The effects of bariatric surgery on kidney oxygenation in obese adults with type 2 diabetes and hyperfiltration

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To assess kidney oxygenation in obese, hyperfiltering adults with T2D before and after bariatric surgery for men and women separately determined by BOLD-MRI

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

Summary

ID

NL-OMON53673

Source
ToetsingOnline

Brief title
ECSTASY

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Appetite and general nutritional disorders
- Renal disorders (excl nephropathies)

Synonym
kidney disease, Kidney hypoxia

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Diabetesfonds en Nierstichting. Er zijn geen

contracten m.b.t. financiering gemaakt met het Diabetesfonds. De subsidie van het diabetesfonds betreft 325.000 euro en van de Nierstichting 100.000 euro. Ook daar zijn geen verplichtingen t.a.v. het publicatie beleid en zijn de voorwaarden van het diabetesfonds overgenomen als hoofdsubsidieverstrekker. De subsidievoorwaarden van het diabetesfonds zijn bijgevoegd.

Intervention

Keyword: bariatric, hyperfiltration, kidney, T2DM

Outcome measures

Primary outcome

Change in kidney oxygenation in obese, hyperfiltering adults with T2D after bariatric surgery for men and women separately using BOLD-MRI

Secondary outcome

Main study parameters and endpoints: Kidney oxygenation: Oxygenation will be assessed by BOLD-MRI. Cortical and Medullary oxygenation will be assessed. Renal blood flow: Blood flow will be assessed by phase-contrast MRI. Kidney fat percentage: Fat percentage will be assessed by a 3-point Dixon MRI. Renal perfusion: Perfusion will be assessed by Arterial spin labeling (ASL). Kidney Renal hemodynamics, (i.e., GFR, ERPF) will be measured by the gold standard Iohexol and PAH clearance method based on timed urine sampling. In addition, renal perfusion will be assessed by use of phase-contrast MRI. Insulin sensitivity: will be measured by inducing a hyperinsulinemic-euglycemic clamp. Metabolic parameters: plasma concentrations of glucose, FFAs and lipids will be determined. Renal tubular function will be measured by 24-hour urine electrolyte excretions; markers of renal damage will include 24-hour urinary albumin excretion, albumin/creatinine ratio (UACR) and markers such as NGAL and KIM-1; Blood pressure and heart rate will be measured by using an automatic

oscillometric device (Dinamap®); body anthropometrics; height, weight, BMI, waist/hip circumference, body water and fat percentage (by bioimpedance analysis); Additional urine and blood will be collected and appropriately stored for conditional determination of metabolic, biochemical and exploratory variables related to this project. VAT gene expression will be analyzed by RNA sequencing.

Study description

Background summary

DKD (diabetic kidney disease) is the leading cause of chronic kidney disease (CKD) and leading to significant morbidity and early mortality. Although multiple mechanisms underlying DKD have been proposed, the exact underlying mechanisms remain uncertain resulting in limited treatment options. Accumulating evidence, derived from animal and human studies has indicated that chronic kidney hypoxia is a key underlying determinant of DKD and recent studies in T2D patients have related truncal obesity to glomerular hyperfiltration and unfavorable kidney hemodynamic function that may drive kidney hypoxia. Hyperfiltration is defined as increased whole-kidney GFR or as single-nephron hyperfiltration in people with GFR in the normal range. Hyperfiltration is an early recognized key factor driving kidney disease progression in people with diabetes as it drives subsequent eGFR loss. Increased and dysfunctional (i.e., altered adipose tissue biology) visceral adipose tissue (VAT) present in central obesity is thought to disturb the balance between kidney oxygen- consumption and delivery through secretion of endocrine signals resulting in induction of insulin resistance, mitochondrial dysfunction and impaired substrate metabolism amongst others. In line with this theory, reduction of abdominal obesity following bariatric surgery has demonstrated to improve kidney outcomes in some but not in all individuals. In part this may be sex-specific. Since women have a lower risk for progression of DKD, the role of kidney hypoxia in DKD need to be studied in this regard individualized for sex. In this study, we will address the effects of bariatric surgery on changes in kidney oxygenation using a sex-specific approach in people with hyperfiltration.

Study objective

To assess kidney oxygenation in obese, hyperfiltering adults with T2D before

and after bariatric surgery for men and women separately determined by BOLD-MRI

Study design

A monocenter, prospective cohort study.

