The GATE trial: Endoscopic sutured Gastroplasty in Type 2 diabetic, obese patients using the Endomina device - a randomized controlled trial, and its effect on incretin hormones

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The primary objective of this study is to evaluate the efficacy of endoscopic sutured gastroplasty with the endomina device (EndoTools Therapeutics S.A.) on glycemic control (reduction in insulin dose), in obese insulin treated type 2 diabetes...

Ethical review	Approved WMO
Status	Pending
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON53331

Source
ToetsingOnline

Brief title
GATE trial

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)
- Gastrointestinal therapeutic procedures

Synonym
Diabetes

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum
Source(s) of monetary or material Support: Bedrijf Endotools Therapeutics,Endotools Therapeutics

Intervention

Keyword: Bariatrics, Diabetes mellitus type 2, Endoscopy, Obesity

Outcome measures

Primary outcome

The primary endpoint is the proportion of subjects with a clinically relevant

reduction of insulin dose. A clinically relevant reduction is defined as a 50%

dose reduction.

Secondary outcome

Secondary endpoints are:

Safety:

1. Rate of Serious Adverse Events (SAE) and Serious Adverse Device Effects

(SADE) during and post procedure at 12 months

2. (Serious) adverse events up to 1-month follow-up for subjects undergoing the

procedure under procedural sedation with propofol

3. Cardiovascular events (stroke/TIA, myocardial infarction, admission for

heart failure) and all-cause mortality

DM2:

4. Proportion of subjects with a clinically relevant decrease of HbA1c after 1

month, 3, 6, and 12 months follow-up. A clinically relevant decrease of HbA1c

is defined as 2.6% (5mmol/mol).

5. Reduction in HbA1c after 1 month, 3, 6, and 12 months follow-up.

6. Reduction in fasting plasma glucose levels after 1 month, 3, 6, and 12 months follow-up.

7. Proportion of subjects with reduced number and/or reduced dose(s) of (oral) glucose lowering medication after 1 month, 3, 6, and 12 months follow-up.

8. Proportion of subjects with remission of diabetes after 6, 9 and 12 months. Remission is defined as HbA1c < 6.5% (48 mmol/mol), fasting glucose of < 5.6 mmol/l without glucose-lowering medication for at least 3 months.

Weight Loss:

9. Proportion of subjects with mean % excess weight loss (EWL) of more than 25% after 1 month, 3, 6, and 12 months follow-up.

10. %EWL after 1 month, 3, 6, and 12 months follow-up.

11. Proportion of subjects with mean % total body weight loss (TBWL) of more than 5% after 1 month, 3, 6, and 12 months follow-up.

12. %TBWL after 1 month, 3, 6, and 12 months follow-up.

Comorbidity:

13. Decrease in blood pressure after 1 month, 3, 6, and 12 months follow-up.

Quality of Life:

14. EQ-5D-5L after 1 month, 3, 6, and 12 months follow-up.

15. DTSQ after 1 month, 3, 6, and 12 months follow-up.

Costs:

16. Costs and cost-effectiveness. Costs including health care recourses used (including intervention including endomina device and TAPES, hospital admissions, visits to specialists and GP, emergency room visits, medications

used), costs for insulin therapy (including medication, administration,

glycemia measurement material)

Substudy:

18. Difference in GLP-1 and ghrelin levels 1 month and 6 months after follow-up

between intervention and control group.

19. Changes in GLP-1 and ghrelin blood levels at 1 month and 6 months after ESG

compared to baseline.

Study description

Background summary

Diabetes mellitus is a chronic disease often associated with long-term macrovascular and microvascular complications (e.g., heart disease, stroke and renal failure) and decreased life expectancy. (2) Approximately 70% of patients with type 2 diabetes mellitus (DM2) is overweight or obese. (3) Findings from a national cohort of US adults showed that the risk for DM2 increases with 4.5% for every kilogram increase in weight. (4) Besides DM2, obesity is associated with impaired quality of life, cardiovascular diseases, arthrosis, cancer and reduced life expectancy. (5)

Weight loss benefits several aspects of DM2, such as improved glycemic control, increased insulin sensitivity and reduced fasting insulin. This results in a reduction of glycated hemoglobin. In addition, coexisting disorders such as hypertension and dyslipidemia improve as well. (2)

