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Duodenal-jejunal Bypass Liner for the management of Type 2 Diabetes and Obesity: A Multicenter Randomized Controlled Trial.

Department of Surgery and Cancer, Imperial College, London, UK (Aruchuna Ruban PhD*), Department of Metabolism, Digestion and Reproduction, Imperial College, London, UK (Alexander D. Miras PhD*); Division of Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, UK (Michael A. Glaysher MD); PsychoNeuroEndocrinology Research Group, Neuropsychopharmacology Unit, Center for Psychiatry and Computational, Cognitive and Clinical Neuroimaging Laboratory, Department of Brain Sciences, Imperial College London, UK (Anthony P. Goldstone PhD); Imperial College London, Department of Public Health, Imperial Clinical Trials Unit, London, UK (Christina G. Prechtl PhD); Imperial College London, Department of Public Health, Imperial Clinical Trials Unit, London, UK (Nicholas Johnson M.Sc.); Psychiatry and Computational, Cognitive and Clinical Neuroimaging Laboratory, Department of Brain Sciences, Imperial College London, UK (Navpreet Chhina MRCP); Diabetes Complications Research Center, University College Dublin, Ireland (Werd Al-Najim PhD); Department of Community Health Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia (Madhawi Aldhwayan PhD); Imperial College London, Department of Public Health, Imperial Clinical Trials Unit, London, UK (Natalia Klimowska-Nassar MSt); Imperial College London, Department of Public Health, Imperial Clinical Trials Unit, London, UK (Claire Smith PhD); Southampton Health Technology Assessment Center, University of Southampton, Southampton, UK (Joanne Lord PhD); Section of Nutritional research, Department of Metabolism, Digestion and Reproduction, Imperial College London, UK (Jia V. Li PhD); PsychoNeuroEndocrinology Research Group, Neuropsychopharmacology Unit, Center for Psychiatry and Computational, Cognitive and Clinical Neuroimaging Laboratory, Department of Brain Sciences, Imperial College London, UK (Lilliam Flores PhD); PsychoNeuroEndocrinology Research Group, Neuropsychopharmacology Unit, Center for Psychiatry and Computational, Cognitive and Clinical Neuroimaging Laboratory, Department of Brain Sciences, Imperial College London, UK (Moaz Al-Lababidi MRes); Department of Endocrinology, King's College Hospital NHS Trust, London, UK (George Dimitriadis MRCP); University Hospital Southampton NHS Foundation Trust, Biomedical Research Center, Southampton, UK (Mayank Patel DM); Primary Care, Population Sciences and Medical Education, University of Southampton Medical School, Southampton, UK (Michael Moore FRCGP); Department of Metabolism, Digestion and Reproduction, Imperial College, London, UK (Harvinder Chahal PhD);

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Department of Surgery and Cancer, Imperial College, London, UK (Ahmed R. Ahmed PhD); Department of Surgery and Cancer, Imperial College, London, UK (Jonathan Cousins FRCA); PsychoNeuroEndocrinology Research Group, Neuropsychopharmacology Unit, Center for Psychiatry and Computational, Cognitive and Clinical Neuroimaging Laboratory, Department of Brain Sciences, Imperial College London, UK (Ghadah Aldubaikhi M.Res); Department of Surgery and Cancer, Imperial College, London, UK (Ben Glover MRCP); Imperial College London, Department of Public Health, Imperial Clinical Trials Unit, London (Emanuela Falaschetti MSc); Department of Surgery and Cancer, Imperial College, London, UK (Hutan Ashrafian PhD); Diabetes Complications Research Center, University College Dublin, Ireland (Prof Carel W. le Roux PhD); Department of Surgery and Cancer, Imperial College, London, UK (Prof Ara Darzi MD); Division of Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, UK (James P Byrne MD); Department of Surgery and Cancer, Imperial College, London, UK (Prof Julian P Teare PhD).

** Equally contributing authors*

Corresponding Author:

Corresponding author: Mr. Michael A Glaysher, Clinical Research Fellow and General Surgical Registrar, Level D, Laboratory & Pathology Block, SCBR - MP 218, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, Hampshire, SO16 6YD. Mobile: 07834897272. E-mail: michaelglaysher@me.com

Running head: DJBL management of Type 2 Diabetes and Obesity

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Mini-Abstract

The duodenal-jejunal bypass liner (DJBL) is an endoscopically-implantable impermeable sleeve which lines 60cm of the proximal small intestine. The addition of the DJBL to intensive medical care for the treatment of type 2 diabetes mellitus and obesity was associated with superior weight loss, improvements in cardiometabolic risk factors and fatty liver disease, but not glycaemia.

Abstract

Objective

To examine the clinical efficacy and safety of the duodenal-jejunal bypass liner (DJBL) whilst *in situ* for 12 months *and* for 12 months after explantation.

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Summary Background Data:

This is the largest randomized controlled trial (RCT) of the DJBL, a medical device used for the treatment of people with type 2 diabetes mellitus (T2DM) and obesity. Endoscopic interventions have been developed as potential alternatives to those not eligible or fearful of the risks of metabolic surgery.

Methods

In this multicenter open-label RCT, 170 adults with inadequately controlled T2DM and obesity were randomized to intensive medical care with or without the DJBL. Primary outcome was the percentage of participants achieving a glycated hemoglobin reduction of ≥20% at 12 months. Secondary outcomes included weight loss and cardiometabolic risk factors at 12 and 24 months.

