The immune system and microbial tone in relation to NAFLD/NASH before and after BARIatric surgery in the morbidly obese in Amsterdam; the BARIA cohort study.

Published: 29-03-2016
Last updated: 20-04-2024

To gain insight in the metabolic, microbiota and immunologic changes after bariatric surgery that drive NAFLD/NASH and weightless resulting in subsequent conversion of malign to benign obesity.

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

Summary

ID

NL-OMON50702

Source
ToetsingOnline

Brief title
BARIA

Condition

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

Synonym
insuline resistance, obesity

Research involving

Human

Sponsors and support

Primary sponsor: Vasculaire Geneeskunde
Source(s) of monetary or material Support: VIDI grand Nieuwdorp

Intervention

Keyword: Bariatric Surgery, Diabetes type 2, Microbiome, NAFLD/NASH

Outcome measures

Primary outcome

1. NAFLD/NASH parameters in liver biopsy

2. 2h Mixed meal tolerance test for level of insulin sensitivity;

3. Presence of bacterial DNA/bacterial metabolites in portal vein blood,

liver and abdominal adipose tissue depots

4. Small intestinal and faecal microbiota composition

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

6. Dietary and satiety lists and excreted metabolites (24h faeces and urine)

7. Clinical data (body weight, waist circumference, blood pressure and

assessment of cardiac output and baroreflex sensitivity (nexfin), in addition

information will be collected regarding medication, comorbidity, complications

of surgery, presence of mental problems, smoking, use of alcohol and a DNA

sample will be taken) up till 10 years after surgery.

8. Ultrasonography for the detection of gallstones

9. Gallbladder tissue and bile acid collection after cholecystectomy surgery

Secondary outcome

1. Fasting blood samples, dietary and satiety lists and excreted metabolites

(24h faeces and urine as well as BIA and questionnaires) and ECG at 12 months;

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 ECG at 24 months;

3. Faecal microbiota composition and peripheral blood inflammatory markers at

2, and 6 weeks, 6 and 12 months, up until 10 years after surgery; also oral

microbiota at baseline, 12 and 24 months up until 10 years.

4. Expression and differentiation of immunological cells (notably ILC*s,

macrophages) and inflammatory markers (IL6, IRX3 and 5) at 12 and 24 months up

until 10 years after surgery

Study description

Background summary

Non alcoholic fatty liver disease (NAFLD) is present in 80 % of all morbidly obese subjects and is a major risk factor for development of non alcoholic steatohepatis (NASH), with the latter becoming the major indication for liver transplantation in the USA. It is increasingly recognized that the immune system is a major player in obesity related disease and the switch from benign to malign (insulin resistance and DM2) obesity is associated with changes in the immune system and development of NAFLD/NASH. In this regard, the intestinal microbiome is thought to play a major role in driving these immunological changes (via portal vein metabolites). Moreover, the innate immune system including the recently discovered innate lymphoid cells (ILC*s) has increasingly gained attention in metabolic disease. However, at this moment it is unknown whether and to that extend intestinal microbiota and immunological

tone can predict metabolic response (improvement in NAFLD/NASH) and improvement in insulin sensitivity upon bariatric surgery. Increased understanding of the pathophysiological mechanism as well as their relationship to metabolic disturbances are thought to be of crucial importance to discover new diagnostic and therapeutical targets in obesity associated NAFLD/NASH and insulin resistance. Moreover, this study will identify the underlying pathophysiological mechanisms that drive NAFLD/NASH reduction upon the surgery (responders) and those that have no beneficial effect on at all (non-responders) . This might help to predict who will benefit from the bariatric surgical intervention and in whom this is not effective.

Study objective

To gain insight in the metabolic, microbiota and immunologic changes after bariatric surgery that drive NAFLD/NASH and weightless resulting in subsequent conversion of malign to benign obesity.

