).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **12**

Fasting plasma levels and gut hormones effect on weight loss and glycaemic control (mean± standard error)

	Baseline	**1 week**	**4 weeks**	**24 weeks**	**p value**
Fasting glucose mmol/litre	12.1±0.7	9.7±1.2	9.2±0.3	10.6±0.7	0.21
Fasting insulin mU/litre	21.5±6.0	11.4±2.5	7.2±1.1	15.5±2.5	<0.05
HOMA-IR	12.4±3.3	4.8±0.9	4.1±0.5	7.3±1.4	<0.05
HbA_{1c} mmol/mol	73.3±4.5		67.7±3.3	61.3±4.0	0.39
GIP, pg/ml	206.5±37.5	142.9±16.6	136.5±13.4		0.20
GLP-1, pM	6.1±1.2	3.2±0.5	4.8±0.7		<0.05
Ghrelin pg/ml	341.2±51.0	651.5±89.5	712.3±95.8		<0.05
Weight (kg)	104.9±3.0	101.3±2.9	99.9±2.9	97.7±3.3	0.39
BMI (kg/m^2)	33.5±0.8	32.3±0.8	31.9±0.8	31.2±1.0	0.24
Fat mass (%)	40.3±1.7	40.0±1.9	35.0±1.9	33.1±1.8	<0.05
C-peptide nmol/l	1.3±0.1	1.1±0.1	1.2±0.1	1.1±0.1	0.52

42% reduction in diabetes medication use (p<0.05) in the first week after implantation of DJBL.

Safety

'No complications due to implantation'.

Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; HOMA-IR, homeostatic model of assessment of insulin resistance; GA, general anaesthesia; GIP, gastric inhibitory peptide; GLP-1, glucagon like peptide-1; HbA_{1c}, glycated haemoglobin; T2DM, type 2 diabetes mellitus.

Study 10 Lasle C (2014)

Details

Study type	**Case report**
Country	Germany
Recruitment period	Not reported
Study population and number	n=**1**
Age and sex	49-year-old man with BMI 40.9 kg/m^2, and HbA_{1c} 9.6%
Patient selection criteria	Not relevant
Technique	DJBL (EndoBarrier) implanted
Follow-up	**4 weeks**
Conflict of interest/source of funding	None

Analysis

Study design issues: standard clinical protocols were used.

Key efficacy and safety findings

Efficacy	Safety
	Number of patients analysed: **1** After 4 weeks, patient presented to emergency unit with an acute abdomen. Peritonitis in the right epigastric region noted. Radiologic imaging revealed free air in the abdomen suggestive of intestinal perforation. The DJBL was removed endoscopically and this was followed by laparoscopic closure of the perforation in the duodenal bulb using a running suture. The abdominal cavity was rinsed and drained. The patient recovered and was discharged 9 days after the surgery.
Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; HbA_{1c}, glycated haemoglobin.	

Study 11 Betzel B (2014)

Details

Study type	**Case series**
Country	Canada (1 centre)
Recruitment period	2007-14
Study population and number	n=**152**
Age and sex	Not reported
Patient selection criteria	Patients aged 18-65 years, BMI 28-45kg/m^2, T2DM, and negative serum *Helicobacter pylori* test were included. Patients using non-steroidal anti-inflammatory drugs or anticoagulant medication were excluded.
Technique	DJBL (EndoBarrier) implanted
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: Conference abstract only.

Key efficacy and safety findings

Efficacy	Safety
	Number of patients analysed: **152** Total explantations performed: (94/152)

Adverse events	**% (n)**
Early explanations due to pain and discomfort	11 (16/94)
Total complications	**10 (15/152)**
Bleeding (of which 2 were arterial bleeding)	5 (7/152)
Pancreatitis	1 (2/152)
Liver abscess	1 (1/152)
Obstruction of the sleeve	1 (1/152)
Oesophageal rupture during explantation	1 (2/152)

Abbreviations used: BMI, body mass index; DJBL, duodenal–jejunal bypass liner; T2DM, type 2 diabetes mellitus

Efficacy

Glycaemic control

A randomised controlled trial (RCT) of 77 patients with obesity and type 2 diabetes compared DJBL treatment in combination with dietary intervention (n=38) against only dietary intervention (n=39) for 6 months. It reported that glycated haemoglobin (HbA_{1c}) levels improved from 8% at baseline to 7% in the DJBL plus diet group but remained at about 8% in the diet-alone group at 6-month follow-up. The difference between the 2 groups was significant (DJBL plus diet versus diet alone; $p<0.05$). At 12-month follow-up (including 6 months of post-DJBL removal), HbA_{1c} was 7% in the DJBL plus diet group and 8% in the diet-alone group ($p=0.95$) [1].

The RCT of 77 patients reported that, at 12-month follow-up (including 6 months after DJBL removal), fasting glucose levels had decreased from 11.0 mmol/litre to 9.0 mmol/litre in the DJBL plus diet group compared with to 9.7 mmol/litre in the diet-alone group. The difference between the 2 groups was not significant (DJBL plus diet versus diet alone; $p= 0.41$)[1].

The RCT of 77 patients reported that, at 12-month follow-up (including 6 months after DJBL removal), fasting insulin levels remained the same in the DJBL plus diet group (15.0 mU/litre), and decreased in the diet-alone group from 17.0 mU/litre to 15.7 mU/litre. The difference between the 2 groups was not significant (DJBL plus diet versus diet alone; $p= 0.73$)[1].

The RCT of 18 patients with obesity and type 2 diabetes comparing DJBL (n=12) against sham endoscopy (n=6) reported that in the intention-to-treat group, HbA_{1c} values decreased by −1.3±0.9% for the DJBL group and by −0.8±0.3% in the sham endoscopy group ($p>0.05$) at 12-week follow-up. At 24-week follow-up, the HbA_{1c} had decreased by 2.4±0.7% in the DJBL group and by 0.8±0.4% in the sham endoscopy group ($p>0.05$). These differences were not statistically significant. Mean postprandial glucose area under the curve was reduced in the DJBL arm by 22% from baseline, compared with a 16% increase in the sham endoscopy group ($p=0.016$)[2].