Results

There were no significant differences in the percentage of patients achieving the primary outcome between both groups at 12 months (DJBL 54.6% [n=30] vs. control 55.2% [n=32]; OR 0.93, 95% CI: 0.44, 2.0; p=.85). 24% (n=16) patients achieved ≥15% weight loss in the DJBL group compared to 4% (n=2) in the controls at 12 months (OR 8.3, 95% CI: 1.8, 39; p=.007). The DJBL group experienced superior reductions in systolic blood pressure, serum cholesterol and alanine transaminase at 12months. There were more adverse events in the DJBL group.

Conclusion

The addition of the DJBL to intensive medical care was associated with superior weight loss, improvements in cardiometabolic risk factors and fatty liver disease markers, but not glycaemia, only whilst the device was *in situ*. The benefits of the devices need to be balanced against the higher rate of adverse events when making clinical decisions.

Authors' contributions

AR: coinvestigator at Imperial College London, performed literature search, conducted patient recruitment and study visits and is the joint first author of this manuscript. **ADM:** coinvestigator at Imperial College London, joint first author of this manuscript. **MAG:** coinvestigator at University Hospital Southampton, conducted patient recruitment and study visits and contributed to the writing of the manuscript and approved the final version. **APG:** coinvestigator at Imperial College London and trial coapplicant, contributed to the writing the manuscript and approved the final version. **CGP:** trial manager at Imperial College London and Imperial Clinical Trials Unit, lead dietician and contributed to the design and concept of this paper and approved the final version. **NAJ:** trial statistician, contributed to writing the

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manuscript and approved the final version. **NC:** coinvestigator at Imperial College London, contributed to the acquisition of the data and provided critical appraisal of current manuscript and approved the final version. **WA-N:** coinvestigator at Imperial College London, contributed to the acquisition of the data and in writing the manuscript and approved the final version. **MA** led patient study visits and data collection at Imperial site, ran analysis of samples, and provided critical appraisal of the manuscript and approved the final version. **N-KN:** edited and provided critical appraisal of current manuscript and approved the final version. **CS:** interpreted the data and provided critical appraisal of current manuscript and approved final version. **JL:** coauthor of approved study protocol, contributed to writing the manuscript and approved the final version. **JVL:** coauthor of approved study protocol, contributed to writing the manuscript and approved the final version. **LF:** led patient study visits and data collection at Imperial site, ran analysis of samples, and provided critical appraisal of the manuscript and approved the final version. **MA-L:** led patient study visits and data collection at Imperial site, ran analysis of samples, and provided critical appraisal of the manuscript and approved the final version. **GD:** provided critical appraisal of the manuscript and approved the final version. **MP**: coinvestigator at University Hospital Southampton, contributed to recruitment and provided critical appraisal of the manuscript and approved the final version. **MM:** trial co-applicant, contributed to trial set-up and recruitment and provided critical appraisal of the manuscript and approved the final version. **HC:** performed diabetic reviews for patients involved in the study and provided critical appraisal of the manuscript and approved the final version. **ARA:** bariatric surgeon who supervised and facilitated endobarrier implants at the Imperial site and provided critical appraisal of the manuscript and approved the final version. **JC:** anaesthetised patients receiving the endobarrier and provided critical appraisal of the manuscript and approved the final version. **GA:** led patient study visits and data collection at Imperial site, ran analysis of samples, and provided critical appraisal of the manuscript and approved the final version. **BG:** led patient study visits and data collection at Imperial site, ran analysis of samples, and provided critical appraisal of the manuscript and approved the final version. **EF:** trial co-applicant, trial statistician, contributed to writing the manuscript and approved the final version. **HA:** contributed to the design and concept of the manuscript, provided critical appraisal of the manuscript and approved the final version. **CLR:** trial co-applicant, contributed to trial set-up and design, provided critical appraisal of the manuscript and approved the final version. **AD:** trial co-applicant, provided critical appraisal of the manuscript and approved the final version. **JPB:** principal investigator at University Hospital Southampton, trial co-applicant, provided critical appraisal of the manuscript and approved the final version. **JPT:** chief investigator, trial co-applicant, provided critical appraisal of the manuscript and approved the final version.

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Introduction

The endoluminal duodenal-jejunal bypass liner (DJBL) is an innovative medical device developed and used for the treatment of adults with T2DM and/or obesity. The aim underlying its conception and design was to mimic part of the impressive metabolic and weight loss effects of intestinal bypass surgical procedures such as the Roux-en-Y gastric bypass.[1] The DJBL consists of a single use impermeable fluoropolymer sleeve which is implanted in the duodenum endoscopically and lines 60 cm of the small intestine.[2] As a result food bypasses the proximal intestinal mucosa by traveling inside the sleeve and comes into contact with biliopancreatic secretions once it exits the sleeve. The device is normally implanted as a day case procedure under general anesthesia or sedation, and explanted electively after 12 months. It is an endoscopic treatment that could fill the large treatment gap between lifestyle/pharmacotherapy and metabolic surgery for T2DM and/or obesity.[2]

Two systematic reviews and meta-analyses of RCTs and observational studies have examined the clinical efficacy of the DJBL in people with obesity with/without T2DM and yielded encouraging results.[3,4] In the first meta-analysis, which was performed predominantly on people with obesity, participants in the DJBL group lost 5.1kg more weight than people that underwent medical care, and whilst HbA1c reduced substantially in both groups there were no significant differences between groups.[3] The second review assessed people with obesity *and* T2DM and reported superior reductions in both HbA1c (1.3% or 13.3 mmol/mol) and weight (total body weight loss 18.9%).[4] The safety profile of the DJBL was considered acceptable and consisted predominantly of self-limiting gastrointestinal side effects. However, the meta-analyses demonstrated significant risk of bias and/or heterogeneity, and called for larger RCTs with longer follow-up.

