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The effect of a duodenal-jejunal bypass liner on lipid profile and blood concentrations of long chain polyunsaturated fatty acids

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Abstract

Background and Aims: Duodenal-jejunal bypass liners (DJBLs) prevent absorption in the proximal small intestine, the site of fatty acid absorption. We sought to investigate the effects of a DJBL on blood concentrations of essential fatty acids (EFAs) and bioactive polyunsaturated fatty acids (PUFAs).

Methods: Sub-study of a multicentre, randomised, controlled trial with two treatment groups. Patients aged 18–65 years with type-2 diabetes mellitus and body mass index 30–50 kg/m^2 were randomised to receive a DJBL for 12 months or best medical therapy, diet and exercise. Whole plasma PUFA concentrations were determined at baseline, 10 days, 6 and 11.5 months; data were available for n = 70 patients per group.

Results: Weight loss was significantly greater in the DJBL group compared to controls after 11.5 months: total body weight loss 11.3 ± 5.3 % versus 6.0 ± 5.7 % (mean difference [95% CI] = 5.27 % [3.75, 6.80], p <0.001). Absolute concentrations of both EFAs, linoleic acid and α-linolenic acid, and their bioactive derivatives, arachidonic acid, eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid, were significantly lower in the DJBL group than in the control group at 6 and 11.5 months follow-up. Total serum cholesterol, LDL-cholesterol and HDL-cholesterol were also significantly lower in the DJBL group.

Conclusion: One year of DJBL therapy is associated with superior weight loss and greater reductions in total serum cholesterol and LDL-cholesterol, but also depletion of EFAs and their longer chain derivatives. DJBL therapy may need to be offset by maintaining an adequate dietary intake of PUFAs or by supplementation.

Trial Registration: ClinicalTrials.gov Identifier NCT02459561

Key words: Endobarrier, Duodenal-jejunal bypass liner, Endoscopic bariatric therapies, Obesity, Lipids, Polyunsaturated fatty acids.

Declarations

Funding

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Conflicts of interest/competing interests

AR reports personal fees from GI Dynamics during the conduct of the study. AG reports funding supported by UK Medical Research Council and Wellcome Trust outside of the submitted work. JPT received travel fees support from GI Dynamics. The remaining authors report no conflicts of interest.

Ethics approval

The trial was conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions. Local research ethics approval was granted by the Fulham Research Ethics Committee, London (Reference 14/LO/0871) on 10th July 2014.

Consent to participate

All trial participants provided informed written consent.

Consent for publication

This research contains no patient identifiable data and all datasets included in this manuscript are completely anonymised.

Availability of data and material

Information concerning the study, patent applications, processes, scientific data or other pertinent information relating to the trial are the property of Imperial College London. The data that support the findings of this study are available from the senior author, upon reasonable request.

Code availability

Not applicable

Authors' contributions

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Abbreviations used: AA: arachidonic acid; ALA: α-linolenic acid; BMI: body mass index; DHA: docosahexaenoic acid; DJBL: duodenal jejunal bypass liner; DPA: docosapentaenoic acid; EBT: Endoscopic Bariatric Therapy; EFA: essential fatty acid; EPA: eicosapentaenoic acid; EPIC FFQ: The European Prospective Investigation of Cancer Food Frequency Questionnaire; FA: fatty acid; FAME: fatty acid methyl ester; GC: gas chromatography; HDL-C: high-density lipoprotein cholesterol; LA: linoleic acid; LDL-C: low-density lipoprotein cholesterol; PPI: proton pump inhibitor; PUFA: polyunsaturated fatty acid; RYGB: Roux-en-Y gastric bypass; SD: standard deviation; T2DM: type 2 diabetes mellitus; TBWL: total body weight loss; TSC: total serum cholesterol

Introduction

Obesity is a major public health concern, with the increasing prevalence resulting in increased risk of type-2 diabetes mellitus (T2DM), cardiovascular disease and several cancers [1,2]. Obesity can be treated with lifestyle modifications, including alterations to diet and patterns of physical activity [3]. However, these modifications can be challenging to implement and many individuals find compliance difficult [4,5]. In such cases, especially with morbid obesity, gastrointestinal surgical procedures become necessary with the aim to reduce the ability of individuals to consume food and to digest and absorb macronutrients. These procedures lead to weight loss and improvement in co-morbidities, including insulin resistance, T2DM, hyperlipidaemia and cardiovascular disease [6-10]. However, these surgical procedures also carry risks of increased morbidity and mortality [11,12]. In addition, one side effect of surgical procedures that aim to reduce nutrient absorption is impaired availability of essential micronutrients [13,14].