Interventions for weight loss in patients with DM2 include lifestyle interventions (diet, exercise), but also pharmacotherapy and bariatric surgery. Bariatric surgery is indicated at a BMI > 35 kg/m², in combination with other comorbidities such as DM2, hypertension or sleep apnea, or a BMI >40 kg/m² with or without any comorbidities. (6) It is associated with better glycemic control and more weight reduction, compared to intensive medical treatment alone, with more than 90% of patients in the surgical group having glycemic control without using insulin. (7) However, it is associated with perioperative and long-term complications, 6% of patients requiring revision surgery, and a mortality risk of 0.1-2%. (8-10) Also, literature shows that only 1% of eligible patients

actually undergo bariatric surgery. This is mainly due to the change in anatomy and the fear of operative risks. (11) Therefore, less invasive and safer techniques are needed.

Endoscopic bariatric therapies are techniques with much less-invasive features (as it does not cross the border of the GI tract) and without the significant risks associated with surgery. Especially, for patients with not adequately controlled DM2 with a BMI between 30 and 35 kg/m², the therapeutic gap could be filled by one of the currently available endoscopic therapies. These therapies can be categorized in three different techniques:
1) inserting of a (temporarily) space-occupying device (balloon) in the stomach aiming to reduce the stomach*s capacity
2) redirecting calories away from the stomach by aspiration therapy or,
3) decreasing the stomach size by endoscopic suturing. (12, 13)

Endoscopic sutured gastroplasty is one of the techniques that decreases the stomach size. This technique can be performed with different devices currently available, e.g., the Incisionless Operating Platform (USGI Medical), Overstitch Endoscopic Suturing System (Apollo Endosurgery) or Endomina (Endo Tools Therapeutics). Previous studies, including meta-analyses have shown a positive effect of ESG on weight loss. (14) However, there is a paucity of data showing the effect of ESG on metabolic comorbidities including DM2. (14) Also, most studies have been performed with the Overstitch device. Therefore, this study aims to compare the efficacy and safety of ESG with the endomina device on glycemic control.

Effect on hormones
Bariatric surgery leads to a greater chance of DM2 remission compared to similar weight loss without surgery. (15) There are several theories on the mechanism that attributes to improved glycemic control after bariatric surgery. These theories can be divided into 4 pathways: 1) cellular alterations, 2) changes in microbiome, 3) histological changes, and 4) hormonal shifts. (15) The latter theory can be further exemplified by several gut hormones, including incretin hormones (GLP-1 and GIP) and ghrelin. These hormones are responsible for the regulation of gastric emptying, feeling of satiety and insulin secretion.

The hormone studied most within this field is GLP-1. This gut hormone is secreted by intestinal L-cells primarily in the distal ileum and colon. L-cells are stimulated by several factors, including nutrient and endocrine factors. Quickly after ingestion of food, particularly when it contains lots of fat and carbohydrates, GLP-1 secretion is stimulated. (16) This has an incretin effect: a stronger stimulation of insulin secretion after oral glucose intake compared to intravenously glucose administration. (17) Other effects of GLP-1 are regulation of glucagon secretion, slowing gastric emptying and providing the feeling of satiety. (18) It is known that the incretin effect is reduced or even absent in patients with DM2. (19)

The effect of bariatric surgery on this incretin effect can possibly explain its benefits on DM2. It is extensively confirmed that GLP-1 levels rise after bariatric surgery. (20-24) Firstly, Roux-and-Y gastric bypass provides the stomach to empty nutrients into the distal part of the small intestine. This equals the location of most L-cells, where GLP-1 secretion is stimulated. (19) Secondly, due to a sleeve gastrectomy the gastric emptying accelerates and delivers nutrients faster in the small intestine, which stimulates GLP-1 secretion. (19) Ghrelin levels on the contrary fall after a meal. It causes the feeling of hunger and appetite and regulates the use of energy. (24, 25) The effect of bariatric surgery on ghrelin levels remains unclear. Theoretically, the levels of ghrelin would reduce after surgical sleeve gastrectomy, since the part of the stomach is removed that is the location of the most ghrelin secreting cells. (25)