Our aim was to determine the position of this device in the treatment algorithm for patients with T2DM and obesity. We thus conducted the largest RCT in the field to compare the clinical efficacy and safety of intensive medical care with the DJBL vs. intensive medical care alone on glycemic control in people with T2DM and obesity whilst the device is in situ for 12 months *and* for the 12 months after explantation.

Methods

Study Design

This was an open-label RCT conducted between November 2014 and January 2019 in two academic clinical centers in the UK, Imperial College London and University Hospital Southampton NHS Foundation Trust. The protocol has been published previously and can be reviewed within Supplemental Digital Content 1, http://links.lww.com/SLA/D182.[5] The trial was funded by the NIHR, sponsored by Imperial College London and managed by the Imperial Clinical Trials Unit. The trial was approved by the Fulham Research Ethics Committee (reference 14/LO/0871) and conducted in accordance with the Declaration of Helsinki.

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Patients

Male and female participants, aged 18–65 years, with a BMI 30–50 kg/m^2 and confirmed diagnosis of T2DM for at least 1 year, who had inadequate glycemic control (HbA1c 7.7–11.0% or 58-97 mmol/mol) and were on glucose-lowering medications, excluding insulin, were eligible for the trial. Following written informed consent, 170 participants were randomized via the InForm database system at a 1:1 ratio, stratified by both site and BMI subgroup (30-40 and 40-50 kg/m^2) to either intensive medical care *with* or intensive medical care *without* the DJBL (control group). A block randomization scheme with a random sequence of block sizes was used to ensure a balanced distribution of participants were assigned to each treatment arm.

Procedures

Participants in both arms received dietary and physical activity counselling.[5] Everyone was advised to follow a low-calorie diet which was based on daily amounts of 1,200 to 1,500 calories for women and 1,500 and 1,800 calories for men. In addition, it was recommended to eat regularly every day (5 times/ day), to control portion sizes, and intake of carbohydrates/ starchy foods, to increase the intake of low glycemic index (GI) and high protein foods, as well as vegetables, and to reduce the intake of foods high in fat, sugar, and alcohol. Participants were also advised to include more physical activity in their daily routine for example to walk more every day. Their goal included 150 minutes (2 ½ hours) a week of moderate intensity and 75 minutes a week of vigorous intensity aerobic activity and muscle strengthening activities more than 2 days a week. Any exercise was adjusted to individual needs and activity levels. Throughout the study, motivation, dietary compliance and the average daily level of physical activity was recorded. The use of Glucose-lowering medications was optimized by three Consultant Diabetologists and reflected best practice at the time of assessment in accordance with the guidelines of the American Diabetes Association.[6-9] Preference was given to medications associated with weight loss or weight neutrality. Liraglutide 1.8mg daily and dipeptidyl peptidase-4 (DPP-4) inhibitors were used throughout the trial and from 2015 onwards sodium-glucose co-transporter-2 (SGLT2) inhibitors were also used. Participants had the DJBL device implanted as a day case under a general anesthetic. The device was electively explanted after 12 months. Following explantation, participants were followed up for a further 12 months. Assessments took place at the NIHR Imperial and Southampton clinical research facilities.

Outcomes

The primary outcome was an HbA1c reduction of ≥20% at 12 months post intervention in accordance with International Diabetes Federation guidelines.[10] Pre-specified secondary endpoints included HbA1c <6% (or <42 mmol/mol), blood pressure <135/85, total body weight loss ≥15%, reduction in the number of medications and rates of adverse events.

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Statistical Analyses

Primary and secondary outcomes were analyzed to investigate treatment effect using multivariate logistic regression, including for stratification variables (BMI group and site). In order to detect a success rate of 35% in the DJBL group vs 15% in the control group with 80% power, 170 subjects were randomized (full details in Supplemental Digital Content 2, http://links.lww.com/SLA/D183). Missing data implications for the primary endpoint analysis were assessed using multiple imputation methods alongside a per-protocol analysis to assess treatment adherence. Exploratory analyses were also undertaken using a mixed-model approach alongside post-hoc multivariate regression and correlation analyses. Statistical tests were carried out using SAS v9.4 and were two-tailed with a 5% significance level and performed according to the intention-to-treat principle with results presented as mean ± SD (unless specified otherwise). To ensure data integrity, a data monitoring and ethics committee (DMEC) met every 6-months to review study progress. Full details of all statistical methodology can be found in the Statistical Analysis Plan within Supplemental Digital Content 2, http://links.lww.com/SLA/D183.

Results

A total of 170 participants underwent randomization from March 2015 through December 2016. Eight patients in the DJBL and 14 in the control group dropped out during the first 12 months, whilst 18 and 7 withdrew between months 12-24. For the primary analysis; 55 and 58 patients (DJBL and control arms respectively) were included within the ITT population at year 1 with 58 and 51 patients at year 2 (Figure 1). Of those randomized, 54% were male, with a mean(±SD) age of 52 (±8) years; BMI 36.3 (±4.6) kg/m2, HbA1c 72 (±10) mmol/mol / 8.8 (±0.9) %, and median [IQR] duration of T2DM 7.2 [4.0-10.2] years (Table 1).