Endoscopic bariatric therapies (EBTs) provide a minimally-invasive therapeutic option to achieve weight loss and treat obesity-related diseases by going beyond what can be achieved through medical and lifestyle interventions alone whilst limiting the potential morbidity and mortality associated with surgery. EBTs include intragastric balloons, duodenal-jejunal bypass liners (DJBLs), transoral gastroplasty procedures, and duodenal mucosal resurfacing [15-18]. The EndoBarrier DJBL (GI Dynamics Inc., Lexington, MA) is an impermeable fluoropolymer sleeve that lines the first 60 cm of the small intestine and delivers undigested chyme directly from the stomach to the jejunum (Figure 1). It therefore creates a non-surgical bypass of the foregut and replicates the bypass element of the Roux-en-y gastric bypass (RYGB). There is an increasing body of evidence to support this intervention as an effective treatment for weight loss and metabolic disease [16,19-23].

158 The proximal small intestine is the site of absorption of dietary fatty acids. The two
159 essential fatty acids (EFAs), linoleic acid (LA; 18:2n-6) and α-linolenic acid (ALA; 18:3n-3),
160 cannot be synthesised in humans but have essential physiological functions and so obtaining
161 them from the diet is vital [24]. LA and ALA are also converted in the body to other bioactive
162 polyunsaturated fatty acids (PUFAs), including arachidonic acid (AA; 20:4n-6) and
163 eicosapentaenoic acid (EPA; 20:5n-3), docosapentaenoic acid (DPA; 22:5n-3) and
164 docosahexaenoic acid (DHA; 22:6n-3) respectively. These PUFAs have important roles in
165 controlling physiological and metabolic functions and may be obtained from the diet or be
166 synthesised endogenously from their EFA precursors [24-28]. Impaired absorption in the
167 proximal small intestine as a result of DJBL therapy could limit the availability of EFAs and
168 their longer chain derivatives present in the diet and also reduce endogenous production of AA,
169 EPA DPA and DHA due to decreased availability of substrate EFAs. This could be
170 compounded by insulin resistance in obese subjects as insulin resistance also results in
171 alterations in endogenous fatty acid metabolism [29]. Specifically, it has been demonstrated
172 that there is attenuated delta-5 and delta-6 desaturase and elongase activity in insulin resistant
173 states, resulting in lower concentrations of AA, EPA and DHA when compared to controls
174 [30,31]. This would make dietary sources of these longer chain PUFAs even more important.
175 Since essential nutrient deficiency following malabsorptive bariatric operations is common
176 [13,14], we sought to investigate the effects of DJBL therapy on circulating concentrations of
177 EFAs and other bioactive PUFAs. We hypothesised that circulating concentrations of these
178 fatty acids would be lower after DJBL treatment than following an alternative weight loss
179 intervention that did not involve restricting nutrient absorption.
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Patients and Methods

Patients and study design

This sub-study was conducted using participants recruited into the EndoBarrier trial (ClinicalTrials.gov Identifier NCT02459561). The trial methodology is fully described elsewhere [32]. The study is a multicentre, randomised, controlled, non-blinded trial with two treatment arms. 170 male and female patients, aged 18–65 years with a BMI 30–50 kg/m^2 and a confirmed diagnosis of T2DM for at least 1 year, who had inadequate glycaemic control and were on oral anti-hyperglycaemic medications, were randomised at a ratio of 1:1 to receive either a DJBL for 12 months or best medical therapy, diet and exercise. Participants were recruited equally across two investigational sites in the United Kingdom: Imperial College Healthcare NHS Trust in London and University Hospital Southampton NHS Foundation Trust. The overall schema for the trial is summarised in Figures 2 and 3.

The primary objective of the trial was to compare the EndoBarrier® with conventional medical therapy, diet and exercise for obesity-related T2DM and their effectiveness on metabolic state as defined by the International Diabetes Federation as a HbA1c reduction of 20% [33]. This primary outcome is reported elsewhere (manuscript submitted).

The trial was conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions. Local research ethics approval was granted by the Fulham Research Ethics Committee, London (Reference 14/LO/0871) on 10th July 2014. All subjects provided informed written consent. The trial was sponsored by Imperial College London.