The question raises, if the same hormonal changes occur in bariatric endoscopy as seen in bariatric surgery. The effect on GLP-1 is mainly analyzed for the duodenal-jejunal bypass sleeve (DJBS), which shows an increase in GLP-1 after 7 days and 24 weeks. (26) Lopez-Nava et al. showed a minimal decrease in ghrelin levels, but no difference in GLP-1 levels before and 6 months after ESG (with an intact fundus). (27) Abu Dayyeh et al. analyzed the effect of ESG on GLP-1 after 3 months, which showed no significant changes. (28) However, both are small non randomized controlled studies. Vargas et al. found a significant increase in total ghrelin 12 months after ESG compared to baseline, although no differences between the intervention (ESG) and control (lifestyle intervention) group were seen. At 18 months, both total ghrelin as GLP-1 were significantly increased compared to baseline. (29) Due to the inconsistent results regarding different hormones, the aim of this sub-study is to analyze the effect of ESG on GLP-1 and ghrelin blood levels within our randomized study population with obesity and diabetes mellitus type 2.

Study objective

The primary objective of this study is to evaluate the efficacy of endoscopic sutured gastroplasty with the endomina device (EndoTools Therapeutics S.A.) on glycemic control (reduction in insulin dose), in obese insulin treated type 2 diabetes patients after 12 months.
Secondary objectives are:
- To evaluate the effect of ESG on:
o HbA1c
o Weight loss
o Blood pressure, in patients with hypertension at inclusion
o Quality of life, measured with the quality-of-life questionnaires EQ-5D-5L and Diabetes Treatment Satisfaction Questionnaire (DTSQ)
after 1 month, 3, 6, and 12 months of follow-up
- To evaluate the possibility and safety of performing ESG under procedural sedation (with propofol).

Substudy:
To evaluate the effect of ESG on GLP-1 and ghrelin blood levels, 1 month and 6 months after ESG.

Study design

Type of study
This study is designed as a prospective randomized controlled trial, conducted in Rijnstate Hospital (Arnhem).

Summary of study design
Screening patients will be performed in several phases:
- Patients (previously) known at the Internal Medicine outpatient population from Rijnstate Hospital or Radboudumc with DM2 will be screened for eligibility using CTcue. Patients diagnosed with DM2, with a BMI between 30 and 40 kg/m2 and treated with insulin are eligible for inclusion.
- After this first screening, a multidisciplinary meeting will be held with the coordinating researcher, a gastroenterologist and an internist to discuss eligibility of the patient (e.g. are there any (already known) contraindications precluding ESG).
- If a patient seems eligible for inclusion, an information letter will be sent to patient*s home address, followed by telephonic contact by their treating physiscian to provide additional information. If the patient seems still eligible and he/she is interested, han outpatient clinic visit will be scheduled with the coordinating researcher to discuss the study in detail. Afterwards, the patient will have 7 days to consider participation and if wanted discuss participation with the treating physician.
- After 7 days, informed consent will be obtained and, a blood test will be performed to check HbA1c. Subjects will be screening failures when the HbA1c is < 7.0% or >11.0%, and will be excluded for enrollment. In addition, subjects will be screened by a psychologist from Vitalys (Bariatric Center Velp), and an anesthesiologist. If this leads to a negative advice, the subject will be excluded from the trial as well. If the HbA1c is between 7.0% and 11.0%, and they passed the screening, subjects will be included in the study and randomized in a 1:1 ratio to either the intervention or control group.

Subjects in the intervention group will receive the ESG, followed by follow-up visits at the outpatient department and one appointment by a dietician from Vitalys to provide information about diet after ESG (e.g. smaller portions, multiple times a day).
Subjects in the control group will receive standard diabetic care, which includes consultation with a dietician for patients with DM2 under insulin therapy. Further standard care will be provided by one of the trial researchers instead of a treating physician. If indicated, consultation with the treating physician will be performed.

The intervention group will have a telephonic follow-up 7 days post-procedure

and outpatient department follow-up visits at 14 days, 1 month, and at 3, 6, 9 and 12 months after ESG. The control group will have videocalls at 14 days after randomization, 1, 6 and 9 months, and follow-up visits at 3 and 12 months after baseline visit. During these visits/calls, primary and secondary endpoints will be assessed.