At 12 months 30 of 55 participants (54.5%) achieved a 20% reduction in HbA1c in the DJBL group, compared to 32 of 58 (55.2%) in the control group (OR 0.93, 95% CI: 0.44, 2.0; p=.85) (Table 2). At the 24-month visit (i.e. 12 months post explantation) 23 of 58 (39.7%) participants in the DJBL group achieved ≥20% reduction in HbA1c levels compared to 19 of 52 (36.5%) in the control group (OR 1.1, 95% CI: 0.52, 2.5; p=.75). Results were unaffected by the per protocol analysis, with 29 of 54 (53.7%) patients achieving the endpoint in the DJBL group, and 29 of 52 (55.8%) in the control group (OR 0.93, 95% CI: 0.39, 2.3; p=.88). Missing data (assumed missing-at-random) did not appear to have any bearing on the outcome of the primary endpoint analysis with multiple imputation using chained equations (MICE) across 50 iterations returning an estimated treatment effect on proportion of 0.025 (95% CI: -0.34, 0.39; p=.89). Likewise, the endpoint rate required within the missing data to establish a change in the primary analysis result is significantly different when compared to the current endpoint rate in both treatment arms (Supplemental Digital Content 3, http://links.lww.com/SLA/D184).

Over time, both treatment groups displayed a reduction in HbA1c levels with the greatest reduction at 3 months (Table 2, Figure 2A, eFigure 2A (Supplemental Digital Content 3,

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http://links.lww.com/SLA/D184)). However, there were no significant differences in the absolute reduction of HbA1c between the groups at either 12 [DJBL -15.9 ± 10.8mmol/mol (1.5 ± 1.0%) vs. control -13.3 ± 14.0mmol/mol (-1.2 ± 1.3%), p=.50] or 24 months [DJBL -8.6 ± 15.8mmol/mol (-0.8 ± 1.4%) vs. control -8.0 ± 12.6mmol/mol (-0.7 ± 1.2%), p=.71]. At 12 months, six (10.9%) patients achieved a HbA1c level of < 42 mmol/mol in the DJBL group, compared with four (6.9%) patients in the control group. Using logistic regression, adjusting for the stratification variables of site and BMI group, the OR estimate for achieving this target in the DJBL group compared with the control group was 2.15 (95% CI 0.54 to 8.55; p = 0.28).

Post explant, at 15, 18 and 24 months, the numbers of patients who reached this HbA1c remission threshold in the DJBL group and the control group were three (5.0%) and two (3.8%), three (5.0%) and two (4.0%), and three (5.2%) and zero (0.0%), respectively. There were no significant differences between the groups in the number of glucose-lowering medications used at baseline, 12 months or 24 months post-intervention (Table 2, Figure 2B).

At 12 months, 16 of 66 participants (24.2%) achieved a ≥ 15% weight loss in the DJBL group, compared to 2 of 54 (3.7%) in the control group (OR 8.3, 95% CI: 1.8, 39; p=.007; Table 2). However, there were no significant differences between the two groups at 24 months. 38 of 66 (57.6%) achieved a weight loss of ≥10% in the DJBL group, compared to 12 of 54 (22.2%) in the control group at 12 months (OR 4.50, 95% CI: 1.99, 10.18; p<.001). However, there were no significant differences between the two groups at 24 months. DJBL resulted in significantly more weight loss at 12 months [(DJBL -10.6 ± 6.2% vs. control -5.4 ± 5.8%, p<.001; (Table 2, Figure 2C, eFigure 2B, eFigure3 (Supplemental Digital Content 3, http://links.lww.com/SLA/D184))]. At 24 months there were no significant differences in weight loss between the two groups (DJBL -5.1 ± 5.4% vs. control -4.6 ± 5.7%, p=.76).

At 12 months, 45 of 66 participants (68.2%) achieved a blood pressure below 135/85 mmHg in the DJBL group, compared to 24 of 54 (44.4%) in the control group (OR 2.6, 95% CI: 1.2, 5.5; p=.01, Table 2). At 24 months, 31 of 58 (53.5%) people in the DJBL group achieved this outcome compared to 33 of 52 (63.5%) in the control group (OR 0.72, 95% CI: 0.33, 1.6; p=.42, Figure 2D). Systolic and diastolic blood pressure were reduced significantly more in the DJBL compared to the control group at 12 months (systolic blood pressure: -6.83 ± 17.75 vs. -1.04 ± 15.16mmHg respectively, p=.004; diastolic blood pressure: -3.88 ± 9.81 vs. -2.19 ± 11.98mmHg respectively, p=.02), but not 24 months (Table 2).

At 12 months, total cholesterol concentration was reduced significantly more in the in DJBL compared to the control group (-0.49 ± 0.80 vs. -0.01 ± 0.98 mmol/l; p=.009, table 3, Figure 2E), but there were no significant differences between groups at 24 months. HDL cholesterol concentration was reduced in the DJBL group but increased in the control group at 12 months (-0.04 ± 0.16 vs. +0.12 ± 0.24 mmol/l; p<.001, Table 3). There were no significant differences between groups in LDL cholesterol (-0.24 ± 0.62 vs. -0.02 ± 0.84 mmol/l) or triglycerides (-0.33 ± 1.26 vs. -0.13 ± 1.11 mmol/l) at 12 months (Table 3). There were no

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differences between the groups in LDL or HDL cholesterol and triglyceride concentrations at 12 or 24 months.