In a case series of 81 obese patients with type 2 diabetes, after 6 months of DJBL implantation more than 70% of patients had HbA_{1c} levels of less than 7%. No further details were reported[3].

A case series of 22 morbidly obese patients with type 2 diabetes (mean BMI 44.8 kg/m^2) reported statistically significant reductions in fasting blood glucose (30.3 mg/dl), fasting insulin (−7.3 mU/ml) and HbA_{1c} (−2%) at last observation carried forward (LCOF) in all patients analysed. At the end of the study 73% (16/22) of patients had an HbA_{1c} under 7% compared with 5% (1/22) at baseline[4].

A case series of 23 moderately obese patients with type 2 diabetes (mean BMI 30 kg/m^2) reported a reduction in fasting plasma glucose (from 207±61 mg/dl to 155±52 mg/dl, p=0.012) and HbA_{1c} (from 8.7±0.9% to 7.5±1.6%,p=0.004) at 1-year follow-up[5].

Glycaemic control after removal of device

The case series of 22 patients with obesity and type 2 diabetes treated with a DJBL reported that improved glycaemic control (mean percentage decrease of −1.7±0.7% in HbA_{1c} from a baseline level of 8.9±1.7%) continued for up to 6 months after device removal in 11 patients [4].

A case series of 16 obese type 2 diabetic patients reported that 1 year after DJBL implantation, the mean HbA_{1c} level and fasting glucose levels decreased (HbA_{1c} to 7.5% from baseline 8.6%; p<0.001) (fasting glucose to 150.2 mg/dl from baseline 203.3 mg/dl; p<0.001) and insulin sensitivity and resistance improved (median Matsuda index score to 2.4 from baseline 1.7; p<0.001), (HOMA-IR score to 4.3 from baseline 6.6; p<0.001). Six months after device explantation all these variables deteriorated. Fasting insulin levels, insulin area under the curve, fasting C-peptide, C-peptide area under the curve, fasting insulin secretion rate after a meal and total insulin secretion rates did not change either during the implantation period or after explantation of DJBL[6].

Percentage of excess weight loss

The RCT of 77 patients with obesity and type 2 diabetes comparing DJBL treatment plus dietary intervention (n=38) against only dietary intervention (n=39) reported a significantly higher percentage of excess weight loss (EWL) at 12-month follow-up (including 6 months of post DJBL removal), for DJBL group than for the diet-alone group (20% versus 12% respectively, p<0.05)[1].

Glycaemic factors associated with weight loss

In a case series of 79 patients (including 21 with type 2 diabetes) univariate analysis identified that fasting glycaemia (r^2=−0.303, p<0.013), insulin resistance determined by HOMA-IR (r^2=−0.457, p<0.019) and glycated haemoglobin HbA_{1c} (r^2=−0.471, p<0.001) were inversely associated with percentage of EWL at 52 weeks after DJBL implantation[7].

The case series of 23 patients reported that the change in body weight loss was not significantly associated with a change in fasting plasma glucose at 1-year follow-up (values not reported)[5].

Change in cardiovascular parameters

The RCT of 77 patients reported that, at 12-month follow-up, blood pressure decreased from 147/92 mmHg to 130/82 mmHg in the DJBL plus diet group and from 152/90 mmHg to 140/85 mmHg in the diet-alone group. The difference between the 2 groups was not significant (DJBL plus diet versus diet alone; p=0.31 for systolic pressure and p=0.38 for diastolic pressure). At 12-month

follow-up, total cholesterol levels in the DJBL group were comparable with baseline (4.4 mmol/litre in both groups [p=0.79])[1].

The case series of 22 patients treated by a DJBL reported significant reductions in total cholesterol (19.7±5.9 mg/dl; p<0.01) and triglycerides (44.8±17.4 mg/dl; p<0.05) at LCOF on or before explantation[4].

Reduction in insulin resistance and metabolic syndrome

The case series of 81 patients reported improvement in insulin resistance, with a significant reduction of the TG/HDL ratio from 5.75 to 4.36 (p<0.001) and 43% of the patients presented a TG/HDL ratio lower than 3.5, 6 months after DJBL implantation[3].

Diabetes medication use

In the RCT of 77 patients, at 12-month follow-up the daily insulin dose and use of sulfonylureas had decreased or the medication had been stopped in the DJBL plus diet group more often than in diet-alone group (p<0.05)[1].

A case series of 12 obese patients reported 42% reduction in diabetes medication use (p<0.05) 1 week after DJBL implantation[9].

Implantation failure or difficulties

In the case series of 81 patients the DJBL could not be implanted in 4% (3/81) of patients because of a short duodenal bulb[3].

Safety

Perforation

Perforation of the duodenal bulb (associated with the DJBL) was observed 4 weeks after implantation of DJBL in a case report of 1 patient. The device was removed endoscopically and the perforation was closed laparoscopically with a running suture. The patient was discharged 9 days after the surgery[10].

Oesophageal perforation (6 cm) during device removal at 6 months (caused by one of the anchor barbs that was not covered by the removal hood), was reported in 1 patient in the DJBL group (n=38) in the RCT of 77 obese patients with type 2 diabetes. This was treated by endoscopic stenting and placement of a feeding tube. The tear resolved without sequelae within 3 weeks[1].

Early device explantation

In the RCT of 18 patients 42% (5/12) of devices were explanted early in the DJBL group, because of device migration (4 because of anchor migration and 1 because of 'device turning or migration') during 12-week follow-up.
Three patients presented with symptoms such as pain, nausea and vomiting and 2 were asymptomatic[2]. In the RCT of 77 patients, 1 patient in the DJBL group (n=38) had an obstruction which was resolved by early device removal[1].