EndoBarrier duodenal-jejunal bypass liner

At visit 4 (0 weeks), participants who had been randomised to receive the EndoBarrier device had it endoscopically implanted under a general anaesthetic. The nickel titanium alloy anchor was deployed in the first part of the duodenum and the 60 cm impermeable, highly-flexible

fluoropolymer sleeve was unfurled under fluoroscopic guidance. The implant is open at both ends to allow for passage of undigested chyme from the stomach into the mid-jejunum and prohibits nutrient absorption along its length by creating a barrier between the partially digested food and the absorptive surface of the small intestine. The Endobarrier was implanted for 12 months but is completely reversible and so could be removed at any time. If relevant, subjects had their dose of sulphonylurea medication reduced by 50% at the time of EndoBarrier implant to avoid potential hypoglycaemic episodes and all patients in the Endobarrier group were prescribed a proton pump inhibitor (PPI; Omeprazole 40 mg twice daily). Control group participants did not routinely receive a PPI. The device was removed at visit 11 (12 months) under sedation or general anaesthetic and participants were followed up for a further 12 months.

Liquid diet

To avoid disruption of the device in the immediate period following implantation, all patients across both groups were prescribed a liquid diet for the 7 days before and 13 days after the intervention visit (visit 4). The liquid diet was guided by a specialist dietitian and comprised of 125 ml Fortisip Compact drinks (Nutricia, UK): 5 per day for males, 4 per day for females, containing per 100 mL: 240 kcal, 9.6 g protein (16% total energy), 29.7 g carbohydrate (49% total energy), 15 g sugars, 9.3 g fat (35% total energy; 2.7 g of PUFAs). Patients were also allowed to consume sugar-free squashes, smooth/clear soup (1 medium bowl per day), tea or coffee without sugar, or unsweetened puree.

Dietary counselling and physical activity

All patients were regularly reviewed by a specialist dietitian and participants in the control arm of the trial had an additional review by the dietitian in place of the DJBL implantation and removal. Participants were recommended to consume between 1200 and 1500 kcal each day

for women and between 1500 and 1800 kcal for men. In accordance with standard dietary practice, participants were advised: to eat 5 meals per day; to control their portion sizes and intake of carbohydrates/starchy foods; to increase their intake of low glycaemic index and high protein foods, as well as vegetables; and to reduce their intake of alcohol and of foods high in fat and sugar. Participants were advised to include 150 minutes per week of moderate intensity and 75 minutes per week of vigorous intensity aerobic activity and muscle strengthening activities on more than 2 days a week.

Outcome measurements

At visits 3 (-2 weeks ± 7 days), 5 (+ 10 days ± 7 days), 8 (+ 6 months ± 7 days) and 10 (+ 11.5 months ± 7 days) fasted whole blood samples were collected from all participants for the measurement of plasma concentrations of PUFAs and serum lipids. Total lipids were extracted from plasma using chloroform:methanol (2:1) in accordance with the methods of Folch et al. [34]. Fatty acid methyl esters (FAMEs) were prepared by incubating the purified lipid fraction with methanol with 2% (vol:vol) H_2SO_4 as a methylation reagent at 50ºC for 2 hours. FAMEs were separated by gas chromatography (GC) on a Hewlett-Packard 6890 GC using a SGE BPX-70 fused silica capillary column (30 m x 0.25 µm x 0.25 µm) with temperature control and a flame ionising detector [35]. Split ratio was programmed at 25:1. The injector port was set at 300°C with a helium carrier gas (flow rate 1.0, pressure 14.6 and velocity 29). To separate FAMEs, the oven was held at 115°C for 2 minutes, then increased by 10°C min^{-1} up to 200°C, where it was then held for 18.5 min. For the next cycle, temperature was increased at a rate of 60°C min^{-1} up to 245°C, where it was held for 4 min. The flame ionisation detector was held at 300°C. FAME chromatograms were analysed with Agilent Chemstation software. Peaks from each fatty acid were identified automatically and, following peak integration, the area under each peak was calculated and compared to internal standards in order to quantify absolute

fatty acid concentrations (µg/ml). Absolute concentrations of EFAs (LA and ALA) and their n-3 (EPA, DPA, and DHA) and n-6 (AA) derivatives were recorded. Serum triglyceride, total serum cholesterol (TSC) and HDL-C concentrations were measured using an automated lipid profile analyser (AU5800: Beckman Coulter, High Wycombe, UK). LDL-C concentrations were then extrapolated from these measurements. Units are expressed as mmol/L.

Height (cm) and weight (kg) were recorded at each study visit and BMI (= weight (kg)/(height (m))^2), Total Body Weight Loss (TBWL, kg), %TBWL (Total Body Weight Loss (%) = (TBWL (kg)/baseline weight (kg)) x 100) were extrapolated.