At 12 months, both serum ALT and AST concentrations were reduced significantly more in the DJBL compared to the control group at 12 months (ALT: -20.0 ± 22.0 vs. –11.8 ± 15.7 IU/l, p<.001; AST: -9.3 ± 14.7 vs. –6.6 ± 9.2 IU/l, p=.003, Table 3, Figure 2F). There were no significant differences in ALT or AST concentrations between the groups at 24 months (ALT: -9.4 ± 20.1 vs. -6.5 ± 18.9 IU/l, p=.32; AST: -6.0 ± 12.7 vs. -3.4 ± 10.4 IU/l, p=.07).

857 adverse events were reported amongst 151 (89%) of randomized subjects. 50 of these were SAEs, which occurred amongst 39 (23%) subjects (Table 4, eTable 1 (Supplemental Digital Content 3, http://links.lww.com/SLA/D184)). Of the 50 SAEs, 45 (90%) were reported in the DJBL and 5 in the control group. Of the 45 SAEs in the DJBL group, 26 (58%) were attributed to the intervention. Of the 5 SAEs in the control group, none were attributed to the intervention. There were 19 early explantations in the DJBL group. The majority of these were due to migration of the device (7), abdominal pain (5), upper gastrointestinal bleeding (2), cholecystitis (2), liver abscess (1), anticoagulation (1) and withdrawal of consent (1). A total of 8 torn devices were noted on explantation. The clinical outcomes of these 8 patients were similar to the entire DJBL group suggesting that the tears probably took place late after implantation and were not extensive enough to impact on clinical outcomes. There was one case of a liver abscess requiring explantation of the device and CT-guided drainage with the patient subsequently making a full recovery. In one patient, the device could not be removed endoscopically due to technical difficulties and required laparoscopic removal with no permanent sequelae.

Discussion

In this trial, the addition of the DJBL to an intensive medical intervention was not associated with significantly higher rates of participants achieving a ≥20% reduction in HbA1c. However, participants in the DJBL group lost significantly more weight than patient in the control group at 12 months. The percentage of participants achieving a clinically meaningful reduction in weight of 15%, was 6 times higher in the DJBL compared to the control group at 12 months. Participants in the DJBL group also experienced superior reductions in blood pressure, serum total cholesterol, ALT and AST at 12 months. The beneficial effects of the DJBL on weight and cardiometabolic markers dissipated following explantation, with only marginal differences between the groups at 24 months. Nevertheless, both groups sustained part of their achievements in terms of HbA1c and weight loss reductions at 24 months thus demonstrating the effectiveness of the intensive behavioural modification programme. There were significantly more adverse events in the DJBL group.

We were surprised to not detect a significant difference in glycemic control between the two groups. This finding is in line with the first meta-analysis on the DJBL, but contradicts the findings of the most recent meta-analysis, in which the DJBL was superior to behavioural modification both in terms of glycaemia and weight loss.[3,4] Indeed, the DJBL was originally

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conceived as a metabolic rather than an obesity intervention. An explanation of our findings could be the rapid improvements in the modern management of T2DM which has been revolutionized in the last few years. The combination of the intensive lifestyle modification with pharmacotherapy might have achieved a glucose-lowering "floor effect", thus limiting our ability to detect any additional beneficial effects of the DJBL. This combination of impactful interventions was not available when previous studies were conducted.

Participants in the DJBL group experienced statistically superior and clinically relevant improvements in cardiometabolic risk factors including blood pressure, plasma lipid concentrations, and also markers of non-alcoholic fatty liver disease. These took place whilst the device was *in situ* and then gradually dissipated after explantation.

There were more adverse events in the DJBL group with rates similar what has been reported previously.[3,4] The majority of AEs associated with the DJBL were classified as mild to moderate and occurred within the first few weeks of receiving the implant. The most common were abdominal pain and nausea. All participants made a full recovery, including those who experienced SAEs. The early explantation rate is in keeping with previous studies.[11,12] There was one case of a liver abscess in the 75 successful implantations performed (1.3%). This complication rate is similar to post-marketing surveillance data and lower than the 3.5% rate of liver abscesses that led to the discontinuation of the ENDO trial (NCT01728116) in the USA in 2015. The liver abscesses in that trial also settled without the need for surgical intervention and with no long-term sequelae. After review of the relevant safety data, the FDA and Institutional Review Board approved the new STEP-1 pivotal trial (NCT04101669) of the Endobarrier™ in the USA in February 2019. The trial is actively enrolling participants. The manufacturers have also made technical modifications and reacquisition of CE mark status in Europe and the Middle East is expected in the first half of 2020.

The strengths of this trial include its randomized design, sample size, 12 and 24 month follow-up, multidisciplinary care and delivery of a truly intensive medical intervention, and conduct across two trial sites. The main limitation is the open-label design which could be a source of bias. High-dose Liraglutide (Saxenda) and weekly GLP-1 receptor agonists were not used during the trial, the former because it not reimbursable by the National Health Service and the latter because they were not available at the time. Likewise, whilst the withdrawal rate was higher than forecast, the primary finding from the trial held robustly when testing for missing data effects.

Endoscopic interventions offer the opportunity to fill the treatment gap between medical and surgical interventions for T2DM and obesity for people who do not have access or do not wish to undergo metabolic/bariatric surgery.[13] Medical devices can also be used for people who urgently need weight loss and metabolic optimization before a life-changing procedure like an organ transplant or joint replacement surgery. Whilst the safety profile of the DJBL was similar to what has been previously reported, the rates of serious adverse events or adverse events leading to early explantation remain high in absolute terms. These will need to

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be reduced through manufacturing modifications for the device to become more acceptable to patients and competitive in the current T2DM treatment landscape.

