The effects of the Laparoscopic Roux-en-Y Gastric Bypass and the Laparoscopic Mini Gastric Bypass on the remission of type 2 Diabetes Mellitus and the pathophysiological mechanisms that drive the conversion of malign to benign obesity

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Primary objective is to evaluate and compare the glycaemic control in T2DM within the first year of LRYGB and LMBG. Secondary aim is to gain insight in the pathophysiological mechanisms that drive the conversion of malign to benign obesity.

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

Summary

ID

NL-OMON50364

Source
ToetsingOnline

Brief title
DIABAR

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Gastrointestinal conditions NEC
- Hepatic and hepatobiliary disorders

Synonym
obesity, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: VIDI grant Prof. dr. M. Nieuwdorp

Intervention

Keyword: Mini Gastric Bypass, pathophysiology, Roux-en-Y Gastric Bypass, Type 2 Diabetes Mellitus

Outcome measures

Primary outcome

The main study parameter is to assess glycaemic control as measured by the difference in Hba1C at twelve months after LRYGB and LMGB.

Secondary outcome

Glycaemic control (as measured by the difference in HBa1c) at 6, 24, 36, 48, 60 months and 10 years after surgery. The remission of T2DM (as determined by use of anti-diabetic medication) at 6, 12, 24, 36, 48, 60 months and 10 years after LRYGB and LMGB.

To identify microbial, immunological and metabolic markers for NAFLD/NASH and metabolic response before and after LMGB or LRYGB and to apply systems biology approach to identify hierarchy of driving mechanisms (microbial, immunological and metabolic markers) involved in the long term beneficial effects of LRYGB and LMGB that can be used for personalised medicine. To study the (long-term) effects of bariatric surgery on blood pressure, cardiac output and baroreflex

sensitivity. To correlate changes in blood pressure, cardiac output and baroreflex sensitivity to changes in metabolic and other parameters. To determine the relation of NAFLD/NASH and the development of gallstones in relation to gallbladder bile composition and its combined effect on metabolism, T2DM and weight loss after bariatric surgery.

To this end, we will collect before, during surgery and up to 10 years follow up:

1. NAFLD/NASH parameters in liver biopsy
2. 2h Mixed meal tolerance test for level of insulin sensitivity and dietary and satiety lists and excreted metabolites (24h faeces and urine as well as BIA and questionnaires) and Electrocardiogram (ECG) at 12 and 24 months;
3. Presence of bacterial DNA/bacterial metabolites in portal vein blood, liver and abdominal adipose tissue depots
4. Small intestinal and faecal microbiota composition and peripheral blood inflammatory markers at 2, and 6 weeks, 6 months, as well as 12, 24, 36, 48,60 months and 10 years after surgery; also oral microbioma at baseline, 12, 24, 36, 48,60 months and 10 years.
5. Expression and differentiation of intestinal immunological cells in GALT (Peyer*s patches), visceral/subcutaneous adipose tissue, liver and peripheral blood (notably ILC*s, macrophages, T/B-cells and dendritic cells) in relation to inflammation gene expression (IL -1β, IL-6, IL-8, IL-18, CXCR2 TNF-α and TLR 1, 2, 4, 5 and 6) in PBMCs.B cells will be isolated from peripheral blood and B cells will be sorted on CD19, CD27, CD20, IgA; CD19, CD27, CD20, IgM, or CD19,

CD27, CD20, IgG and will be cultured with CD40L expressing feeder cells and IL-21 to induce antibody production. RNA will be isolated from CD19 cells. DNA will be isolated from whole blood to measure bacterial DNA.