Participants who provided additional consent to take part in the "Food Preference" sub-group of the trial (sub-group 3) were asked to complete The European Prospective Investigation of Cancer Food Frequency Questionnaire (EPIC FFQ) and a trained dietitian performed a detailed 24-hour dietary recall assessment [36]. Furthermore, participants were asked to complete a food diary, detailing all food and drink consumed in the 72 hours immediately prior to the study visit. Information gathered from food diaries and the 24-hour dietary recall were entered and analysed using Dietplan7 software (Forestfield Software Ltd, UK) to obtain total calories (kcal) and macronutrients (carbohydrates, protein, and fat). Macronutrients are expressed as the percentage contribution to total calories per day. Data obtained from the EPIC FFQ were evaluated using the FETA system to quantify total calorific and macronutrient intake.

Statistical analysis

This paper reports secondary outcomes from a randomised controlled trial and, as such, no formal power calculation was performed for these outcomes. The trial was powered according to the primary outcome of a reduction in HbA1c concentration of 20% at 12 months. It was estimated that 15% of patients in the control arm and 35% of the DJBL group would achieve

this outcome [37,38]. 73 patients per group would give 80% power to detect this as a significant effect. Adding 10% loss of follow-up increased the sample size to 80 per group. Analysis of anthropometric, nutritional, serum lipid and fatty acid data were undertaken using a mixed-model approach. Fatty acid data were logarithmically transformed (base 10) prior to analysis. Within the model, treatment group, visit and the corresponding interaction term were specified as fixed effect with a random effect specified per subject for the intercept. To assess for differences within and between groups, post-hoc pairwise comparisons were undertaken on the estimated marginal means (EMM) at each visit. Adjustments for multiple testing were based on Least Significant Differences (LSDs). No further adjustments for missing data were undertaken outside of the default used within the mixed-model. Analysis was performed using SPSS® 25.0 software (SPSS, Chicago, IL, USA).

Results

The primary and secondary outcomes for the Endobarrier randomised controlled trial are fully reported elsewhere (manuscript submitted).

Patient characteristics and baseline data

Figure 4 summarises the flow of participants that were included in fatty acid sub-group analysis. Missing or insufficient plasma samples account for unavailable data. For the purposes of fatty acid analysis, visit 3 (i.e. pre-intervention) served as the baseline visit and the patient characteristics of each study arm are summarised in Table 1. In total, data were analysed from 70 participants in each arm of the trial; they were matched with regard to age, sex and weight. An investigative independent samples t-test produced a significant difference in BMI between the groups at baseline ($p = 0.033$).

306 ***Anthropometric outcomes***

307 Anthropometric outcomes are summarised in Table 1. Weight loss significantly increased in
308 both groups up until 6 months and then plateaued. TBWL was significantly greater in the
309 Endobarrier group compared to the control group at all time points: 10 days = 5.7 ± 2.5 %
310 versus 4.3 ± 1.7 % (mean difference [95% CI] = 1.42 % [0.02, 2.82], p = 0.047), 6 months =
311 10.4 ± 4.4 % versus 6.1 ± 5.1 % (4.35 % [2.88, 5.82], p <0.001) and 11.5 months = 11.3 ± 5.3
312 % versus 6.0 ± 5.7 % (5.27 % [3.75, 6.80], p <0.001).