In conclusion, this trial has demonstrated that the addition of the DJBL to an intensive medical intervention for people with T2DM and obesity results in superior weight loss, improvements in cardiometabolic risk factors and markers of fatty liver disease, but not glycaemia, compared to the intensive medical intervention alone. These differences were observed only for the 12 months the device was *in situ*. The benefits of the device need to be balanced against the rate of adverse events when making clinical decisions.

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Figure Legends

Figure 1 CONSORT Diagram

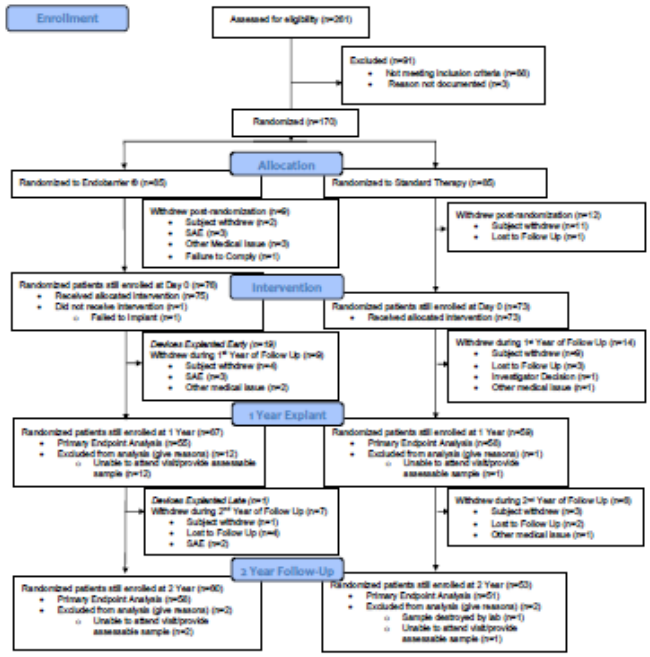

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Figure 2. Changes in Measures of Diabetes Control

* p< .05, ** p< .01, *** p< .001; P-Value is derived from testing the fixed effect for treatment group in a mixed-model analyzing absolute value at time point adjusted for fixed effect covariates; baseline, age, BMI group, site and a random effect for intercept. Data shown in plots A, C, E, F comprise of mean ± SD. DJBL = Duodenal Jejunal Bypass Liner, ALT = Alanine aminotransferase. Plot A, absolute HbA1c values by treatment group over time. B, percentage of patients taking x number of glucose-lowering medications at M0, M12 and M24 by group. C, percentage weight-change values by treatment group over time. D, proportion of patients with normal blood pressure (≤135/85) at M0, M12 and M24 by group. E, change in total cholesterol concentration values by treatment group over time. F, change in serum ALT concentration values by treatment group over time.

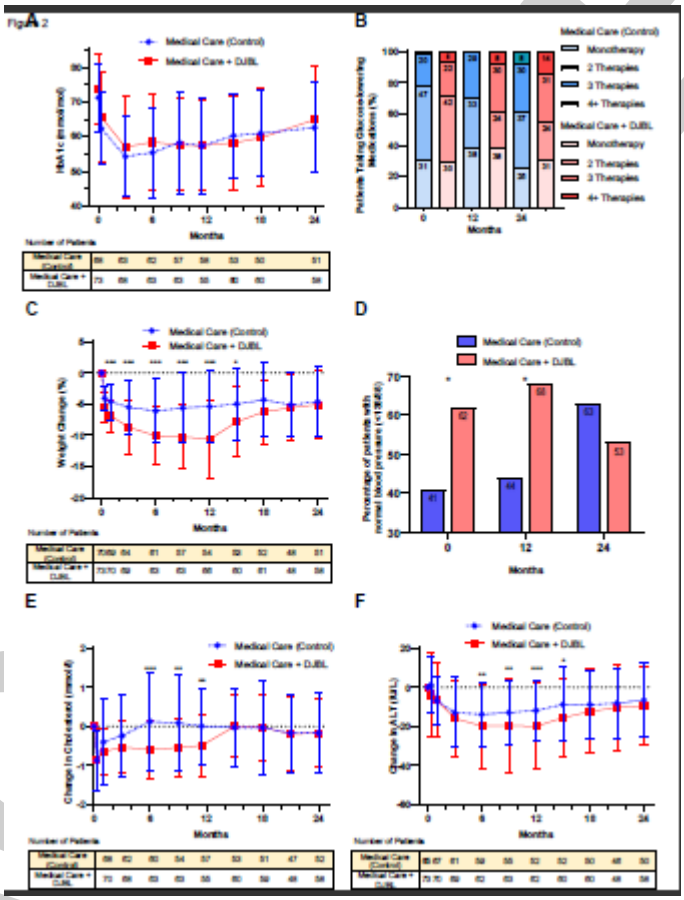

Table 1. Baseline Characteristics [a]