Early removal was needed in 40% of the patients (in the case series of 22). This was because of: device migration or rotation in 3 patients (at 48 weeks after implantation); gastrointestinal bleeding in 1 patient (at 4 weeks); abdominal pain in 2 patients (at 24 and 30 weeks); principal investigator request because of non-compliance with follow-up in 2 patients (at 20 and 32 weeks); and discovery of an unrelated malignancy (at 17 weeks; n=1)[4].

In the case series of 79 patients, 26% (21/79) of devices were explanted early due to device migration (n=8), device obstruction (n=5), abdominal pain (n=2), liver abscess (n=1), upper gastrointestinal bleeding (n=1), cholangitis (n=1), ulcerative colitis (n=1), acute cholecystitis (n=1) and patient request (n=1)[7].

Nausea, vomiting and abdominal pain

Upper abdominal pain, minor gastrointestinal symptoms or discomfort were reported in 63% (25/38) of patients in the DJBL group and 28% (11/39) of patients in the diet-alone group in the RCT of 77 patients. Nausea or vomiting occurred in 24% (9/38) of patients in the DJBL group and in 18% (7/39) in the diet-alone group, all of whom were managed conservatively[1].

Back pain

Device-related back pain was reported in 23% (5/22) of patients in the case series of 22 patients[4].

Hypoglycaemia

Mild-to-moderate hypoglycaemia was reported in 24% (9/38) of patients in the DJBL group and 26% (10/39) patients in the diet-alone group in the RCT of 77 patients[1].

Iron deficiency

Metabolic and nutritional disorders, including hypoglycaemia and iron deficiency, occurred in 61% (14/23) of patients in a case series of 23 patients[5].

Validity and generalisability of the studies

- Most of the studies published were small and implanted the device for a period of 3, 6 or 12 months only. One of the randomised clinical trials (Rodrigues L 2009[1]) included a first generation DJBL.
- The evidence comes mainly from studies in South America and Europe (none from the UK).
- The studies included only patients with type 2 diabetes and obesity.
- There is a lack of data on management after explantation.

- There is a lack of long-term data on how long any beneficial effect may last after removal of the device.
- There is a lack of patient-reported outcomes data.
- The majority of the studies are sponsored by the manufacturer.
- There is overlap of patients between the Cohen RV[5,6] studies.
- Limitations of the evidence base, such as uncertainties over method of response and lack of long-term data.

Existing assessments of this procedure

A Horizon Scanning Prioritising Summary Report conducted for Australia and New Zealand in 2010 concluded that 'EndoBarrier appears to have the potential to induce significant weight loss and improve diabetic symptoms'. It is mainly based on evidence from 4 RCTs[1–4]. In addition, it concludes that 'additional comparative studies with appropriate controls are necessary as the evidence base for this device is limited and lacks long-term follow-up results'[12].

The American College of Surgeons' report on endoluminal treatments for obesity in 2010 assessed the DJBL procedure using EndoBarrier. It concluded that 'the early evidence on the effectiveness of the EndoBarrier was encouraging. In comparison to diet control alone, patients who had the EndoBarrier lost significantly more weight and also experienced considerable improvements in their diabetic symptoms. However, when compared to patients who had sham endoscopy, those who underwent EndoBarrier treatment did not lose significantly more weight compared to the sham controls at 20 weeks' follow-up. Self-limiting nausea (up to 77%) and upper abdominal pain (up to 30%) were common in patients who had the EndoBarrier and some serious complications were evident, with early removal being required in 20% to 40% of patients'. It considered that 'additional long-term comparative studies (with appropriate controls) are necessary before any firm conclusions can be made regarding the safety and efficacy of the emerging procedures and devices. Until then these procedures and devices should only be used in a clinical trial setting'. In addition, it concluded that 'future research is necessary to determine if there are any particular patients' subgroups that may particularly benefit from certain procedures'. It also recommends that 'these procedures and devices are new and are undergoing active development and should be monitored as refinements will alter their safety and efficacy profiles'[13].

A recent published position paper by 3 German scientific societies (German Diabetes Society, the German Society for General and Visceral Surgery and the German Society for Gastroenterology, Digestive and Metabolic Disease suggested that 'for obese patients with type 2 diabetes DJBS represents a therapy option and supplement to conventional therapy'. It recommended

'consideration of the DJBS as a therapy alternative for the treatment of adult patients with type 2 diabetes mellitus and overweight (BMI 30–45 kg/m^2) when these patients cannot reach their individual therapy goals over a period of 3 to 6 months under the therapy algorithm in accordance with the National Disease Guideline for the therapy of type 2 diabetes. Currently there is no other promising therapy option for this patient population. For morbidly obese patients (BMI 45–60 kg/m^2) the use of DJBS is also medically advisable when a bariatric operation is medically indicated, but due to the increased operative risk for preparation for such an operation a preoperative weight reduction (stage concept/'bridging') is clinically necessary'[14].

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Implantation of a duodenal–jejunal bypass sleeve for managing obesity. NICE interventional procedures guidance 471 (2013). Available from http://guidance.nice.org.uk/IPG471

Clinical guidelines

- NICE clinical guideline 43 (2006). Available from http://guidance.nice.org.uk/CG43
- NICE clinical guideline 87 (2009) Available from http://guidance.nice.org.uk/CG87

Public health guidance

- Preventing type 2 diabetes: population and community-level interventions. NICE public health guidance 35 (2011). Available from http://guidance.nice.org.uk/PH35

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Mr James Byrne, James Hopkins, Kesava Mannur (Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland); Dr Barbara McGowan, Dr

Bob Ryder, Dr Stephanie A Amiel (Association of British Clinical Diabetologists (ABCD).

