Endoscopic application of pulsed electric fields using the Endogenex Generation 2 ReCET* system for duodenal mucosal regeneration for EliMination of INsulin in the treatmENT of type 2 diabetes: a randomized double-blind sham controlled trial to evaluate safety, feasibility and efficacy study

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

Summary

ID

NL-OMON53757

Source
ToetsingOnline

Brief title
EMINENT-2 study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Endogenex,Unrestricted grant door Endogenex.

Intervention

Keyword: Duodenum, Regeneration, Type 2 diabetes

Outcome measures

Primary outcome

• Safety: Incidence rate of adverse events.

• Feasibility: Procedure time and technical success rate

• Primary efficacy: Protocol driven free of insulin at 6 months and HbA1c <= 7.5

% in the active group, compared to the control group

Secondary outcome

• Secondary efficacy:

- Time in range (flash glucose monitoring),

- liver fat fraction (MRI-PDFF) and fibrosis

- sympathovagal activity (Nexfin device).

- bloodL HbA1c, HOMA-IR, Fasting Plasma Glucose

- Weight, BMI, waist circumference

- lipid panel, liverenzymes etc.

- micro albumin

- glucoregulatory hormones (Mixed Meal Test)

- Microbiota diversity oral and fecal

- Intake registration

In the active group, compared to the control group at 6 months

Study description

Background summary

T2D is managed by lifestyle interventions and a variety of pharmacological agents. Nevertheless, only 50% of T2D patients achieve their treatment targets. For many patients, exogenous insulin administration remains the final treatment option to manage their hyperglycemia. However this approach does not treat the root phenomenon of the disease, i.e., insulin resistance, and the resulting hyperinsulinemia contributes to weight gain and further deterioration of the patients metabolic health.

T2D can, however, be effectively treated by bariatric surgery. Patients undergoing Roux-en-Y gastric bypass surgery demonstrate major improvements in glycaemic control and metabolic and cardiovascular health, which occur virtually immediately after surgery and well before any significant weight loss is established. Reintroduction of nutrients into the bypassed duodenal limb quickly returns patients to their previous dysmetabolic state, highlighting the importance of the duodenum in the insulin-sensitizing effect of bariatric surgery and in the pathogenesis of the metabolic syndrome.
The important role of the duodenal mucosa is highlighted by specific endoscopic procedures to treat T2D and concomitant metabolic diseases. In a recent published European multicenter study that examined patients with sub-optimally controlled T2D (using oral glucose-lowering medication), a single duodenal mucosal resurfacing (DMR) procedure entailing hydrothermal ablation of the duodenal mucosa, elicited a substantial improvement glycaemia, insulin resistance, and liver transaminases at 12 and 24 months post-procedure. A subsequent one-armed pilot study found that 69% (11/16) of formerly insulin-dependent T2D patients, had adequate glycemic control 6 months after their insulin was replaced by a single DMR, GLP-1 RA and lifestyle counselling.
Moreover, the patients that were adequately controlled, experienced improved glycemic and metabolic health, as reflected by

significant decreases in HbA1c, HOMA-IR and weight and liver fat %. These studies strongly suggest that regeneration of duodenal mucosa improves insulin sensitivity and glycaemic regulation similar to bariatric surgery but trough a less invasive procedure. However, the handling of the Revita system is very challenging and the procedure is time consuming, which makes upscaling of this procedure difficult. Moreover, the use of a balloon in the DMR technique causes *patched* ablation areas, which possibly impedes the efficacy of DMR. Overlapping ablations, or ablations of non-lifted duodenal mucosa, have shown to be risk factors for a post-procedural duodenal stenosis.
Re-Cellularization via Electroporation Therapy (ReCET) is a minimally invasive endoscopic procedure that uses the Endogenex device (Endogenex Inc., Plymouth, MN, USA) to deliver Pulsed Electric Fields (PEF) to the duodenum. The treatment is non-thermal and does not require mucosal lifting for protecting submucosal tissue. This The system uses a through-the-scope design that greatly improves technical feasibility and will reduce procedure time. PEF induces mucosal renewal via cell apoptosis and subsequent rapid regeneration. Data from animal and clinical studies using thermally induced DMR suggest that this is followed by an insulinsensitizing effect that resembles the metabolic improvements after bariatric surgery. PEF-induced DMR may allow for a more complete ablation with regards to the mucosal area treated and a more controlled ablation with regards to the depth of ablation minimizing the risk of damaging the deeper layers of the duodenal wall (i.e. deep submucosa and muscularis propria).
In addition, ReCET uses another type of energy, e.g. electroporation, that might restore sympathovagal balance. Many studies have shown a functional gut-brain axis in which gut-derived peptides, microbiota, metabolites, and neuronal feedback inform the brain about energy status and then elicit an appropriate feeding and metabolic response. It is thought that the gut brain-axis modulates central control of food intake and metabolism specifically via the production of short-chain fatty acid butyrate. Oral butyrate supplementation affected sympathestic tone and intestinal transit times as well as physical activity and reduced liver fat in mice before. Therefore, ReCET could result in even bigger changes in the neuronal feedback from the gut to the brain that elicits improvement in metabolic health.

Study objective

The objective of this first-in-human study is to evaluate the safety, feasibility and efficacy of Re-Cellularization via Electroporation Therapy (ReCET) by the (Endogenex system) combined with (GLP-1 receptor agonist) in subjects with insulin dependent

type 2 diabetes mellitus and an adequate beta cell reserve. The aimed effect is an adequate or improved glucose
regulation without the need for insulin therapy. Secondary effects include improved cardiovascular, hepatological en metabolic
parameters.

