

Effect of the EndoBarrier Gastrointestinal Liner on obesity and type 2 diabetes: protocol for systematic review and meta-analysis of clinical studies

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ABSTRACT

Introduction: Obese patients with type 2 diabetes undergoing bariatric surgery experience significant and lasting weight loss and improved glycaemic control. However, bariatric surgical procedures such as Roux-en-Y gastric bypass are irreversible and associated with considerable short-term and long-term risks. The EndoBarrier Gastrointestinal Liner or duodenal-jejunal bypass sleeve (DJBS) is a fully reversible procedure that has been developed to treat obesity and type 2 diabetes. We aim to perform a systematic review and meta-analysis of safety and efficacy of DJBS.

Methods and analyses: A systematic review with meta-analysis (as per the preferred reporting items for systematic reviews and meta-analyses) of randomised controlled trials of the device (vs no intervention, sham and/or low-calorie diet) will be performed. Primary endpoints include change in body weight and glycated haemoglobin and safety. Secondary endpoints constitute changes in other glycaemic parameters and blood lipids and the proportion of patients discontinuing antidiabetic medication. MEDLINE, EMBASE, The Cochrane Library and Science Citation Index will be sought electronically along with manual searches. The primary meta-analysis will use random effects models due to an expected intertrial heterogeneity. Fixed effect meta-analysis will be executed to assess the impact of small trials. Dichotomous data will be analysed using risk difference and continuous data using weighted mean differences, both with 95% CIs.

Ethics and dissemination: The study will describe the impact of DJBS on obesity and type 2 diabetes and possibly contribute to clinical decision-making. The results of this study will be disseminated by peer-reviewed publication and scientific presentations.

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INTRODUCTION

Lack of physical exercise and excess nutrient intake constitute important factors leading to

ARTICLE SUMMARY

Strength and limitations of this study

- Our group has great experience in conducting a systematic review with meta-analysis.
- This study may help guide clinical decision-making and procure better treatment of obesity and type 2 diabetes.
- Small studies with high heterogeneity and varying quality may be this study's limitation.

obesity and overweight. Worldwide, more than 1.4 billion adults (≥ 20 years old) are overweight with a body mass index (BMI) ≥ 25 kg/m². Of these, approximately 500 million adults are obese (BMI ≥ 30 kg/m²). WHO estimates that the number of obese persons has doubled since 1980.¹ Overweight and obesity are risk factors that increase the risk of cardiovascular disease, musculoskeletal disorders, cancer, type 2 diabetes and premature death. Dietary treatments are ineffective in the long-term treatment of overweight and obesity and the current antiobesity medications are few and largely ineffective.² In contrast, bariatric surgery has proven effective—also in the longer term—and leads to an improved glucose homeostasis. Patients with type 2 diabetes undergoing bariatric surgery experience improved glycaemic control or remission of diabetes, reducing or even eliminating their need for medication.³

Current clinical practice—the bariatric surgical procedure Roux-en-Y gastric bypass

Interestingly, rerouting of nutrient flow through the gastrointestinal tract (bypassing the proximal small intestine) following the surgical bariatric procedure Roux-en-Y gastric bypass (RYGB) has been shown to dramatically improve glucose metabolism within a few days—prior to any weight loss occurrence—among obese patients with type

2 diabetes. Depending on the definition of remission, remission rates of 40%⁴ to 80%² have been reported. The predominant hypotheses on the physiological background for the metabolic advantages after bariatric surgery include the changed release of gastrointestinal hormones (increased secretion of hormones with anti-diabetic and/or antiobesity properties, eg, glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) and reduced secretion of 'diabetogenic' hormones, for example, glucose-dependent insulinotropic peptide (GIP) combined with surgery-induced restriction of food intake. Despite the short-term and long-term benefits RYGB provides for obese patients with type 2 diabetes, the procedure—like most other bariatric surgical procedures—is invasive, irreversible and potentially lethal. In a meta-analysis from 2004, Buchwald *et al*² report a 30-day mortality after gastric banding, RYGB and biliopancreatic diversion of 0.1%, 0.5% and 1.1%, respectively. The most frequent short-term causes of mortality after RYGB are venous thromboembolism and cardiorespiratory disease.⁵ Additionally, several short-term and long-term complications are associated with the procedures including anastomotic leaks, bleeding, infections, small-bowel obstruction, hernias, dumping syndrome and malabsorption of micronutrients and macronutrients.^{5 6} Finding a less invasive bariatric procedure to treat obesity and type 2 diabetes would be of great interest not only for the patients but also for the society in general. The minimally invasive and fully reversible duodenal-jejunal bypass sleeve (DJBS) may represent an alternative to the most commonly used bariatric techniques. With this protocol, we intend to investigate the efficacy and safety of DJBS.