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Parameter	Control Group				Endobarrier DJBL Group			
	Baseline n= 70	**+ 10 days n = 70**	**+ 6 months n = 62**	**+11.5 months n = 59**	**Baseline n = 70**	**+ 10 days n = 70**	**+ 6 months n = 61**	**+11.5 months n = 52**
Age, years	52.3 ± 8.3	-	-	-	51.6 ± 7.8	-	-	-
Sex, female (%)	31 (44.3)	-	-	-	32 (45.7)	-	-	-
Weight, kg	103.6 ± 13.9	99.2 ± 13.3*	97.8 ± 14.7*φ	97.2 ± 14.6*φ	107.8 ± 17.1	101.7 ± 16.8*	96.2 ± 16.7*§	94.9 ± 14.9*§
BMI, kg/m^2	35.4 ± 3.7†	33.9 ± 3.7*	33.3 ± 4.0*φ	33.2 ± 4.0*φ	37.0 ± 5.0†	34.9 ± 5.0*	33.3 ± 5.0*§	32.7 ± 4.3*§
TBWL, kg	-	4.4 ± 1.9†	6.3 ± 5.4φΔ	6.2 ± 6.3φΔ	-	6.1 ± 2.8†	11.1 ± 5.2§Δ	12.2 ± 6.6§Δ
TBWL, %	-	4.3 ± 1.7†	6.1 ± 5.1φΔ	6.0 ± 5.7φΔ	-	5.7 ± 2.5†	10.4 ± 4.4§Δ	11.3 ± 5.3§Δ
Triglycerides, mmol/L	1.95 ± 0.85	1.48 ± 0.59*	1.69 ± 0.95**	1.86 ± 1.52φ	2.01 ± 1.14	1.68 ± 0.66**	1.56 ± 0.64*	1.71 ± 0.79 **
Total cholesterol, mmol/L	4.50 ± 1.04	3.60 ± 1.07*	4.53 ± 1.36§†	4.36 ± 0.96§†	4.55 ± 0.93	3.73 ± 1.10*	3.99 ± 0.89*†	4.10 ± 0.96*φ†
LDL-C, mmol/L	2.45 ± 0.94	1.82 ± 0.95*	2.44 ± 1.00§†	2.32 ± 0.88§	2.49 ± 0.86	1.96 ± 0.97*	2.19 ± 0.71*α†	2.25 ± 0.76**α
HDL-C, mmol/L	1.16 ± 0.31	1.12 ± 0.25**	1.29 ± 0.32*§†	1.29 ± 0.32*§†	1.16 ± 0.27	1.03 ± 0.26*	1.16 ± 0.29§†	1.15 ± 0.30§†
Total cholesterol:HDL-C	4.08 ± 1.22	3.32 ± 1.12*†	3.64 ± 1.13*§	3.54 ± 1.00*α	4.07 ± 1.13	3.74 ± 1.27**†	3.55 ± 0.83*α	3.70 ± 0.90*
α-Linolenic acid (ALA; 18:3n-3), µg/ml	14.9 (11.5 - 22.0)	11.5 (8.0 - 15.0)*	13.1 (9.0 – 19.9)**α†	12.5 (10.2 – 19.2)α†	13.8 (11.0 – 19.8)	10.9 (8.0 – 13.5)*	11.1 (15.2 – 9.0)*†	12.4 (8.5 – 16.5)*α†
Eicosapentaenoic acid (EPA; 20:5n-3), µg/ml	17.4 (12.8 – 26.0)	9.3 (6.4 – 13.6)*	18.5 (12.6 – 24.7)§Δ	19.1 (12.9 – 23.1)§†	17.3 (11.6 – 25.7)	8.1 (5.9–12.7)*	14.2 (9.7 – 19.3)*§Δ	14.4 (10.4 – 20.4)*§†
Docosapentaenoic acid (DPA; 22:5n-3), µg/ml	11.5 (9.3 – 15.4)	8.3 (7.1 – 10.7)*	10.8 (8.9 – 14.7)§†	11.7 (9.6 – 14.4)§†	11.5 (8.9 – 15.2)	8.5 (6.4 – 10.7)*	9.7 (6.8 – 11.9)*α†	9.9 (7.6 – 13.3)*§†
Docosahexaenoic acid (DHA; 22:6n-3), µg/ml	40.9 (30.3 – 53.0)	33.6 (27.4 - 41.5)*	41.4 (30.4 – 49.4)§†	42.6 (31.7 – 50.7)§†	36.3 (26.2 – 48.3)	30.3 (23.2 – 38.3)*	31.7 (26.2 – 44.6)**†	34.1 (26.3 – 40.5)**†
Linoleic acid (LA; 18:2n-6), µg/ml	500.5 (406.0 – 615.6)	397.5 (303.4 – 509.8)*	485.1 (407.0 – 591.8)§†	489.9 (392.1 – 603.5)§	567.9 (432.1 – 654.5)	389.1 (295.1 – 515.6)*	429.7 (345.6 – 502.6)*α†	470.4 (354.8 – 558.5)*§
Arachidonic acid (AA; 20:4n-6), µg/ml	149.8 (129.3 – 189.8)	136.6 (115.7 – 165.0)*	148.2 (134.6 – 188.5)§†	159.9 (128.6 – 188.8)§†	146.8 (113.9 – 187.5)	131.4 (110.0 – 160.5)*	134.9 (104.8 – 161.5)*†	151.9 (111.7 – 174.6)**α†

Data presented as mean ± SD except for fatty acid data which is represented as median (IQR). Mixed model analysis performed on Log10 transformed data.

* denotes $p < 0.001$ compared to baseline within the same group, ** denotes $p < 0.05$ compared to baseline within the same group, § denotes $p < 0.001$ compared to 10 days within the same group, α denotes $p < 0.05$ compared to 10 days within the same group, φ denotes $p < 0.05$ compared to 6 months within the same group, † denotes $p < 0.05$ between groups, Δ denotes $p < 0.001$ between groups.

BMI, body mass index; DJBL, duodenal-jejunal bypass liner; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; kg, kilograms; LDL-C, low-density lipoprotein cholesterol; TBWL, total body weight loss.