- Two specialist advisers have performed the procedure at least once and 4 specialist advisers have never performed it but have taken part in patient selection or referred patients for this procedure. One adviser stated that it is performed in specially selected patients or those in clinical trials.
- Four specialist advisers considered the procedure to be novel and of uncertain safety and efficacy, 1 considered it to be the first in a new class of procedure and 1 thought that it was an established practice and no longer new as it has been around for a few years.
- Specialist advisers listed the relevant comparators as diet and exercise, medical management of type 2 diabetes, bariatric surgery procedures such as gastric banding, gastric bypass (laparoscopic proximal Roux-en-Y), biliopancreatic diversion (duodenal switch) or laparoscopic sleeve gastrectomy.
- The procedure is likely to be performed by less than 10% of specialists.
- Advisers stated that there is some controversy as to whether the procedure is performed by medical endoscopists or bariatric surgeons and, if widely adopted, there could be tensions between bariatric surgeons practising within established bariatric surgical practice, gastroenterologists and endocrinologists.
- Key efficacy outcomes listed include: reduced insulin resistance leading to improved glycaemic control; reduction in HbA_{1c}, antidiabetic medication use, fasting insulin, C-peptide and HOMA-IR; and improvement in percentage of weight loss, percentage of excessive weight loss, maintenance of weight loss, hypertension and quality of life both in the short and long term (that is, after the implant has been removed).
- Specialist advisers stated that the main concerns relate to variable efficacy between patients, the extent of improvement in diabetes and weight loss, duration of improvement in diabetes and weight loss (including long-term

efficacy after device removal), and lack of evidence from randomised controlled trials.

- Theoretical adverse events reported include gastrointestinal tract laceration, oropharyngeal, oesophageal, gastric or bowel perforation, peritonitis, bleeding, aspiration, infection; small bowel obstruction (with knotting or kinking of the liner), device intolerance, migration or erosion, vitamin and mineral deficiency, dehydration, constipation, belching, bloating, diarrhoea, hypoglycaemia, hyperglycaemia, flatulence, gastro-oesophageal reflux disease, oesophagitis, pseudopolyps, nausea, vomiting, gastrointestinal pain, peptic ulcer disease, duodenitis, local inflammation, back pain and adynamic ileus.
- Anecdotal adverse events listed include difficulties in deploying the device, halting the procedure after endoscopy due to residual food in stomach, nausea, vomiting, gastrointestinal pain, cramping, intussusception, recurrence of previous neurological leg pain, bowel obstruction, perforation, gastric bleeding due to inappropriate prescription of nonsteroidal anti-inflammatory drugs, pharyngeal obstruction during explantation, liver abscess (due to the device being left in situ for more than 2 months beyond the recommended implant duration) and misplacement of device hood in pharynx during device removal.
- Specialist advisers stated that availability of the bariatric multidisciplinary team for patient selection and follow-up, surgeons with experience in bariatric surgery and good upper gastrointestinal endoscopic skills are needed to implant and remove the device and deal with rare complications. Advisers also stated that good training under supervision by an experienced proctor in the technique and standard operating theatre facilities with fluoroscopy, endoscopy equipment and anaesthetic support are needed. Patient selection and adjustment of diabetes medication need to be accommodated.
- Specialist advisers stated that the National Bariatric Surgery Registry (NBSR) hosts an EndoBarrier registry for UK EndoBarrier cases and the manufacturer is also setting up an international registry. One adviser stated that the ABCD

has a presence on N3, the NHS broadband network, and is volunteering to host the international registry

- There are few studies currently in progress (2 from the UK) that are likely to inform practice.
- Two advisers stated that the likely speed of diffusion cannot be predicted at present as it depends on how effective, safe and cost effective the procedure turns out to be. One adviser stated that it could be a major procedure in people with a BMI of less than 35 kg/m^2 in the next 5 years and may surpass the surgical treatments.
- One adviser stated that currently the procedure is mainly done in the private sector and is expensive for widespread adoption as costs are similar to bariatric surgical procedures. He suggests that it should be introduced in the NHS after review of long-term evidence.
- Three advisers stated that the procedure is likely to be carried out in a minority of hospitals, but at least 10 in the UK (mainly in teaching hospitals and major district general hospitals) if it is safe and efficacious.
- In terms of patient numbers and use of resources, 3 advisers stated that the impact on the NHS would range between moderate to minor and 2 advisers stated that it would be major because of the large number of people who are eligible for this procedure (obese and have type 2 diabetes, tried previous treatments but have failed treatment or did not tolerate it). One adviser stated that DJBL has the potential as a medium-term aid to significant weight reduction initially to prepare vulnerable patients for definitive surgery but also as a stand-alone treatment to start significant weight reduction with metabolic improvement. Another adviser stated that, if found safe and efficacious, the procedure can be offered as part of the bariatric procedures on offer for obesity and type 2 diabetes, with patients having to fulfil requirements for lifestyle and dietetic programmes before being eligible.

Patient commentators' opinions

NICE's Public Involvement Programme sent 35 questionnaires to 2 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 5 completed questionnaires.

The Patient Commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

- The device has not yet received US Food and Drug Administration (FDA) approval.
- Several additional studies are ongoing:
  - NCT01114438: Post Marketing Study in Subjects Who Have Type 2 Diabetes Using the EndoBarrier™ Gastrointestinal Liner; type: open-label single-group assignment; location: United Kingdom (Imperial College/St. Mary's Hospital, London; Trafford General Hospital/NOSC, Manchester; Southampton General Hospital, Southampton); estimated enrolment: 45 patients; inclusion criteria: subjects with type 2 diabetes for more than 1 and up to 10 years who are on oral diabetic medications and/or insulin, with an HbA_{1c} level over 7.5 and up to 10.0 and a BMI over 30 and under 50 kg/m^2; primary outcome: HbA_{1c} at 12 months; estimated primary completion date: January 2013 (status: completed, but not yet published).
  - NCT00986349 Study of EndoBarrier Liner for Treatment of Type 2 Diabetes; location: Brazil; type: open-label single-group assignment; estimated enrolment: 20 patients; inclusion criteria: subjects with type 2 diabetes who have been treated for ≤10 years and are on oral diabetic medications, with an HbA_{1c} level over 7.5 and under 10% and with a BMI over 26 and under 50; estimated study completion date: November 2012 (completed).
  - NCT00985114: Safety and efficacy study of EndoBarrier in subjects with type II diabetes and obesity; type: multicentre RCT with crossover (after