6. Clinical data (body weight, waist circumference, medication, blood pressure and assessment of cardiac output, systemic vascular resistance and baroreflex sensitivity (with use of a nexfin device), bioelectrical impedance analysis (BIA) comorbidity, complications of surgery, presence of mental problems, smoking, use of alcohol and DNA sample (for epigenetic testing, taken from EDTA sample))

7. Expression and differentiation of immunological cells (notably ILC*s, macrophages) and inflammatory markers (IL6, IRX3 and 5) at 12, 24, 36, 48,60 months and 10 years months after surgery

8. Ultrasonography for detection of gallstones

9. Gallbladder tissue and bile acid collection after cholecystectomy, if applicable

10. Subjects with clinical suspicion of NASH or advanced fibrosis based on liver biopsy obtained during the primary bariatric surgery will be referred to the NAFLD outpatient clinic. If the clinician deems it necessary to repeat the liver biopsy based on clinical grounds during this consultation, a small part of the liver sample taken for clinical diagnosis will be collected for gene expression/protein westernblot if the subjects has given permission. In addition, in the case of referral to a gastroenterologist for clinical evaluation of upper gastro-intestinal complaints after surgery, the subjects might undergo an gastroduodenoscopy. If that is the case and the

gastroenterologist finds it necessary to perform a gastroduodenoscopy based on

clinical grounds, a small part of the small intestinal biopsy will be collected

for gene expression/protein westernblot if the subjects has given permission.

Study description

Background summary

It is estimated that there will be 439-552 million people with type 2 diabetes mellitus (T2DM) globally in 2030. Type 2 Diabetes Mellitus is present in one quarter of patients at the bariatric outpatient clinic. It is undecided which metabolic surgery grants best results in the remission of T2DM and which procedure does that at the lowest rate of surgical complications, long term difficulties and side effects.
Non alcoholic fatty liver disease (NAFLD) is present in 80% of all morbidly obese subjects and is a major risk factor for development of insulin resistance and non alcoholic steatohepatis (NASH). It is increasingly recognized that the immune system, possibly driven by innate lymphoid cells (ILC*s), and the intestinal microbiome are major players in this obesity related disease and the switch from benign to malign (insulin resistance and T2DM) obesity. However, the exact mechanisms of action behind the surgery-driven switch back from malign to benign obesity are unknown.

Study objective

Primary objective is to evaluate and compare the glycaemic control in T2DM within the first year of LRYGB and LMBG. Secondary aim is to gain insight in the pathophysiological mechanisms that drive the conversion of malign to benign obesity.

Study design

Multi-center, open randomized controlled clinical trial with two arms: LRYGB (control) versus LMGBP (intervention).

Intervention

Randomisation between the Laparoscopic Roux-en-Y Gastric Bypass (control) and the Laparoscopic Mini Gastric Bypass (intervention)

Study burden and risks

Patients will be recruited from the bariatric outpatient clinic at MC Slotervaart during regular screening for bariatric/metabolic surgery and will be included in the study after informed consent is obtained. Following this, the patient will be randomized in the LRYGB (control) or LMGB (intervention) group. Subsequently, the patient will have an appointment with the researcher to undergo a mixed meal test, Bioelectrical impedance analysis (BIA). Blood pressure, cardiac output, systemic vascular resistance and baroreflex sensitivity will be measured (with use of a nexfin device) and patients will fill out questionnaires. An ultrasound of the gallbladder will be performed as well. Within one week prior to surgery patients will be asked to fill out a meal-list and to collect a 24 hour feces and urinary sample. An oral swab will be used to collect the oral micriobiome. During surgery, samples of peripheral and portal blood are collected and samples of liver, mesenterial and subcutaneous fat are taken. Two weeks, six weeks and six months after surgery, three regularly scheduled visits will be used for sample collection of blood and feces. In the two years following surgery, two visits to Spaarne Gasthuis or AMC will be scheduled for 24-hour feces and urine sample collection, oral microbiome, subcutaneous fat biopsies and performing 2h mixed meal tests, together with BIA. Blood pressure, cardiac output, systemic vascular resistance and baroreflex sensitivity will be measured (with use of a nexfin device). The ultrasound of the gallbladder will be repeated as well. An ECG will be made and patients will fill out questionnaires. This will amount to a total of 30 hours of study time in addition to regular procedures and ends ten years after surgery. After the patients ended the first two years of follow up, we will ask them if they want to continue follow up. In the upcoming years at 3,4,5 and 10 years after surgery we will collect fecal and urine samples, oral microbiome, bloodsamples, dietlist,circumference measurement and questionnaires.
The two treatments, i.e. the LRYGB and the LMGB, are established surgical procedures for more than 20 years, with known specific risks. The effect of treatment in the control and the intervention arm are the same, possibly more favourable in terms of expected weight loss and complication rate (within 30 days of surgery) in the LMGB arm. Metabolic remission is thought to be good in both arms, with a hypothesized and suggested (unpublished data) benefit on diabetic remission in the intervention arm encompassing faster and greater effect on glycaemic control. Other possible benefits of LMGB are seen during surgery and are related to the need of one instead of two anastomoses and tension-free anastomosis of the gastrojejunostomy after LMGB, which can be challenging in the superobese patients in LRYGB. After LMGB internal herniations (IHs) are rarely seen, as opposed to the LRYGB. After LRYGB IH-rates up to 6,2% are reported and reoperation is urged to prevent HIs and/or cure small bowel obstruction due to IH, which is considered a particularly serious complication. A concern of the LMGBP is the possibility of biliary reflux into the gastric remnant and esophagus and mucosal changes after long term exposure; however, the evidence is conflicting. Symptomatic biliary reflux can give reason to revise LMGB to LRYGB. Extensive experience is present among the surgeons performing the necessary liver and fat biopsies following the METC approved BARIA protocol (P1633). The risk of bleeding from the biopsy sites is