Table 1 Participant characteristics/data in control and DJBL groups at baseline and during the course of the study.

Serum lipid concentrations

Serum lipid concentrations are summarised in Table 1. Serum triglyceride concentrations significantly decreased in both groups but there were no statistically significant differences between treatment groups at any of the follow-up visits. TSC concentrations were significantly decreased in the Endobarrier group at 10 days and then increased again but remained significantly lower than baseline levels at 11.5 months follow-up. In the control group, levels significantly decreased by 10 days and then increased back up to baseline levels by the 6 months follow-up visit. TSC concentrations were significantly lower in the Endobarrier group compared to the control group at 6 months (3.99 ± 0.89 mmol/L versus 4.53 ± 1.36 mmol/L; mean difference [95% CI] = 0.64 [0.28, 0.99], p = 0.001) and 11.5 months (4.10 ± 0.96 mmol/L versus 4.36 ± 0.96 mmol/L; mean difference [95% CI] = 0.40 [0.03, 0.76], p = 0.035). LDL-C concentrations followed the same trend as TSC in both study groups. LDL-C concentrations were significantly lower in the Endobarrier group compared to the control group at 6 months (2.19 ± 0.71 mmol/L versus 2.44 ± 1.00 mmol/L; mean difference [95% CI] = 0.34 [0.03, 0.65], p = 0.031) but no difference was seen between groups at 11.5 months. HDL-C concentrations were significantly decreased in the Endobarrier group at 10 days and then returned to baseline levels by 6 months and were maintained at 11.5 months follow-up. In the control group, HDL-C concentrations were also significantly decreased by 10 days but then increased to be significantly greater than baseline levels by 6 months follow-up and were maintained at 11.5 months. HDL-C concentrations were significantly higher in the control group than in the Endobarrier group at 6 months (1.16 ± 0.29 mmol/L versus 1.29 ± 0.32 mmol/L; mean difference [95% CI] = 0.13 [0.03, 0.23], p = 0.008) and 11.5 months (1.15 ± 0.30 mmol/L versus 1.29 ± 0.32 mmol/L; mean difference [95% CI] = 0.14 [0.05, 0.24], p = 0.004). The total cholesterol:HDL-C ratio

improved significantly in both treatment arms but there were no significant differences between groups at 6 months or 11.5 months.

Changes in long chain PUFA concentrations

Changes in plasma PUFA concentrations in the control and Endobarrier arms of the trial are summarised in Table 1 and Figure 5.

Essential fatty acids: ALA and LA

EFA concentrations decreased significantly between the baseline visit and 10 days follow-up visit in both treatment groups (i.e. following the intervention and calorie-controlled liquid-diet phase of the trial). There were no significant differences between groups at either of these visits. In the control group, ALA and LA concentrations significantly increased between 10 days and 11.5 months back to baseline levels. In the Endobarrier group, concentrations also increased but remained significantly lower than baseline levels at the 11.5 months follow-up visit. ALA concentrations were significantly lower in the Endobarrier group than in the control group at both 6 and 11.5 months. Similarly, LA concentrations were also significantly lower in the Endobarrier group at 6 months but were not significantly different to the control group at 11.5 months.

Long chain PUFA derivatives: AA, EPA, DPA and DHA

As seen with the essential fatty acids, concentrations of AA, EPA, DPA and DHA decreased significantly between the baseline visit and 10 days follow-up visit in both treatment groups and were not significantly different between groups. In the control group, all of these PUFAs returned to baseline levels by 6 months and remained stable at 11.5 months follow-up. In the Endobarrier group, concentrations of these PUFAs also increased between 10 days and 6 months but then plateaued and remained significantly lower than baseline levels at 11.5

369 months. AA, EPA, DPA and DHA concentrations were all significantly lower in participants
370 with the Endobarrier when compared to controls at 6 and 11.5 months.

Nutritional assessment outcomes

Nutritional assessment outcomes are summarised in supplementary Tables 1 – 5. Forty-seven participants took part in this food preference sub-group of the trial. Total caloric intake per day obtained from the EPIC FFQ, 24-hour dietary recall and 3-day food diaries was significantly reduced within both groups at all-time points compared to baseline, but there were no significant differences between the groups. There was a significant reduction in the % contribution from carbohydrates and a significant increase in the % contribution from protein to daily caloric intake within both groups. However, there were no significant differences between the groups. There was no significant reduction in the % contribution from fat either within or between groups.