12-month washout); location: Netherlands; estimated enrolment: 70 patients; inclusion criteria: type 2 diabetes treated for under 10 years, BMI over 30 and under 50, with an HbA_{1c} level over 7.5 and under 10%; primary endpoint: percentage of patients who achieve a greater than 0.5% reduction in HbA_{1c} at 24 weeks or last visit from baseline; study completion date: January 2012 (status: completed, in press).

- NCT01728116: Safety and efficacy of EndoBarrier in subjects with type 2 diabetes who are obese (ENDO); type: RCT; location: USA; estimated enrolment: 500; inclusion criteria: HbA_{1c} over 8% and under 10%, BMI over 30 and under 50; primary outcome: improvement in HbA_{1c} at 12 months; estimated study completion date: June 2015 (currently recruiting).
- NCT01718457: EndoBarrier treatment in obese subjects with type 2 diabetes; type: interventional, single-group assignment; location: Israel; estimated enrolment: 45; estimated study completion date: January 2018 (not recruiting).
- NCT02055014: Randomisation to EndoBarrier alone versus with incretin analogue in sustained diabesity (REVISE-Diabesity). Type: RCT (EndoBarrier with continued liraglutide 1.2 mg for 12 months; EndoBarrier alone for 12 months; or liraglutide 1.8 mg without EndoBarrier); study population: patients with type 2 diabetes and obesity (HbA_{1c} ≥7.5%, BMI ≥35kg/m^2) despite previous GLP-1RA therapy; outcomes: HbA_{1c}, mmol/mol; % [24 months], weight [24 months]; location: UK; estimated enrolment:72; estimated study completion date: December 2016 (currently recruiting).
- NCT01724060: Effects of obesity treatments (including EndoBarrier) on food preferences and metabolism (FPS); type: observational case-control study; location: UK; estimated enrolment: 400; estimated study completion date: October 2014 (currently recruiting).
- NIHR EME sponsored randomised study in UK (Southampton and London); Type: RCT; estimated enrolment: 160 patients randomised to either EndoBarrier or best medical treatment; presently in ethics, to recruit September 2014 and will report in 2017/8.

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Appendix A: Additional papers on implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
de Moura et al (2012). Six month results of the duodenal-jejunal bypass liner for the treatment of obesity and type 2 diabetes. J Gastroint Dig Syst S2:003.doi:10.4172/2161-069X.S2-003	Case series n=22 Obese and T2DM patients for bariatric surgery EndoBarrier implanted. Follow-up=24 weeks	100% technical success. At week 24 mean weight loss was 14kg ($p<0.001$). BMI dropped on average 5.4 points and excess weight loss was 22.2%. Fasting blood glucose significantly reduced (baseline 171.8 mg/dl, week 24=141.5mg/dl). Glycosated haemoglobin level significantly reduced from 8.8% to 7.3%. Anti-diabetic medication use reduced except metformin.	Study with longer follow-up included in table 2.
de Jonge C, Rensen SS et al (2013). Endoscopic duodenal-jejunal bypass liner rapidly improves plasma parameters of nonalcoholic fatty liver disease. Clinical Gastroenterology & Hepatology 11 (11) 1517-1520.	Case series n=17 Obese T2DM patients Mean BMI 37kg/m^2, HbA_{1c} 8.4% Follow-up=24 weeks	All nonalcoholic fatty liver disease (NAFLD) related parameters decreased (aspartate aminotransferase [AST] from 35±0.4 IU/L to 28±3 IU/L; alanine aminotransferase [ALT] from 54±5 IU/L to 32±2 IU/L; glutamyltransferase [GT] from 66±14 IU/L to 44±7 IU/L; CK-18 from 214.4 to 140.6U/L; L-FABP from 29.3 to 18.2, all $p<.05$) at 3-month follow-up. After 6 months, levels of ALT, GT decreased further, whereas AST, CK-18,L-FABP stabilised. Six months after removal, levels of ALT, CK-18, GT were still reduced ($p<.05$) whereas AST and L-FABP returned to near baseline levels (p=not significant)	Focusing on fatty liver and not diabetes.
de Jonge C, Rensen SS et al (2014). Six months of treatment with the endoscopic duodenal-jejunal bypass liner does not lead to decreased systemic inflammation in obese patients with type 2 diabetes. Obesity Surgery 24 (2) 337-341.	Case series n=17 Obese T2DM patients Mean BMI 37kg/m^2, HbA_{1c} 8.4% Follow-up=24 weeks	Tumour necrosis factor alpha (TNF alpha) levels have increased from 1.8±0.1 to 2.1± 0.1 pg/ml, whereas interlukein-6 (IL-6) increased from 2.7 ±0.3 to 4.0 ±0.5 pg/ml ($p<0.05$) at 3-month follow-up. Plasma C-reactive protein (CRP) and myeloperoxidase (MPO) also increased but the differences were not significant. After 6 months, the levels of all parameters were similar to baseline levels (all p=ns) and did not lead to decreased systemic inflammation	Focusing on systemic inflammation and not diabetes.
Escalona A, Yanez R et al	Case series	Devices implanted and	Implantation of a