	DJBL [b] (N=85)	Control (N=85)
Sex		
Male	46 (54%)	46 (54%)
Female	39 (46%)	39 (46%)
Age (years)	51.6 (7.9)	51.9 (8.5)
Ethnic origin		
White	70 (82%)	62 (73%)
Black	3 (4%)	13 (15%)
Asian	11 (13%)	9 (11%)
Other	1 (1%)	1 (1%)
Weight (kg)	107.9 (17.1)	104.2 (14.9)
Waist Circumference (cm)	118.7 (12.3)	117.8 (16.0)
Body Mass Index (kg/m2)	36.8 (5.0)	35.8 (4.2)
HbA1c (mmol/mol)	73.7 (10.3)	71.2 (9.7)
HbA1c (%)	8.9 (0.9)	8.7 (0.9)
Duration of T2DM [b] (years)	7.1 (4.4)	7.8 (4.5)
Number of T2DM b control medications taken [median (IQR)]	2 (1-2)	2 (1-3)
Patients with hypertension at baseline [n (%)]	50 (59%)	53 (62%)
Systolic Blood Pressure (mmHg)	130.3 (11.6)	133.3 (15.0)
Diastolic Blood Pressure (mmHg)	82.0 (9.7)	83.5 (10.6)
Total Cholesterol (mmol/l)	4.55 (0.96)	4.42 (1.00)
High-density Lipoprotein Cholesterol (mmol/l)	1.15 (0.25)	1.15 (0.30)
Low-density Lipoprotein Cholesterol (mmol/l)	2.47 (0.85)	2.43 (0.91)
Triglycerides (mmol/l)	2.02 (1.09)	1.85 (0.82)
Aspartate Transaminase (IU/l)	28.7 (12.8)	28.0 (11.9)
Alanine Aminotransferase (IU/l)	41.1 (24.1)	37.6 (20.2)
Alkaline Phosphatase (IU/l)	87.7 (25.1)	89.6 (24.7)

[a] Baseline Values taken at Visit 3 or nearest preceding visit. Unless units are stated values are presented as mean (SD).

[b] DJBL = Duodenal Jejunal Bypass Liner; T2DM = Type 2 Diabetes Mellitus.

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Table 2. Primary and Secondary End Points at 12 and 24 months[a]

	DJBL [b]	Control	P-Value
Primary endpoint – HbA1c			
Patients who achieved reduction of 20% at 12 months	30 (54.6%)	32 (55.2%)	.85 [c]
Patients who achieved reduction of 20% at 24 months	23 (39.7%)	19 (36.5%)	.75 [c]
12-month HbA1c (mmol/mol)	57.4 (12.9)	57.3 (13.7)	.50 [d]
24-month HbA1c (mmol/mol)	64.8 (15.3)	62.6 (12.9)	.71 [d]
Secondary endpoints - HbA1c			
Patients with HbA1c < 42 mmol/mol at 12 months	6 (10.9%)	4 (6.9%)	.28 [c]
Patients with HbA1c < 42 mmol/mol at 24 months	3 (5.2%)	0 (0.0%)	N/A
Secondary endpoints - Weight			
Patients who achieved reduction of 15% at 12 months	16 (24.2%)	2 (3.7%)	.007 [c]
Patients who achieved reduction of 15% at 24 months	3 (5.2%)	1 (1.9%)	.39 [c]
12-month Weight (kg)	96.1 (16.1)	96.7 (14.4)	<.001 [d]
24-month Weight (kg)	100.7 (16.2)	98.0 (14.7)	.76 [d]
Secondary endpoints - Rates of Hypertension & Blood Pressure			
Patients who were non-hypertensive at 12 months	45 (68.2%)	24 (44.4%)	.01 [c]
Patients who were non-hypertensive at 24 months	31 (53.5%)	33 (63.5%)	.42 [c]
12-month Systolic Blood Pressure (mmHg)	123.8 (14.1)	132.7 (14.8)	.004 [d]
24-month Systolic Blood Pressure (mmHg)	130.6 (16.2)	125.7 (13.9)	.07 [d]
12-month Diastolic Blood Pressure (mmHg)	77.7 (9.3)	81.5 (9.2)	.02 [d]

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24-month Diastolic Blood Pressure (mmHg)	80.1 (9.9)	78.1 (8.4)	.21 [d]
Secondary endpoints - Diabetes Medication			
Number of medications taken at 12 months [median (IQR)]	2 (1-3)	2 (1-3)	.37 [e]
Number of medications taken at 24 months [median (IQR)]	2 (1.5-3)	2 (1-3)	.55 [e]

[a] Above figures are derived from the Intention-to-Treat Population. Unless units are stated values are presented as mean (SD).

[b] DJBL = Duodenal Jejunal Bypass Liner

[c] P-Value derived from Logistic Regression model testing value at timepoint against treatment group, adjusting for covariates Site and BMI Group

[d] P-Value is derived from testing the fixed effect for treatment group in a mixed-model analysing absolute value at timepoint adjusted for fixed effect covariates; baseline, age, BMI group, site and a random effect for intercept.

[e] P-Value derived from Regression model testing number of medications at timepoint against treatment group, adjusting for covariates Site and BMI Group

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Table 3. Fasting plasma lipid and liver function concentrations at 12 and 24 months [a]