Study design

Prospective cohort study

Study burden and risks

Participants will be recruited from the outpatient clinics of Surgery and internal medicine at Spaarne Gasthuis. After informed consent, they will collect faeces sample and will undergo mixed meal test within one month prior to scheduled surgery, preferably during their regular hospital admission. In addition to length, weight and blood pressure, they will be instrumented with a non-invasive finger plethysmography (nexfin) for the assessment of central haemodynamics (cardiac output, systemic vascular resistance) and baroreflex sensitivity (BRS). During the mixed meal test, an ultrasonography of the gallbladder will be performed for the detection of gallstones.
During surgery, tissue including liver biopsy and blood will be collected.
During 2 months after surgery, 3 (regularly scheduled) visits will be used for extra sample collection. In the two years following surgery 2 visits to the AMC or Spaarne Gasthuis (decided by the participant) will be scheduled for sample collection and performing one 2h mixed meal tests,. At these visits weight, blood pressure, central haemodynamics and baroreflex sensitivity will again be measured. The ultrasonography of the gallbladder will also be performed again during this follow-up visits. After the first two years after surgery, the intensity of the study will be drastically decreased. Only at 5 and 10n years after surgery, the participant will be asked to collect a faeces sample, urine sample, oral swab and will be asked to fill in a psychological questionnaire. A final visit will take place 10 years after surgery. This will amount to a total of 30 hours of study time additional to the normal procedure.
It is known that 8-10% of all bariatric surgery patient need to undergo

revision surgery within the next 1-2 years (Li et al, Surg Endosc. 2009 Jul;23(7):1640-4). If patients will be scheduled for abdominal surgery (revision of bypass or cholecystectomy) in the 10 years following the first surgery. These patients will be asked to give permission to again obtain samples (liver biopsy and portal blood as well as adipose tissue) during this abdominal surgery. In addition, subjects with definite 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 finds it necessary to repeat the liver biopsy based on clinical grounds, a small part of this sample taken for clinical reasons will be collected if the subjects has given permission. In addition, in the case of referral to a gastroenterologist for upper gastro-intestinal complaints, the subjects might undergo an endoscopy. If the gastroenterologist finds it necessary to perform an endoscopy, a small part of the intestinal biopsy will be collected if the subjects has given permission.
The risk of bleeding from the biopsy sites and portal vein sample during the bariatric surgery procedure is very low because the biopsy sites are completely visible to the surgeon and local haemostasis will be checked. Moreover, bleeding disorders are an exclusion criterion. The adipose tissue biopsies after surgery will be performed under local anaesthesia, there is a chance of a localized temporary haematoma. The risk associated with blood pressure measurement and assessment of non-invasive haemodynamics by fingerphotoplethysmography (Nexfin) is negligible. The burden consists of the extra time invested in the instrumentation and measurement. The risk associated with the ultrasonography of the gallbladder is negligible, the time burden (5min done in parallel with Nexfin) is also negligible since the ultrasonography is performed during the 2 hour mixed meal test. This study will identify the subjects that will have great weight gain upon the surgery (responders) and those that have no beneficial effect on weight at all (non-responders) and for whom the surgery is not effective. We therefore believe that the scientific insight of our findings will outweigh the minimal risks for the participating subjects in this study. Total blood amount taken is 210 ml (2x mixed meal test at 65 ml per test, 1x baseline+DNA 40ml, 10 ml for portal vein plasma and 3x 10ml follow up).

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

- BMI>40 kg/m2 or >35 kg/m2 with obesity related co-morbidity
- Reasonable supervised attempts to lose weight
- 18-65 years of age
4.2 Inclusion criteria
- Scheduled for bariatric surgery
- Ability to provide informed consent

Exclusion criteria

Primary lipid disorder
All medical and psychiatric conditions except for obesity related disease
Coagulation disorders (prolonged PT, aPTT)
Uncontrolled hypertension (RR>150/9 mmHg)
Renal insufficiency (creatinin >150 umol/L)
Excessive alcohol intake (>14 units/week)
Pregnancy, females who are breastfeeding

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2016
Enrollment:	1500
Type:	Actual

Ethics review

Approved WMO Date:	29-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2020
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	NL55755.018.15