(2010). Initial human experience with restrictive duodenal-jejunal bypass liner for treatment of morbid obesity. Surgery for Obesity & Related Diseases 6 (2) 126-131.	n=10 BMI: 40.8kg/m^2 DJBL combined with a restrictor orifice (flow restrictor). Follow-up=12 weeks	removed after 12 weeks. The % EWL and TWL at explantation was 40% +/- 3% and 16.7 +/- 1.4 kg. The 4-hour GE was 98% +/- 1% at baseline, 72% +/- 6% at 4 weeks (p= 0.001 versus baseline), and 84% +/- 5% at 12 weeks (p<0.05 versus baseline). After explantation, the rate of GE returned to normal in 7 of 8 subjects, but remained slightly delayed in 1 subject (84% at 4 hours). Episodes of nausea, vomiting, and abdominal pain required endoscopic dilation of the restrictor orifice with a 6-mm through-the-scope balloon in 7 patients and a 10-mm balloon in 1, with no clinically significant adverse events.	flow restrictor with DJBL to induce weight loss (adjunct procedure).
Escalona A, Pimentel F, Sharp A et al (2012). Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. Annals of Surgery 255 (6) 1080-1085.2012.	Case series n=42 morbidly obese patients 6 patients with T2DM DJBL Follow-up=1 year/52 weeks	At end of follow-up, total body weight change from baseline was -22.1 kg (p<0.0001) corresponding to 47% excess weight loss. Significant improvements in waist circumference, blood pressure, total and LDL cholesterol, triglycerides and fasting glucose). No procedure related complications. 15 early endoscopic removals.	Only 6 T2DM patients.
Fischer S, Zechmeister-Koss I, and Huic M. Duodeno-jejunal bypass liner (DJBL) for patients with obesity, with/without type 2 diabetes mellitus (Structured abstract). Health Technology Assessment Database (1) 2013.	Systematic review Patients with obesity > grade II or > grade III without comorbidities; patients with T2DM+obesity > grade I	Studies suggest a short-term reduction of body weight in obese patients. Overall the evidence is insufficient to assess the efficacy and safety of the intervention for obesity +comorbidities, or T2DM +obesity.	Non English (German article)
Fishman E, Melanson D et al (2008).Conference Proceedings: A novel endoscopic delivery system for placement of a duodenal-jejunal implant for the treatment of obesity and type 2 diabetes. Annual International-3.2008.	Clinical study n=12 Case series Follow-up=12 weeks	All implanted successfully. No procedure related complications.	Patients awaiting gastric bypass surgery (study included in IP986).
Gersin KS, Keller JE, et al (2007). Duodenal- jejunal	Case report n=1	Device placed with no complications.	Larger studies with longer

bypass sleeve: a totally endoscopic device for the treatment of morbid obesity. Surgical Innovation 14 (4) 275-278.	36-year-old woman BMI: 45.2kg/m^2 DJBL Follow-up= 3 months	Device removed after 3 months. Total weight lost was 9.09 kg.	follow-up included in table 2.
Gersin KS, Rothstein RI, Rosenthal RJ et al (2010). Open-label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointestinal Endoscopy 71 (6) 976-982.	RCT n=56 (27 DJBL versus 29 sham endoscopy) Obese patients needing to lose weight before bariatric surgery Follow-up=12 weeks	EWL: DJBL versus sham=11.9% versus 2.7% p<.05 10% or more EWL: 62% versus 17% p<.05 Total weight change:-8.2 kg versus 2.1 kg p<0..05) DJBL: 8 terminated early due to: GI bleeding (n=3), abdominal pain (n=2), nausea and vomiting (n=2) and an unrelated pre-existing illness (n=1). No further clinical symptoms after explantation.	Non diabetic patients.
Koehestanie, P., Betzel, B., Dogan, K., Berends, F., Janssen, I., Aarts, E., Groenen, M., and Wahab, P. The feasibility of delivering a duodenal-jejunal bypass liner (EndoBarrier) endoscopically with patients under conscious sedation. Surgical Endoscopy 28 (1) 325-330.2014.	Case series (prospective) n=56 28 conscious sedation 28 general anaesthesia DJBL	Both groups were comparable. All the devices were placed successfully, and no complications occurred in either group. Comparison of the CS group with the GA group respectively showed a mean total operation time of 29 versus 56 min, a mean propofol use of 170 versus 258 mg, and a mean hospital stay of 11 versus 22 hours.	Compares DJBL procedure under general anaesthesia with conscious sedation.
Levine A, Ramos A, et al (2009). Radiographic appearance of endoscopic duodenal-jejunal bypass liner for treatment of obesity and type 2 diabetes. Surgery for Obesity & Related Diseases 5 (3): 371-374.	Case series n=8 (from 3 studies, 3 centres) DJBL (EndoBarrier) Radiographic appearance of the device *in vivo* by contrast swallow or direct injection of water soluble contrast media.	The anchor on the device provides a good seal that remains intact for <197 days. 1 leak from a tear in the proximal end of liner material was observed at removal (occurred *in vivo* as a result of inadequate fabrication techniques that have subsequently improved. Considerable variability in the position and orientation of anchor in images.	Study reports radiographic appearance of device *in vivo*. Larger studies with longer follow-up included in table 2.
Lale C, Laubner K et al (2014). Minimally invasive treatment of a duodenal perforation associated with the EndoBarrier duodenal-jejunal bypass liner. Endoscopy.46: E171-E172.	Case report	49 year old man presented with acute abdominal pain 4 weeks after DJBL implantation. Imaging revealed intestinal perforation. This was treated by a combined endoscopic and laparoscopic procedure.	Safety event already covered in overview.