Description of the intervention

The EndoBarrier Gastrointestinal Liner (a polymer DJBS) consists of a nickel–titanium anchor and a 60 cm impermeable sleeve made of fluoropolymer (figure 1). The device, which is open at both ends, is endoscopically placed in the duodenum through an over-the-wire system. The anchor is fixed to the intestinal wall within the duodenal bulb by small barbs grasping the intestinal mucosa.⁷ Ingested nutrients pass down to the stomach and onwards directly and mostly undigested into the sleeve. The pancreatic and bile juices pass naturally into the intestinal tract, flowing down between the sleeve and the intestinal wall. They mix together with the

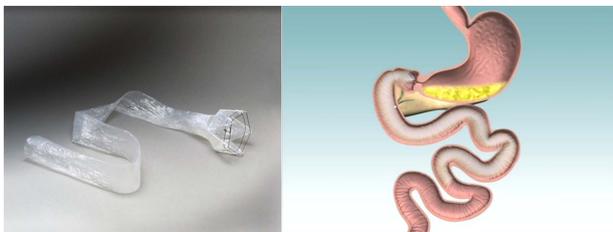


Figure 1 The EndoBarrier Gastrointestinal Liner (left)—and in situ (right, animated).

undigested nutrients at the distal end of the DJBS, that is, in the jejunum.⁸ Placing the DJBS endoscopically makes the procedure minimally invasive. Furthermore, DJBS has the advantage of being fully reversible; the device can easily be removed using an endoscope.⁹ The producer of the device (GI Dynamics Inc) recommends that treatment with DJBS is accompanied with dietetic counselling to optimise the effect and to prevent device malfunction. Currently, the device is approved for a maximal treatment period of 12 months. In 2010, DJBS received European *Communauté Européenne* (CE) marking and achieved conditional approval by the US Food and Drug Administration in August 2012.

How the intervention might work

The mechanisms behind the body weight lowering and antidiabetic effects of DJBS are unknown, but are thought to involve less absorption of nutrients and have been speculated to encompass changes in gut hormone secretion. Up to now, several human studies with a duration from 12 to 52 weeks report that implanted participants lose weight and achieve improvements in their diabetic state after treatment with the device. Tarnoff *et al*¹⁰ reported in their 12 week open-label prospective randomised controlled trial an excess weight loss (EWL) of 22.1% and 5.3%, respectively, for implanted participants and participants treated with a low-calorie diet. Another randomised sham-controlled trial showed EWL of 11.9% and 2.7%, respectively, for the device group and the sham group.⁸ Regarding changes in glycaemic parameters, Rodriguez *et al*¹¹ and Schouten *et al*¹² have reported improved glycaemic control (greater reduction in glycated haemoglobin (HbA1c)) when treated with DJBS compared to controls. De Jonge *et al*¹³ report in their study of 17 obese participants with type 2 diabetes that DJBS changes the gut hormone secretion favouring postprandial release of GLP-1 and lowering the secretion of GIP within 1 week after implantation before any significant weight loss occurred. This emphasises that changes in gut hormones may constitute one of the mechanisms by which DJBS exerts antidiabetic antiobesity effects.

Why it is important to do this review

As aforementioned, overweight and obesity represent major concerns for the individual and the society. The growing number of obese people has also led to a worrying increase in the incidence of people with type 2 diabetes. Nearly 350 million people suffer from this disease worldwide.¹⁴ Bariatric surgery has proven to be effective as a method of reducing body weight and improving type 2 diabetes. However, the potentially serious complications during and following the invasive and irreversible surgical procedures are incontrovertible. Thus, there is currently a strong need for new and less invasive, safer and preferably reversible alternatives to bariatric surgical procedures. DJBS may provide a modality fulfilling these conditions. Current data on the effects of DJBS stem from rather small studies. Therefore, it seems

of major importance to compile and analyse current evidence of the effect of DJBS on obesity and/or type 2 diabetes. Such evidence may help guide clinical decision-making and procure better treatment of obesity and type 2 diabetes.