Study burden and risks

This study consists of three visits (one screening visit and two test day visits) during which a total amount of 286 ml blood will be drawn. For healthy controls this study consists of two visits (one screening visit and one test day visit) during which a total amount of 151 ml blood will be drawn. Participants will have to adhere to a *normal-salt* (9-12 grams or 150-200 mmol per day) and -protein (1.0 g/kg per day) diet and will be asked to keep a food journal in the three days prior to the testing day. Moreover, participants will have to abstain from alcohol (24 hours), caffeine (12 hours) and nicotine (12 hours) and heavy exercise prior to and during the visits. Patient will undergo an MRI during both visits which will last 30-45 min approximately. Iohexol, PAH, insulin and glucose will be infused during both testing days. The infusion of Iohexol can lead to a warm, sometimes painful sensation. Very rare adverse effects (never experienced in > 800 test days in our center) include are headache, stiffness, nerve pain, nausea, vomiting, fever, hives, stomach pain, hallucinations and neurological symptoms. In patients with an allergy for Iohexol it can elicit hypersensitive reactions, therefore we specifically check a for this allergy at screening. The infusion of PAH can lead to a sensation of warmth, or the desire to urinate or defecate during or shortly following the infusion. Extremely large doses may cause osmotic diuresis. The side- and adverse effects of insulin and glucose are negligible in the context of this study.
During bariatric surgery visceral adipose tissue will be collected. The risk of bleeding from the biopsy sites during surgery procedure is very low because the biopsy sites are completely visible to the surgeon and local haemostasis will be checked. In our
previous BARIA study (METC 2015.357), currently about 500 subjects included no adverse events were seen during biopsies).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Group 1: Patients with obesity and hyperfiltration • ; man or women aged >=18 years and <70 years. • BMI >=35 • eGFR>90 ml/min calculated as by CKD-EPI • Provision of signed and dated, written informed consent prior to any study specific procedures • Hypertension should be controlled, i.e., <= 155/95 mmHg. • Scheduled for gastric bypass or gastric sleeve Group 2: Non-diabetic lean controls • male of female aged >=18 years and <40 years. • Provision of signed and dated, written informed consent prior to any study specific procedures. • Normal glucose tolerance confirmed by HbA1c • No hypertension • BMI >=18,5 and <25 kg/m² Group 3: T2DM controls with overweight and eGFR 60-90 ml/min • Caucasian; man or women aged >=18 years and <55 years. Females must be pre-menopausal • Type 2 diabetes mellitus or pre-diabetes with HbA1c >=45mmol/mol and <10% (<94mmol/mol) • BMI >=25 • eGFR 60-90 ml/min calculated as by CKD-EPI • Hypertension should be controlled, i.e., <= 155/95 mmHg. Group 4: Non-diabetic controls with overweight and eGFR 60-90 ml/min • Caucasian; male of female aged >=18 years and <55 years. Females must be pre-menopausal • Normal glucose tolerance confirmed by HbA1c • eGFR 60-90 ml/min calculated as by CKD-EPI • Hypertension should be controlled, i.e., <= 155/95 mmHg. • BMI >=25

Exclusion criteria

Group 1 • Diagnosis of type 1 diabetes mellitus • Cardiovascular disease event

in the last 6 months prior to enrollment as assessed by the investigator, including: myocardial infarction, cardiac surgery or revascularization (CABG/PTCA), unstable angina, heart failure, transient ischemic attack (TIA) or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia. • Chronic use of sodium-glucose transporter-2 inhibitors, oral glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), immune suppressants, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs), diuretics, or monoamine oxidase inhibitors. • Current urinary tract infection or active nephritis • History of allergy/hypersensitivity to any of the test agents • Contra-indication for MRI • Any other condition that prevents participation as judged by investigator. Group 2: Non-diabetic lean controls Exclusion criteria: • Macro-albuminuria (defined as UACR>30 mg/mmol) • . • Cardiovascular disease event in the last 6 months prior to enrollment as assessed by the investigator, including: myocardial infarction, cardiac surgery or revascularization (CABG/PTCA), unstable angina, heart failure, transient ischemic attack (TIA) or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia. • Chronic use of renin-angiotensin-system blockers, sodium-glucose transporter-2 inhibitors, DPP-4 inhibitors, oral glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), immune suppressants, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs), diuretics ormonoamine oxidase inhibitors. • Current urinary tract infection or active nephritis • History of allergy/hypersensitivity to any of the test agents • Contra-indication for MRI Group 3: T2DM controls with overweight and eGFR 60-90 ml/min Exclusion criteria: • Diagnosis of type 1 diabetes mellitus • Post-menopausal females (defined as no menses >1 year and follicle stimulating hormone (FSH) >31 U/L) • Cardiovascular disease event in the last 6 months prior to enrollment as assessed by the investigator, including: myocardial infarction, cardiac surgery or revascularization (CABG/PTCA), unstable angina, heart failure, transient ischemic attack (TIA) or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia. • Chronic use of sodium-glucose transporter-2 inhibitors, oral glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), immune suppressants, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs), diuretics, or monoamine oxidase inhibitors. • Current urinary tract infection or active nephritis • History of allergy/hypersensitivity to any of the test agents • Contra-indication for MRI • Any other condition that prevents participation as judged by investigator. Group 4: Non-diabetic controls with overweight and eGFR 60-90 ml/min • Post-menopausal females (defined as no menses >1 year and follicle stimulating hormone (FSH) >31 U/L) • Cardiovascular disease event in the last 6 months prior to enrollment as assessed by the investigator, including: myocardial infarction, cardiac surgery or revascularization (CABG/PTCA), unstable angina, heart failure, transient ischemic attack (TIA) or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmia. • Chronic use of sodium-glucose transporter-2 inhibitors, oral glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), immune suppressants, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs), diuretics, or monoamine oxidase inhibitors. •

Current urinary tract infection or active nephritis • History of allergy/hypersensitivity to any of the test agents • Contra-indication for MRI • Any other condition that prevents participation as judged by investigator.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-07-2023
Enrollment:	100
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	20-06-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2023
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2024
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	NL83191.018.23