Substudy:
In addition to the main study procedures, subjects will undergo a Mixed Meal Tolerance Test (MMTT) 3 times during follow-up to measure changes in GLP-1 and ghrelin concentrations before and after bariatric endoscopy.

The first test will take place at baseline, for the intervention group at the utmost of 2 weeks prior to the procedure. Subjects have to withdraw their oral anti-diabetic medication 12 hours before admission, skip their morning dose of insulin at the day of admission, but can continue their evening insulin dose the day before admission. In addition, they have to fast for 12 hours before the test.

Blood samples will be collected for GLP-1 and ghrelin measurements before the start of the test. Then, the subject has to eat a standardized meal in 15 minutes (2 slices of bread, 10grams of margarine, 1 slice of cheese, 1 slice of ham, 1 cup of tea without sugar), and the measurements will be repeated at 30, 60, 90 and 120 minutes. The MMTT will be repeated after 1 month and 6 months.

Intervention

Subjects in the intervention group will be treated with an ESG with the endomina ® and TAPES devices (Endo Tools Therapeutics S.A.), both CE-marked for endoscopic gastroplasty. The endomina is a device that can be attached to an endoscope and allows remote actuation of the device during a peroral intervention. Thanks to a therapeutic channel that can be angled perpendicularly to the axis of vision of the endoscope, it allows the possibilities of making transoral full thickness tissue apposition and performing, via a transoral route, large plications with tight serosa to serosa apposition in the stomach. (Figure 1) This suturing will be done from the incisura to the upper body of the stomach, along the great curvature (Figure 2) with TAPES, a single use needle preloaded with suture (Figure 3).
In addition to the endomina device, any other required endoscopic accessories can be used during the procedure (e.g., grasping forceps, loop cutter).

See chapter 7.3 in the protocol for a more detailed description of the procedure.

Subjects in the intervention group will receive one meeting with a dietician from Vitalys, to provide information about adjusting their diet to the reduced stomach capacity (e.g. eating smaller portions, multiple times a day). Study follow-up visits will replace standard diabetic care during follow-up.

Subjects in the control group will receive standard diabetic care. At baseline, one of the researchers will emphasize the importance of guidance by a dietician.

Adjustments in glucose lowering medication doses (including insulin) will be performed according to the local protocol.

Study burden and risks

Benefits:
Several studies have been published evaluating the safety and efficacy of ESG with the endomina device. The efficacy mainly focussed on weight loss. One case report published in 2018 showed 2 patients that underwent ESG with the endomina device. Both patients had a BMI > 35 kg/m². After 3 months, both patients had relevant weight loss of 7kg and 14kg respectively. No long-term follow-up is available. Another safety and feasibility study showed a mean percentage excess weight loss of 9% after 1 month, and 41% after 6 months. No adverse events were observed. A multi centre prospective trial in 45 obese patients showed a 29% excess weight loss, and 7% total weight loss after ESG with the endomina. No adverse events occurred during follow-up. Lastly, a randomized trial presented the short-term safety and effectiveness of the endomina system on weight loss in 71 patients with a BMI of 30-40 kg/m². This study showed a 25% better excess weight loss after 6 months in patients that underwent a combination of lifestyle modification and endoscopic suture gastroplasty with the endomina, compared with lifestyle modification alone. This also led to a substantial improvement in quality of life. No procedure-related or device-related severe adverse events were seen. In 2022, it was shown that weight loss is independent from the suturing pattern in a prospective randomized trial evaluating 3 different patterns.

Other studies are published evaluating the effect of ESG using other devices than the endomina device. Recently, Abu Dayyeh et al. published a RCT doing ESG with the Apollo device. They mainly focussed on weight loss as well, which showed a significant difference in mean excess weight loss of 49.2% (SD 32.0) for the ESG group and 3.2% for the control group (SD 5.0) ($p<0.0001$). As a secondary outcome measure they evaluated diabetes related outcomes as well, showing a significant improvement in HbA1c levels in the intervention group compared to the control group. However, a decrease in dose of glucose lowering medication or diabetes remission was not mentioned.

