Preoperative predictors of weight loss and improved metabolic health after bariatric surgery

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Primary ObjectiveTo validate biomarkers of response to bariatric surgery and to develop algorithms, which combine these variables, to predict individual responses. Secondary Objectives* To establish the predictive value of selected preoperative...

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

Summary

ID

NL-OMON56270

Source
ToetsingOnline

Brief title
Predictors of weight loss and metabolic health after bariatric surgery

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Appetite and general nutritional disorders
- Gastrointestinal therapeutic procedures

Synonym
Obesity, overweight

Research involving
Human

Sponsors and support

Primary sponsor: Endocrinologie&metabolisme

Source(s) of monetary or material Support: Medtronic/NOK

Intervention

Keyword: Bariatric surgery, Metaboic health, Obesity, Predictors

Outcome measures

Primary outcome

The main study parameters are the preoperative blood samples and urine used for GWAS analysis, urine samples will be collected to evaluate predictors of response to surgery , based on results of GWAS analysis and omics analyses performed in previous SOPHIA studies.

Secondary outcome

- To study the predictive value of the measured preoperative biomarkers metabolic response and weight loss 3, 18 and 60 months after bariatric surgery. Specifically, we will assess:

* pro- and anti-inflammatory circulating cytokines and chemokines

* fasting insulin and glucose to calculate insulin sensitivity index and HbA1C

* cardiorespiratory fitness and handgrip strength

* questionnaires to assess eating behavior and psychological traits

Metabolic response is defined as an improvement in insulin sensitivty assessed by HOMA-IR.

- To get more mechanistic insight, the following metabolic assessment will be performed after an overnight fast:

* Resting energy expenditure and substrate oxidation using indirect calorimetry after an overnight fast and during the hyperinsulinemic euglycemic

clamp

* Assessment of hepatic and muscle tissue insulin sensitivity using a stable isotope tracer (6,6 2H2 glucose) during a 2-step hyperinsulinemic euglycemic clamp

* Assessment of adipose tissue insulin sensitivity by calculating the adipose tissue insulin resistance index and by measuring the percentage suppression of fatty acids during low dose insulin infusion (this method was previously validated by our group)

* Assessment of the insulin signaling pathway in biopsies of skeletal muscle and subcutaneous fat by measuring mRNA expression and phosphorylation of key insulin signalling proteins

* Assessment of liver fat and NAFLD criteria, mRNA expression and phosphorylation of the insulin signaling pathway as well as mRNA expression of key components (transcription factors and enzymes) in the de novo lipogenesis pathway in liver biopsies harvested during bariatric surgery

Study description

Background summary

Obesity is the result of a complex interplay between genetic and epigenetic predisposition, environment, physical activity, nutrition and psychology. It is a debilitating disorder and a risk factor for the development of metabolic disorders such as dyslipidaemia, hypertension and hyperglycaemia as well as certain cancers. Bariatric surgery has proven to be the most effective treatment for morbid obesity with established long-term results of weight loss, remission of comorbid conditions and the improvement of Quality of Life (QoL). However, variability in these results after bariatric surgery is well known. Identifying preoperative predictors of postoperative weight loss and metabolic health is of clinical priority. Predictors could help further improve the

efficacy of care for obesity by tailoring treatment to the individual, based on their predicted response and therefore optimize outcome after bariatric surgery. This study is part of an international multicentre European research project: SOPHIA (Stratification of Obese Phenotypes to Optimize Future Obesity Therapy).

Study objective

Primary Objective
To validate biomarkers of response to bariatric surgery and to develop algorithms, which combine these variables, to predict individual responses.

Secondary Objectives
* To establish the predictive value of selected preoperative biomarkers and changes in biomarkers to predict metabolic response and weight loss 3, 18 and 60 months after bariatric surgery.
* To study changes in psychological factors (depression, anxiety, binge eating, eating behavior, food craving, body image) and how these factors are associated with weight loss, metabolic health and improvement of QoL 3, 18 and 60 months after bariatric surgery.
* Assessment of hepatic, muscle and adipose tissue insulin sensitivity using stable isotope tracers and assessment of insulin signaling pathways and protein kinase C family in tissue biopsies.
* To determine the correlation of preoperative measured candidate predictors with selected gene and protein expression (metabolic pathways involved in substrate metabolism) in insulin sensitive tissues (liver, muscle and adipose tissue) in a subset of 40 patients.