	DJBL	Control	P-Value [b]
LIPIDS			
Total cholesterol			
12-month Cholesterol (mmol/l)	4.07 (0.95)	4.36 (0.98)	-
24-month Cholesterol (mmol/l)	4.41 (0.86)	4.19 (0.89)	-
12-month change from baseline in Cholesterol (mmol/l)	-0.49 (0.80)	0.01 (0.98)	.009
24-month change from baseline in Cholesterol (mmol/l)	-0.17 (0.89)	-0.17 (1.03)	.31
High-density lipoprotein (HDL) cholesterol			
12-month HDL (mmol/l)	1.14 (0.30)	1.29 (0.32)	-
24-month HDL (mmol/l)	1.26 (0.26)	1.21 (0.30)	-
12-month change from baseline in HDL (mmol/l)	-0.04 (0.16)	0.12 (0.24)	<.001
24-month change from baseline in HDL (mmol/l)	0.10 (0.15)	0.04 (0.22)	.04
Low-density lipoprotein (LDL) cholesterol			
12-month LDL (mmol/l)	2.23 (0.76)	2.33 (0.88)	-
24-month LDL (mmol/l)	2.40 (0.70)	2.15 (0.74)	-
12-month change from baseline in LDL (mmol/l)	-0.32 (0.62)	-0.02 (0.84)	.09
24-month change from baseline in LDL (mmol/l)	-0.15 (0.74)	-0.13 (0.82)	.30
Triglycerides			
12-month Triglycerides (mmol/l)	1.72 (0.80)	1.84 (1.53)	-
24-month Triglycerides (mmol/l)	1.62 (0.74)	1.85 (1.04)	-
12-month change from baseline in Triglycerides (mmol/l)	0.33 (1.26)	-0.13 (1.11)	.63
24-month change from baseline in Triglycerides (mmol/l)	-0.32 (1.03)	0.20 (0.72)	.32
LIVER FUNCTION TESTS			
Alkaline phosphatase (ALP)			
12-month ALP (IU/l)	89.5 (25.20)	77.8 (22.77)	-

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24-month ALP (IU/l)	82.2 (25.35)	82.1 (24.31)	-
12-month change from baseline in ALP (IU/l)	2.2 (18.95)	-11.7 (16.97)	<.001
24-month change from baseline in ALP (IU/l)	-4.5 (13.63)	-8.6 (15.53)	0.21
Alanine aminotransferase (ALT)			
12-month ALT (IU/l)	21.6 (12.49)	28.5 (11.95)	-
24-month ALT (IU/l)	30.9 (21.34)	34.7 (23.66)	-
12-month change from baseline in ALT (IU/l)	-20.0 (22.03)	-11.8 (15.72)	<.001
24-month change from baseline in ALT (IU/l)	-9.4 (20.28)	-6.5 (18.94)	0.32
Aspartate aminotransferase (AST)			
12-month AST (IU/l)	20.7 (6.85)	23.1 (7.74)	-
24-month AST (IU/l)	24.1 (10.78)	25.7 (9.27)	-
12-month change from baseline in AST (IU/l)	-9.3 (14.65)	-6.6 (9.23)	.003
24-month change from baseline in AST (IU/l)	-6.0 (12.68)	-3.4 (10.80)	.07

[a] Above figures are derived from the Intention-to-Treat Population. Unless units are stated values are presented as mean (SD)

[b] P-Value is derived from testing the fixed effect for treatment group in a mixed-model analysing absolute value at timepoint adjusted for fixed effect covariates; baseline, age, BMI group, site and a random effect for intercept.

DJBL = Duodenal Jejunal Bypass Liner

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Table 4. Serious Adverse Events [a]

Event		**DJBL** [b] **(N=85)**	**Control (N=85)**
Gastrointestinal Disorders	Abdominal Pain	9 (11%)	.
	Vomiting	4 (5%)	.
	Nausea	2 (2%)	.
Device issues	Device Malfunction	8 (9%)	.
	Device Migration	7 (8%)	.
Surgical and Medical Procedures	Cardioversion	1 (1%)	.
	Dental Operation	.	1 (1%)
	Renal Stone Removal	1 (1%)	.
	Spinal Decompression	1 (1%)	.
	Thyroidectomy	.	1 (1%)
	Vaginal Hysterectomy	1 (1%)	.
Renal and Urinary Disorders	Nephrolithiasis	1 (1%)	.
	Pyelonephritis	1 (1%)	.
	Renal Colic	1 (1%)	.
	Ureterolithiasis	1 (1%)	.
Cardiovascular Disorders	Acute Coronary Syndrome	1 (1%)	.
	Stroke	.	1 (1%)
	Ventricular Fibrillation [c]	1 (1%)	.
Investigations	Laparoscopy	1 (1%)	.
	Liver Function Test Abnormal	1 (1%)	.
	Nuclear Magnetic Resonance Imaging Abnormal	1 (1%)	.
Hepatobiliary Disorders	Acute Cholecystitis	1 (1%)	.
	Liver Abscess	1 (1%)	.
Metabolism and Nutrition Disorders	Dehydration	2 (2%)	.
Vascular Disorders	Upper Gastrointestinal Haemorrhage	2 (2%)	.
Respiratory, Thoracic and	Pneumonia	1 (1%)	.

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Mediastinal Disorders			
General Disorders and Administration Site Conditions	Surgical Failure [d]	1 (1%)	.
Infections and Infestations	Sepsis	1 (1%)	.
Musculoskeletal and Connective Tissue Disorders	Clavicle Fracture	1 (1%)	.
Nervous System Disorders	High-Grade Glioma	.	1 (1%)
Skin and Subcutaneous Tissue Disorders	Shingles	.	1 (1%)

[a] Figures are per patient with percentage in parentheses. In the event where a reported SAE contains more than one affliction both classes/terms have been counted.

[b] DJBL = Duodenal Jejunal Bypass Liner

[c] Patient had no coronary disease but severely dilated and impaired LV function. He responded well to direct current cardioversion and Amiodarone.

[d] Failed DJBL removal at planned 12-month visit. At the time of gastroscopy, food debris was present in the stomach and first part of the intestine. The device sleeve was visible in D2/D3 but the crown was completely obscured by food debris despite multiple washings and probing. It was deemed unsafe to proceed safely and so the procedure was rebooked.

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