As assessed by EPIC FFQ, there was a significant reduction in the consumption of carbohydrates within the Endobarrier group at all-time points compared to baseline. There was a significant reduction in the consumption of fat within the Endobarrier group at all-time points compared to baseline, and at one year in the control group. At 12 months, consumption of fats and oils was significantly greater in the Endobarrier group than in the control group. There was a significant reduction in the consumption of nuts and seeds within the Endobarrier group at 6 months only, but not in the control group. There was also a significant reduction in the consumption of meat and meat products within the Endobarrier group at 11.5 months compared to baseline, but not in the control group. The following food groups were not significantly different between groups or within groups at any time point: protein, alcohol, cereal and cereal products, eggs and eggs dishes, fish and fish products, fruit, milk and milk products, non-alcoholic beverages, potatoes, soups and sauces, sugars; preserves and snacks, and vegetables.

Discussion

In this study cohort, treatment with the Endobarrier DJBL alongside intensive medical therapy resulted in significantly greater weight loss than in patients treated with best medical therapy and dietary interventions alone with a %TBWL of 11.3% and 6.0% achieved in each group respectively after 11.5 months. This finding

is in keeping with the best available systematic review and meta-analysis in the field and other published literature on the Endobarrier device [19,21,23,39-43]. In the food-preference sub-group of patients, we were able to demonstrate that there were no significant differences in caloric intake between study arms and, beyond the baseline visit, food preferences and calorific intake were matched between groups except for a significantly greater intake of fats and oils in the Endobarrier group at 12 months when compared to the control group. We can therefore reasonably assume that weight loss is achieved through mechanisms, not yet fully understood, which go beyond calorie restriction alone.

In line with weight-loss, we have also been able to demonstrate positive changes in the blood lipid profile of those patients implanted with the Endobarrier device for 11.5 months compared to control subjects. Notably, total TSC was significantly lower in the Endobarrier group after 11.5 months and LDL-C concentrations were significantly lower at 6 months, but this difference was not maintained at 11.5 months. Although triglyceride concentrations and TSC:HDL-C ratios were significantly decreased in both groups, there were no significant differences between groups. Again, these findings match the best available literature, which supports overall reductions in TSC and LDL-C concentrations with variable reports of changes in triglyceride concentrations. In this study, HDL-C concentrations were unchanged in the Endobarrier group at 1 year follow-up, which also agrees with outcomes reported elsewhere [19,21,42,44-47]. In the control group, however, HDL-C concentrations significantly increased to above baseline levels that were statistically higher than in the Endobarrier group. This is a unique finding which cannot be explained by the weight loss or nutritional assessment outcomes in the current study.

This is the first study to report on the effect of an endoscopic bariatric therapy on fatty acid concentrations. Common to both study groups is that calorie restriction with a liquid diet for 20 days resulted in a significant decrease in all measured PUFA concentrations. Following this period, patients resumed *ad libitum* eating and thereafter there were no significant differences in dietary habits between treatment arms, except for a greater intake of fats and oils in the Endobarrier group, as evaluated from food diaries, 24-hour dietary recall and the EPIC food frequency questionnaire. Correspondingly, between 10 days and 11.5 months,

all PUFA concentrations trended upwards in both groups, most likely as dietary fat intake increased. However, PUFA concentrations were significantly lower in the Endobarrier group at 6 and 11.5 months follow-up when compared to control patients, except LA for which there was no difference at 11.5 months. This difference between groups possibly reflects impairment of absorption of fatty acids from the diet. There was also an observed reduction in the EPA:AA ratio in the Endobarrier group (0.12 at baseline vs 0.09 at 11.5 months), which remained unchanged in the control group (0.12 vs 0.12). This data therefore supports the notion that the Endobarrier device depletes absolute plasma concentrations of EFAs and their PUFA derivatives. Lower EFAs could result from reduced dietary intake and/or reduced absorption. For the longer chain derivative PUFAs there could be reduced dietary intake, reduced absorption or reduced endogenous synthesis because of less availability of the EFA substrates.

It is well documented that RYGB and other bariatric operations result in significant changes in FA pool concentrations [29,31,48-51]. These reports, however, do conflict with respect to the changes observed. Our findings match those studies that report an overall decrease in serum or plasma long chain PUFAs following weight-loss surgery [31,48,50]. This is possibly a consequence of reduced dietary intake coupled with increased liberation from adipose stores and increased fatty acid oxidation during significant weight loss [31,49]. Furthermore, it has been observed that fat malabsorption occurs with biliopancreatic limb lengths of 150 cm or less [52,53]. Although fat absorption was not formally measured in the current study, bypass of the duodenum with the Endobarrier is analogous with a 60 cm bypass and we can assume that fat malabsorption likely contributes to the observed changes in fatty acid concentrations. This is supported by the observation that patients undergoing laparoscopic sleeve gastrectomy, in which there is no bypass of the small intestine, have less profound and sustained changes in fatty acid concentrations when compared to bypass procedures [31]. Garla et al. [48] also propose that decreased intestinal expression of the fatty acid desaturase-1 (FADS1) gene, which encodes the delta-5 desaturates enzyme, may also be responsible, in part, for the observed reduction in EPA.