OBJECTIVES

The primary objectives of the present protocol are to evaluate the effect of the DJBS on weight loss as assessed by change from baseline or the per cent of excess weight lost (%EWL), glycaemic control as assessed by HbA1c, and safety. Secondary objectives include evaluation of the proportion of patients with type 2 diabetes being able to reduce or discontinue antidiabetic medication and changes in glycaemic parameters other than HbA1c (fasting plasma glucose or fasting blood glucose) and total cholesterol.

METHODS AND ANALYSES

The systematic review will be performed according to the recommendations specified in the Cochrane Handbook for Intervention Reviews.¹⁵ The reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.¹⁶

Criteria for considering studies for review

Types of studies

The review will include randomised clinical trials, prospective non-randomised trials, case-control studies and case series investigating the effects of the DJBS, irrespective of blinding and publication status. Unpublished trials will be included if data and methodology are accessible in written form.

Types of participants

Adult overweight or obese patients (age 18 years or older) with or without type 2 diabetes treated with DJBS will be included. Preferably the definition of overweight, obesity and type 2 diabetes should follow the criteria from WHO, the European Association for the Study of Diabetes or the American Diabetes Association,¹⁷ but if necessary, trials will be included using the author's definition of obesity and type 2 diabetes.

Types of interventions

The comparisons will assess implantation of DJBS versus no intervention, sham-endoscopy and/or low-calorie diet.

Types of outcome measures

The outcome measures will be assessed based on analysis of individual patient data from included trials or from published reports when available.

Primary outcomes

- ▶ Mean weight loss in kilograms at end of intervention
- ▶ Change in HbA1c
- ▶ Safety

Secondary outcomes

- ▶ Proportion of patients with type 2 diabetes reducing or discontinuing antidiabetic medication after end of intervention
- ▶ Change in fasting plasma glucose or fasting blood glucose
- ▶ Change in total cholesterol

Search methods for identification of studies

Electronic searches

Electronic searches will be performed in The Cochrane Library, MEDLINE, EMBASE and Web of Science using the strategy below. Only English literature will be included.

- ▶ *The Cochrane Library*: djb OR djbs OR djbl OR endobarrier OR duodenal-jejunal OR duodenal jejunal AND diabetes.
- ▶ *Medline (PubMed)*: (djb[All Fields] OR djbs[All Fields] OR djbl[All Fields] OR endobarrier[All Fields] OR duodenal-jejunal[All Fields] OR ("duodenum"[MeSH Terms] OR "duodenum"[All Fields] OR "duodenal"[All Fields]) AND ("jejunum"[MeSH Terms] OR "jejunum"[All Fields] OR "jejunal"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]).
- ▶ *EMBASE*: djb or djbs or djbl or endobarrier or duodenal-jejunal or duodenal jejunal and diabetes. mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
- ▶ *Web of Science*: duodenal-jejunal bypass sleeve (#1); endobarrier gastrointestinal liner (#2); diabetes mellitus (#3); diabetes (#4), duodenal-jejunal (#5); weight loss (#6); #6 AND #5 AND #4 AND #3 AND #2 AND #1

Searching other resources

Manual searches will include scanning of reference lists in relevant papers, specialist journals and conference proceedings. Additional trials will be sought through the WHO Trial Register¹⁸ and through correspondence with experts. The website of the producer of the DJBS device (GI Dynamics Inc) will be sought for available material.¹⁹

Data collection and analysis

Two authors (UR and NH) will independently extract data and resolve disagreements through discussion before analysis. In case of unresolved matters, a third party will be involved. If necessary data are not included in the published trial reports, the authors of the included trial will be contacted for further information.

Selection of studies

The trials identified through electronic and manual searches will be listed. Included trials will be selected using the aforementioned criteria. Trials that are excluded will be listed with the reason for exclusion. All authors will participate in the selection of trials.