		The DJBL was removed endoscopically and this was followed by laparoscopic closure of the perforation in the duodenal bulb using a running suture. The patient was discharged 9 days after surgery.	
Malik A, Mellinger JD et al. (2006) Endoluminal and transluminal surgery current status and future possibilities. Surgical Endoscopy, 20: 1179-92	Review		Literature review, no new data.
Montana R, Slako M, and Escalona A (2012). Implantation of the duodenal-jejunal bypass sleeve under conscious sedation: A case series. Surgery for Obesity and Related Diseases.8 (5): pp e63-e65.	Case series n=3 BMI: 36 to 48 kg/m^2 DJBL under conscious sedation.	Mean procedure time 23 minutes. Patients remained stable during recovery phase. No adverse effects were observed. Discharged next day tolerating a liquid diet.	Larger studies with longer follow-up included in table 2.
Munoz R. and Escalona A. Duodenal-jejunal bypass liner to treat type 2 diabetes mellitus in morbidly obese patients. Current Cardiology Reports 16 (3) 454-2014.	Preclinical and clinical studies review of evidence	Early studies reported significant improvements in several parameters of glucose homeostasis in morbidly obese patients with T2DM. Larger clinical studies, focused primarily on the effect of the DJBL on T2DM treatment, have corroborated initial observations not only in morbidly obese patients but in non-morbidly obese diabetic patients as well.	Review. Studies already included in table 2.
Patel SR, Hakim D et al. (2013) The dueodenal-jejunal bypass sleeve (Endobarrier Gastrointestinal Liner) for weight loss and treatment of type 2 diabetes. Surgery for Obesity Related Disorders Feb 4. pii: S1550-7289(13)00034-8. doi: 10.1016/j.soard.2013.01.015. [Epub ahead of print]	Non-systematic review DJBL	Most studies used 12-week excess weight loss (EWL) as a primary outcome measure with results ranging from 11.9%–23.6%. One study to date used 52-week EWL as its primary measure with a significant outcome of 47%. Our group has seen this technology cause significant weight loss, resolution of type 2 diabetes, and improvement in cardiovascular risk factor profile.	Non-systematic review
Rodriguez-Grunert L, Galvao Neto MP, Alamo M et al (2008). First human experience with endoscopically delivered and retrieved duodenal-jejunal bypass sleeve. Surgery for Obesity & Related Diseases 4 (1) 55-59.	Case series n=12 obese patients awaiting gastric bypass surgery (4/12 had T2DM) Mean BMI: 43kg/m^2	Average % EWL for 12 weeks was 23.6% All patients achieved 10% EWL. 4 T2DM patients had normal fasting plasma glucose levels without glycaemic medication, 3 had	Only 4 T2DM patients

	DJBL Follow-up=12 weeks	decreased HbA_{1c} of 5%. device related adverse events: 6 episodes of abdominal pain, 18 of nausea, and 16 of vomiting within 2 weeks of implantation. 2 partial pharyngeal tears occurred during explantation. Implant site inflammation occurred in all patients. 2 underwent explantation after 9 days secondary to poor device placement.	
Sandler BJ, Rumbaut, R, Swain CP et al (2011). Human experience with an endoluminal, endoscopic, gastrojejunal bypass sleeve. Surgical Endoscopy 25 (9) 3028-3033.	Case series n= 24 Device: GDJBL (ValenTX) Mean BMI: 42kg/m^2 7 patients with diabetes. Follow-up=12 weeks	22 patients implanted with device. 17 maintained it for 12 weeks. 39.7% excess weight loss noted at 12 weeks. Device was explanted early because of early postoperative dysphagia. All patients with diabetes had normal blood glucose levels and none required antihyperglycemic medications. All 4 patients with elevated hemoglobin A1c levels preoperatively showed improvement.	Different device (gastroduodenojejunal bypass sleeve, ValenTX) of longer length (120 cm) secured at the esophagogastric junction with endoscopic and laparoscopic techniques.
Schouten R, Rijs CS, Bouvy ND et al (2010). A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. Annals of Surgery 251 (2) 236-243.	RCT (multicentre) n=41 (30 DJBL, 11 diet control) BMI DJBL 48.9; diet control BMI 47.4. Pre-surgical weight loss before bariatric surgery in obese patients. T2DM: (DJBL 8, control 2) DJBL Follow-up=3 months	26/30 devices implanted successfully. Mean EWL after 3 months= 19% versus 6.9% p<0.002; absolute change in BMI at 3 months=5.5 versus 1.9kg/m^2. T2DM in7/8 patients in DJBL arm improved (low glucose levels, HbA_{1c} and medication) 4 devices explanted prior to initial protocol end point due to migration=1, dislocation of the anchor =1,sleeve obstruction=1, and continuous epigastric pain=1. No procedure-related events. Post-procedure events: 100% DJBL had at least one AE, mainly abdominal pain and nausea in the first week.	Only 8 T2DM patients
Tarnoff M, Rodriguez L, Escalona A, Ramos A et al	RCT n=47 (DJBL arm:	Mean EWL 22% versus 5%, p<0.001 at 12 weeks. No	Only 4 T2DM patients

(2009). Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery. Surgical Endoscopy 23 (3) 650-656.	21, sham arm: 26) pre op weight loss before bariatric surgery in obese patients. DJBL Follow-up=12 weeks	significant adverse events in 20/25 at 12 weeks. 20% (5/25) were explanted early due to: upper GI bleeding at a mean 13.8 days (n3), anchor migration on day 47 which manifested as abdominal pain (n=1) and sleeve obstruction with abdominal pain and vomiting on day 30 (n=1). 8/25 underwent 2-week post implant EGD and mild degrees of residual duodenal inflammation were noted.	
Zechmeister-Koss I., Huic, M, Fischer S, and European Network for Health Technology Assessment (EUnetHTA). The duodenal-jejunal bypass liner for the treatment of type 2 diabetes mellitus and/or obesity: a systematic review. Obesity Surgery 24 (2) 310-323.2014.	Systematic review on DJBL for patients with obesity, with/without type 2 DM n=10 studies 342 patients. Includes studies on both patients with obesity, with/without T2DM.	In high-grade obese patients, short term excess weight loss was observed. For remaining end points and patient populations evidence was not available or ambiguous.	Studies on patients with obesity and T2DM already included in table 2.