Several studies have reported on proportional changes in PUFAs (as opposed to absolute concentrations as reported in the current study) and observed that, although absolute concentrations of these fatty acids decreased, relative proportions were actually increased following metabolic surgery, thus creating a more favourable lipid profile [29,48,51]. In the study by Walle et al., however, subjects were instructed to consume 3 teaspoons of rapeseed oil and 6 tea spoons of mainly rapeseed oil based spreads daily for at least 1–2 years after their weight loss operation and were instructed to consume fish 2–3 times a week. Rapeseed oil is a source of ALA and fish is a source of EPA, DPA and DHA. It is therefore unclear whether the observed changes are as a result of increased dietary intake following surgery or occurred due to enhanced elongase and desaturase activity secondary to weight loss [29].

In view of the mounting evidence that very long chain n-3 PUFAs have an essential protective role against cardiovascular and cerebrovascular disease it seems prudent to identify whether or not participants undergoing metabolic procedures, such as Endobarrier implantation, are at risk of fatty acid deficiency [54,55]. The findings of the current study, and from others involving metabolic surgery, suggest that these patients are indeed at risk of low concentrations of EFAs and bioactive longer chain PUFAs. These PUFAs have roles in regulating blood lipid concentrations, cardiac function, inflammation, thrombosis and many other systems [23-27]. Thus, lowered concentrations of long chain PUFAs could adversely affect these systems resulting in poor long term outcomes. The lowered PUFA concentrations could be offset by maintaining an adequate dietary intake of n-3 PUFAs or by supplementing the diet. Given the findings in this study that absolute concentrations of n-3 and n-6 PUFAs decline following Endobarrier implantation, dietary supplementation may need to be considered. Of note, n-3 PUFA supplementation prior to metabolic surgery has been examined in one randomised controlled trial and resulted in greater perioperative weight loss and reduced post-operative pain and C-reactive protein levels [56].

Unlike RYGB, the Endobarrier is a temporary measure and implantation is currently limited to 12 months. Literature on the Endobarrier to date suggests that there is weight regain following explantation of the device but several studies have reported sustained weight loss up to one year after explant [57,58]. It can

be postulated, given the general increase in absolute PUFA concentrations observed in this study beyond the end of the initial calorie restriction, that the reductions in PUFA concentrations are unlikely to be maintained following explantation, but this is unknown.

The current study is a well-powered, randomised controlled trial in which we have provided the first convincing evidence that duodenal bypass with the Endobarrier DJBL results in significant reductions in plasma concentrations of important long chain PUFAs when compared to dietary modification and lifestyle advice alone. However, we recognise some important limitations to this study, including the lack of healthy weight controls as a comparator and also the lack of correlation of our findings with quantitative measurements of fat absorption or gene expression (e.g. desaturase genes). We have also limited our examination to PUFAs in the plasma and further examination of the effect of EBTs on fatty acid metabolism should look at other fatty acid pools and correlations with other potential confounding factors, such as changes in lipid lowering medications. Finally, fatty acid analysis was limited to only the implant period and the change to plasma PUFA concentrations following removal of the device remains unknown.

In conclusion, 11.5 months of therapy with the Endobarrier DJBL in patients with obesity and type-2 diabetes mellitus resulted in superior weight loss and significantly greater reductions in total serum cholesterol and LDL-C concentrations when compared to dietary modification and lifestyle advice alone. Furthermore, absolute plasma concentrations of EFAs and their long chain PUFA derivatives were significantly lower in those subjects receiving 11.5 months of Endobarrier therapy. In view of this, maintaining an adequate dietary intake of n-3 and n-6 PUFAs or supplementing the diet should be considered in these patients.

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Figure legends

Figure 1 EndoBarrier duodenal-jejunal bypass liner

Figure 2 Study interventions and follow-up schedule (- 4 weeks to + 12 months)

Figure 3 Study interventions and follow-up schedule (+ 13.5 months to + 24 months)

Figure 4 Consort flow chart of participants included in the fatty acid analysis. FA, fatty acid

Figure 5 Long chain PUFA concentrations in Endobarrier and Control group participants. * denotes $p < 0.05$ compared to baseline within the same group, § denotes $p < 0.05$ compared to 10 days within the same group, Δ denotes $p < 0.05$ between groups