minimised as the biopsy sites are visible to the surgeon and the surgeon will check upon local haemostasis before termination of the surgery. Upon the proposal of this study multiple portal vein samples are taken by one surgeon within the context of the BARIA protocol. Patients with bleeding disorders will be excluded from participation. The adipose tissue biopsies after surgery will be performed under local anaesthesia, there is a chance of a localized temporary haematoma. Total blood amount taken is 250 ml (3x mixed meal test at 50 ml per test, 1x baseline+DNA 40ml, 10 ml for portal vein plasma and 5x 10ml follow up).
This study will evaluate whether the LRYGB or the LMBG is more beneficial to patients with T2DM and it will identify the subjects that will have metabolic response upon the surgery (responders) and those that have no response. We therefore believe that the scientific insight of our findings will outweigh the risks for the participating subjects in this study.

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

Age >=18 and <=65 years
BMI >=35 at the day of the intake on the bariatric ward and <=50 kg/m2 on the day of surgery
Diagnosis and (starting of) treatment of T2DM at intake at bariatric ward with anti-diabetic medication
American Society of Anaesthesiologist Classification (ASA) <=3
All patients are required to lose 6 kilograms of weight prior to surgery

Exclusion criteria

Known genetic basis for insulin resistance or glucose intolerance
Type 1 DM
Prior Bariatric surgery
Patients requiring a concomitant intervention (such as cholecystectomy, ventral hernia repair)
Auto-immune gastritis
Known presence of gastro-esophageal reflux disease confirmed by endoscopic investigation or the use of proton-pump inhibitor indicated by complaints of gastro-esophageal reflux (i.e. not indicated by polyfarmacia).
Known presence of large hiatal hernia requiring concomitant surgical repair
Coagulation disorders (PT time > 14 seconds, aPTT ((dependent on laboratory methods) or known presence of bleeding disorders (anamnestic))
Known presence of hemoglobinopathy
Uncontrolled hypertension (RR > 150/95 mmHg)
Renal insufficiency (creatinine > 150 umol/L)
Pregnancy
Breastfeeding
Alcohol or drug dependency
Patients who are considered incapable to fully understand the study and implications of participation in the study, as a consequence of a language barrier, psychiatric disease or mental disabilities, as judged by the surgeon or the coordinating researcher
Participation in any other (therapeutic) study that may influence primary or secondary outcomes, Notably, patients that use vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (i.e. NOACs (Factor Xa inhibitors)) and in whom peri-operative bridging with a therapeutic dose of heparin is indicated, will not undergo intra-operative tissue and/or portal vein sampling.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-10-2017
Enrollment:	220
Type:	Actual

Ethics review

Approved WMO Date:	18-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2020
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	NL61882.048.17