Appendix B: Related NICE guidance for implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes

Guidance	Recommendations
Interventional procedures	**Implantation of a duodenal–jejunal bypass sleeve for managing obesity. NICE interventional procedure guidance 471 (2013).** **1. Recommendations** 1.1 Current evidence on the safety and efficacy of implantation of a duodenal–jejunal bypass sleeve (DJBS) for managing obesity is limited in quality and quantity. Therefore, this procedure should only be used in the context of research. 1.2 Clinicians should review local clinical outcomes and enter details about all patients undergoing implantation of a DJBS for managing obesity onto the National Bariatric Surgery Register when the facility for this is available. 1.3 Well-controlled studies are needed to support the current limited evidence on weight loss in the short term. They should document patient selection, all complications (while the device is in place and after its removal) and technical problems associated with placing and removing the device. **6 Committee comments** 6.1 The Committee considered that the quality of randomised controlled trials was poor, with substantial loss of patients to follow-up and potential for bias. 6.2 The Committee was advised that appropriate indications for implantation of a duodenal–jejunal bypass sleeve (DJBS) are uncertain. The specialist advisers stated that it might be used for improvement of control of diabetes in patients with obesity (but not in patients with diabetes who are not obese); for weight loss alone (but the durability of its effects may be limited); or for weight reduction before planned bariatric surgery. The literature reported heterogeneous outcomes relevant to these various indications, and also reported improvements in control of hypertension and blood lipid levels. The Committee was also advised that the device used in some of the studies was a prototype rather than a device that has been introduced into clinical practice. 6.3 The Committee noted specialist advice that this procedure should only be used in units specialising in the treatment of obesity, as one of a range of treatment options and as part of a package of care.
Clinical guidelines	**Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43 (2006). Available from**

	www.nice.org.uk/CG43 1.2.6 Surgical interventions Adults and children 1.2.6.1 Bariatric surgery is recommended as a treatment option for people with obesity if all of the following criteria are fulfilled: • they have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant disease (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight • all appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months • the person has been receiving or will receive intensive management in a specialist obesity service • the person is generally fit for anaesthesia and surgery • the person commits to the need for long-term follow-up. See recommendations 1.2.6.12 and 1.2.6.13 for additional criteria to use when assessing children, and recommendation 1.2.6.7 for additional criteria for adults. 1.2.6.2 Severely obese people who are considering surgery to aid weight reduction (and their families as appropriate) should discuss in detail with the clinician responsible for their treatment (that is, the hospital specialist and/or bariatric surgeon) the potential benefits and longer-term implications of surgery, as well as the associated risks, including complications and perioperative mortality. 1.2.6.3 The choice of surgical intervention should be made jointly by the person and the clinician, and taking into account: • the degree of obesity • comorbidities • the best available evidence on effectiveness and long-term effects • the facilities and equipment available • the experience of the surgeon who would perform the operation. 1.2.6.4 Regular, specialist postoperative dietetic monitoring should be provided, and should include: • information on the appropriate diet for the bariatric procedure • monitoring of the person's micronutrient status • information on patient support groups • individualised nutritional supplementation, support and guidance to achieve long-term weight loss and weight maintenance. 1.2.6.5 Arrangements for prospective audit should be made, so that the outcomes and complications of different procedures, the impact on quality of life and nutritional status, and the effect on comorbidities can be monitored in both the short and the long term.

	1.2.6.6 The surgeon in the multidisciplinary team should: • have undertaken a relevant supervised training programme • have specialist experience in bariatric surgery • be willing to submit data for a national clinical audit scheme. **Type 2 diabetes - newer agents (partial update of CG66). NICE clinical guideline 87 (2009) Available from http://guidance.nice.org.uk/CG87** The guideline does not cover any endoscopic or surgical interventions.
Public health guidance	**Preventing type 2 diabetes: population and community-level interventions in high-risk groups and the general population. NICE public health guidance 35 (2011). Available from http://guidance.nice.org.uk/PH35** The guideline does not cover any endoscopic or surgical interventions

Appendix C: Literature search for implantation of a duodenal–jejunal bypass liner for managing type 2 diabetes

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	07/10/2014	Issue 10 of 12, October 2014
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	07/10/2014	Issue 3 of 4, July 2014
HTA database (Cochrane Library)	07/10/2014	Issue 3 of 4, July 2014
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	07/10/2014	Issue 9 of 12, September 2014
MEDLINE (Ovid)	07/10/2014	1946 to September Week 4 2014
MEDLINE In-Process (Ovid)	07/10/2014	October 06, 2014
EMBASE (Ovid)	07/10/2014	1974 to 2014 Week 40
PubMed	07/10/2014	n/a
JournalTOCS	07/10/2014	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Duodenum/su [Surgery]
2	Jejunum/su [Surgery]
3	((Duoden* or jejun*) adj4 surg*).tw.
4	((bypass or gasterointest* or gastrojejun* or gastro-jejun* or gastric* or gastrect*) adj4 (sleeve* or line* or tube* or implant*)).tw.
5	(Duoden* adj4 (sleeve or line* or tube* or implant*)).tw.
6	(jejun* adj4 (sleeve* or line* or tube* or implant*)).tw.
7	DJBL.tw.
8	DJBS.tw.
9	or/1-8
10	Diabetes Mellitus, Type 2/

11	(Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).tw.
12	((Maturit* or adult* or slow* or late*) adj4 onset* adj4 (diabete* or diabetic*)).tw.
13	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).tw.
14	((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).tw.
15	Waist Circumference/
16	((raise* or great* or increase* or improve* or large* or big*) adj4 waist* adj4 circumference).tw.
17	NIDDM.tw.
18	or/10-17
19	9 and 18
20	Endobarrier*.tw.
21	19 or 20
22	Animals/ not Humans/
23	21 not 22
24	limit 23 to ed=20140401-20141031