Study design

Randomized double blind shamcontrolled monocenter study

Intervention

ReCET or shamprocedure in combination with GLP1-RA (semaglutide)

Study burden and risks

To participate in this clinical study, subjects have to consent with 11 visits, including blood samples drawn at every visit, physical examination (once during screening and on indication during following visits) and potential burden associated with undergoing MRI for liver fat fraction + fibrosis measurement (like claustrophobia), flash blood glucose monitoring and questionnaires. Subjects also have to consent with undergoing 2 endoscopies (including 1 follow-up endoscopy) with duodenal mucosal biopsies (cold snares). There are risks related to any endoscopic procedure. Specific risks associated with this procedure include: abdominal pain, bleeding, delayedgastric emptying, dental injury, diarrhea, difficulty swallowing, fever, gastric dumping syndrome, headache, hypoxia, infection, injuryto esophagus, nausea, non-healing ulcer, nutritional mal-absorption, pancreatitis, perforation, pneumoperitoneum, pulmonaryaspiration, sore throat, stomach or duodenal mucosa stricture and obstruction, tightness and cramping and worsening diabeticsymptoms including hypoglycemia. Many of these risks and complications associated with the procedure are similar to thoseassociated with other commonly performed endoscopic procedures such as duodenal biopsies and endoscopic mucosal resection.
In addition to the risks listed above, the Endogenex system has unique risks associated with its catheters and control consoles used to complete the procedure. This includes risks associated with the materials selected, its design and construction.

These risks include See section 4.4 (protocol) for more information:
The following steps have been taken to minimize risks associated with the procedure.
The medical consequences and morbidity associated with T2D has been well studied and documented and includes renal failure,blindness, peripheral neuropathy, amputation, increased risk of myocardial infarctions, stroke and peripheral vascular disease. In addition, treatment with insulin is associated

with weight gain and the risk of hypoglycemia. A successful intervention may enable subjects to more effectively control their glycaemic levels or even reduce or discontinue use of medications needed to treat their disease, including insulin. This procedure potentially allows subjects to reduce morbidity of the disease and through improvedglycaemic and metabolic health. As noted above, there are substantial potential benefits associated with the procedure and the risk associated with the device and procedure have been identified and minimized where possible. Thus, the balance of potential risks and benefits associated with the Endogenex procedure warrants clinical research and justifies its investigation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosed with type 2 diabetes mellitus
2. 28 -75 years of age
3. On daily long acting insulin dose <= 1 U/kg
4. BMI >= 24 and <= 40 kg/m2
5. HbA1c <= 8.0% (64 mmol/mol)
6. Fasting C-peptide >= 0.2 nmol/L (0.6 ng/ml)
7. Willing to comply with study requirements and able to understand and comply with signed informed consent

Exclusion criteria

1. Diagnosed with Type 1 Diabetes or with a history of ketoacidosis 2. Current use of multiple daily doses insulin or insulin pump. 3. Current use of a GLP-1 analogue. 4. Known autoimmune disease, as evidenced by a positive Anti-GAD test, including Celiac disease, or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder 5. Previous GI surgery that could affect the ability to treat the duodenum such as subjects who have had a Bilroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions 6. History of chronic or acute pancreatitis 7. Known active hepatitis or active liver disease 8. Symptomatic gallstones or kidney stones, acute cholecystitis or history of duodenal inflammatory diseases including Crohn*s Disease and Celiac Disease 9. History of coagulopathy, upper gastro-intestinal bleeding conditions such as ulcers, gastric varices, strictures, congenital or acquired intestinal telangiectasia 10. Use of anticoagulation therapy (such as phenprocoumon and acenocoumarol) which cannot be discontinued for 3-5 days before and 48 hours after the procedure and novel oral anticoagulants (such as rivaroxaban, apixaban, edoxaban and dabigatran) which cannot be discontinued for 48 hours before and 48 hours after the procedure in accordance with the local protocol 11. Use of P2Y12 inhibitors (clopidogrel, pasugrel, ticagrelor) which cannot be discontinued for 5 days before and 48 hours after the procedure in accordance with the local protocol. Use of aspirin is allowed. 12. Unable to discontinue NSAIDs (non-steroidal anti-inflammatory drugs) during treatment through 4 weeks post procedure phase 13. Taking corticosteroids or drugs known to affect GI motility (e.g. Metoclopramide) 14. Receiving weight loss medications such as Meridia, Xenical, or over the counter weight loss medications 15. Anemia, defined as Hgb < 6.2 mmol/l 16. Known history of severe permanent cardiac arrhythmia*s with clinical symptoms 17. Significant cardiovascular disease, including known history of valvular disease or myocardial infarction, heart failure, transient ischemic attack, or stroke within 6 months prior to the screening visit 18. With any implanted electronic devices or duodenal metallic implants 19. eGFR or MDRD < 30 ml/min/1.73m^2 20. Active systemic infection 21. Active malignancy within

the last 5 years 22. Not potential candidates for surgery or general anesthesia 23. Active illicit substance abuse or alcoholism 24. Pregnancy or wish getting pregnant in next year 25. Participating in another ongoing clinical trial of an investigational drug or device that can interfere with the current study 26. Any other mental or physical condition which, in the opinion of the investigator, makes the subject a poor candidate for clinical trial participation

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-08-2023
Enrollment:	32
Type:	Actual

Medical products/devices used

Generic name:	Endogenex System
Registration:	No

Ethics review

Approved WMO

Date:	21-06-2023
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL83266.000.22