Risks:
Previous studies have shown small periprocedural adverse events of ESG with the endomina, consisting of small self-contained bleedings, which all stopped when the knot was tightened. For suturing, a needle is attached to a suture and a pre-tied knot. First, the needle is pushed through 2 layers of the gastric wall and the suture and pre-tied knot are released. Then a second plicature is made on the other side of the stomach. Afterwards, the pre-tied knot is tightened.

The small bleedings occurred only in between these 2 steps.
Adverse events shortly after the procedure were transient abdominal cramps (79.4%), transient nausea (66.2%), or vomiting (66.2%). In 71 patients, 1 aspiration pneumonia occurred at extubation, which did not require longer hospitalization or antibiotic treatment. (16) No severe adverse events were observed, no surgical intervention or readmission were needed, and no mortality occurred.

In addition, a meta-analysis evaluating 9 studies (1772 patients) using the Overstitch device for ESG, has shown a severe adverse event rate of 2.2% and no mortality. Reported severe advents were pain and nausea requiring hospitalization (1.08%), upper gastrointestinal bleeding (0.56%), perigastric leak or collection (0.48%), pulmonary embolism (0.06%) and pneumoperitoneum (0.06%).

Procedural sedation has a low risk of adverse events. In a prospective observational study in the Netherlands, almost 12.000 patients were included who received procedural sedation. Minimal adverse events (e.g., vomiting, muscle rigidity, or agitation) were seen in 1517 (12.8%), minor adverse events (e.g., oxygen desaturation 75-90% for less than 60s, airway obstruction, or hypotension) in 113 (1.0%), and major adverse events (e.g., oxygen desaturation <75% or 75-90% for more than 60s, aspiration, or cardiac arrest) in 80 patients (0.7%). Five unfavourable patient relevant outcomes (0.07%) occurred within this study. This included admission to ICU, cardiac arrest and asystole secondary to pneumodilation of the oesophagus. Another retrospective cohort included 2937 procedures, in which no catastrophic events and a low rate of severe events (1.09%) occurred. The most common severe events were severe desaturation (0.6%) and hypertension (0.2%). Moreover, the most common events with potential adverse health consequences were significant desaturation (1.6%) and significant hypotension (8.8%). Nonetheless, no patient experienced health consequences on the long term.

Substudy:
Most common adverse symptoms of the MMTT are hunger (14%), stomach discomfort (6%), and belching (7%). These symptoms disappear after finishing the test.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Age between 18-70 years
- Diagnosed with DM2
o since at least 1 year
o currently under stable dose of insulin for at least 6 months
o with or without use of any other oral glucose lowering medication (e.g., metformin, GLP-1 receptor agonist)
- HbA1c level of 6.1-11.0% (43-75 mmol/mol) prior to inclusion
- BMI of 30-40 kg/m²
- The maximum attainable therapeutic options within standard reimbursed care are obtained (e.g., lifestyle intervention like GLI or dietician and pharmacotherapeutic options like sulfonylureas, metformin, SLGT2 inhibitors, GLP1 agonists and insulin).
- Must be eligible for general anesthesia or deep sedation with propofol

Exclusion criteria

• Achalasia and any other esophageal motility disorders
• Severe esophagitis (grade C or D)
• Gastro-duodenal ulcer
• GI stenosis or obstruction
• Any history of esophageal or gastric surgery

• Heart diseases: unstable angina, myocardial infarction within the past year, or heart disease classified within the New York Heart Association*s Class III or IV functional capacity
• Uncontrolled hypertension (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >100 mm Hg under medication) during last 3 months;
• Severe renal, hepatic, pulmonary disease or cancer (cancer in the past 5 years, except basal cell carcinoma)
• Known with, or history of, eating disorder
• Pregnancy, breast feeding or desire to become pregnanct in the coming 12 months
• Any previous bariatric surgery, or endoscopic obesity-related intervention (including POSE, OverStitch, etc.). Intragastric balloon removed within the last 6 months
• Planned gastric surgery 60 days post intervention
• Anticoagulant therapy that cannot be temporarily stopped at the time of the procedure.
• Currently participating in another study (involving change of treatment).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2023
Enrollment:	58
Type:	Anticipated

Medical products/devices used

Generic name:	Endomina

Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	26-04-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	NL82297.091.22

Register	ID
CCMO	NL83606.091.23