Data extraction and management

The following data will be extracted from the included trials:

- ▶ Patient characteristics: inclusion criteria, proportion of patients with type 2 diabetes, mean age, mean BMI, proportion of men/women, mean HbA1c and mean body weight
- ▶ Characteristics of interventions: type and duration of interventions
- ▶ Characteristics of trial: number of clinical sites, country of origin and funding

Assessment of reporting bias

We will compare trial protocols with subsequent publications when available and we will extract whether clinically relevant outcomes are reported.

Assessment of risk of bias in included trials

Owing to the expected inclusion of different types of studies, the following assessment of risk of bias will be used. For *randomised studies*, randomisation methods will be extracted as the primary measure of bias control. The randomisation methods will be assessed on the allocation sequence generation (which will be classified as adequate if based on computer-generated random numbers, a table of random numbers or similar), allocation concealment (which will be classified as adequate if randomisation was performed through a independent central unit, identically appearing treatments, serially numbered opaque sealed envelopes or similar) and incomplete data outcome (whether all patients were accounted for). With regard to blinding (detection and performance bias), data will be extracted in order to assess whether single or double blinding was performed. Blinding methods will be evaluated (eg, use of placebo). Persons who were blinded with regard to the intervention will be assessed (ie, patients, healthcare providers or other persons involved in the trial). For *other types of studies*, incomplete outcome data (attrition bias), for example, patients lost to follow-up, will be evaluated as a measure of attrition bias. Outcome reporting (reporting bias)—the extent to which clinically relevant outcome measures are reported—and differences between trial protocols and subsequent reports will be evaluated and reported as a marker of reporting bias. Other biases will include sample size calculations and the extent to which the planned sample size was achieved. All non-randomised studies will be classified as high risk of bias.

Measures of treatment effect

Dichotomous data will be analysed using risk differences and continuous data using weighted mean differences, both with 95% CIs. Relative risk will be calculated.

Assessment of heterogeneity

The intertrial heterogeneity will be expressed as I^2 values. The general interpretation of I^2 values is:

- ▶ 0–40%: might not be important
- ▶ 30–60%: may represent moderate heterogeneity
- ▶ 50–90%: may represent substantial heterogeneity
- ▶ 75–100%: considerable heterogeneity

Intertrial heterogeneity, small study effects and risk of bias will be evaluated through regression analysis (Egger's test).

Dealing with missing data

Intention-to-treat analyses including all patients randomised will be performed. In the case of patients with missing outcome data, the last observation carried forward will be used. Individual patient data will be sought from the original source or from the published trial reports where individual patient data are unavailable.

Data analysis

STATA (Stata Corp, Texas, USA, V.12) will be used for analyses. The primary meta-analyses will be performed using random effects models due to an expected inter-trial heterogeneity.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed to assess the impact of the patient, intervention, trial characteristics and intertrial heterogeneity. The test for subgroup differences will be calculated for all subgroups and the results presented as p value and I^2 value, respectively.

Sensitivity analysis

To assess the impact of small trials, fixed effect meta-analyses will be executed. Additional sensitivity analyses with exclusion of trials classified as having unclear adequate randomisation will also be performed.

Unit-of-analysis issues

In the analysis, each patient will be counted only once. If necessary, the same follow-up time point will be chosen to have as much data as possible to perform the analysis, even though the follow-up period may be longer for the individual trial. This will increase heterogeneity with regard to follow-up time, but may increase the possibility of reporting bias. Otherwise, the longest follow-up will be used.

ETHICS AND DISSEMINATION

This study will evaluate the impact of DJBS on weight loss, type 2 diabetes (HbA1c) and safety.

Furthermore, the effect on fasting plasma or blood glucose, reduction in antidiabetic medication and changes in blood lipids will be investigated. The study will hopefully shed light on the novel, minimally invasive and reversible technique of DJBS and thus provide knowledge about the use of it in the treatment of obesity and type 2 diabetes. The study will be disseminated by peer-review publication and conference presentation.

Contributors UR and NH have prepared this protocol in collaboration with TV, LLG and FKK. All authors have participated in the search strategy development. UR and NH extracted data and drafted a paper describing the systematic review. The remaining authors critically reviewed the manuscript.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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