Study design

Prospective follow up cohort study.

Study burden and risks

Laparoscopic Roux-en-Y gastric bypass or sleeve gastrectomy surgery will be performed following current procedure protocols and in accordance with Dutch legislations (Wet op de Geneeskundige Behandelings Overeenkomst).

Hyperinsulinemic, euglycemic clamps have been performed by our research group in multiple studies. The stable isotope [6,6-2H2]glucose is used as a tracer, and has no radioactive properties. It behaves like its natural substrate and has been previously used without adverse effects when infused in tracer amounts47-50. During the hyperinsulinemic clamp there is a risk for hypoglycaemia. This is minimized by close monitoring of plasma glucose levels and adjustment of iv glucose, every 5-10 minutes

Surgery will be performed according to standard procedures and current guidelines by an experienced surgeon. During the surgery, biopsies will be taken from the liver, muscle and adipose tissue compartments in the subset of subjects. The number and volume of tissue biopsies will be kept to a minimum. Earlier studies in our group showed that these procedures are safe and were without adverse events.
Possible adverse events related to these procedures are damage to surrounding organs, increased infection risk, pain at biopsy site, and local hematoma and bleeding from the sample site. It should be stated, however, that these adverse events have been described for percutaneous biopsy of abdominal organs, and that taking biopsies during surgery is safer than taking percutaneous biopsies:
* Biopsies are taken under direct vision; surrounding organs can be easily spared;
* All procedures are performed under general anesthesia and under strict sterile conditions in the operating room; there is no increased infection risk;
* There is no percutaneous entry site for liver and adipose tissue biopsies;
* The day(s) after the muscle biopsies, participants will experience a sore feeling at the biopsy location. Local hemostasis can be checked directly after the biopsy and during the surgery: in case of bleeding from the sample site (0.1 to 1% for percutaneous liver biopsy), the surgeon can control this easily and under direct vision.

To further minimize the risk, subjects that use anticoagulants or have coagulation disorders will be excluded from the subgroup and surgeons will check for local hemostasis twice.
It has to be stated that the operative procedure itself is not part of the protocol, but regular patient care.

Placing intravenous cannulas for study purposes can be an unpleasant experience for the subjects. There is a low risk of phlebitis at the intravenous injection sites, this is unpleasant, but not harmful, of temporary nature and self-limiting.
The hyperinsulinemic, euglycemic clamps are generally well tolerated

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

* Ability to provide informed consent
* Patient is >= 18 and <= 75 years old
* BMI >= 40 kg/m2 or >= 35 kg/m2 with obesity related comorbidity
* Scheduled for primary bariatric procedure: Roux-en-Y gastric bypass (RYGB) or Sleeve Gastrectomy (SG)
* Stable weight 3 months prior to inclusion weight (<10% change in body weight for 3 months prior to assessments)

In order to be eligible to participate in the subgroup of this study, we will use the following inclusion criteria:
* We will include only patients who will undergo RYGB;
* Patients who are insulin resistant (impaired fasting glucose (> 5.6 mmol/L) or fasting insulin > 74 pmol/L)
* Postmenopausal women (to prevent bias due to the effect of sex homones on insulin sensitivity)

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
* Patients who do not understand the patient information letter
* Any actual medical condition except for obesity related health issues or well treated hypothyroidism

* Pregnancy anticipated in the first two years following surgery

A potential subject who meet the following criteria will be excluded from participation in the subgroup of this study:
* Coagulation disorders and/or use anticoagulants
* Use of any medication except for statins, antihypertensives (except for ACE- or angiotensin receptor blockers) and thyroid hormone
* Diabetes mellitus type 2

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-01-2023
Enrollment:	1200
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	13-12-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2023

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2023
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	NL77692.018.21