Metabolic Characterization of Type 2 Diabetic, Obese, Lean Sedentary and Endurance Trained Individuals in vivo, ex vivo and in vitro

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON38384

Source
ToetsingOnline

Brief title
Metabolic Phenotyping

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)
- Lipid metabolism disorders

Synonym
diabetes, type 2 diabetes mellitus

Health condition

endurance athletes, obesity, lean sedentary

Research involving
Human

Sponsors and support

Primary sponsor: Human Biology
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Athletes, Cell culture, Substrate metabolism, Type 2 diabetes

Outcome measures

Primary outcome

The Primary Objective is to assess metabolic flexibility in vivo in a broad spectrum of individuals from highly insulin sensitive athletes to those with overt type 2 diabetes (T2D) and their control counterparts.

Secondary outcome

The Secondary Objectives are to assess mitochondrial function in vivo and ex vivo and quantify lipid content and acetylcarnitine concentrations in skeletal muscle of endurance athletes, type 2 diabetes patients and sedentary lean and obese controls. Furthermore, brown adipose tissue activity (Standard Uptake Values (SUV)) and brown adipocyte recruitment in WAT will be measured in the endurance athletes and lean sedentary subjects. UCP-1 and beta-receptor polymorphisms.

The Tertiary Objective is to establish primary myoblast cell lines from endurance athlete, sedentary lean and obese, and type 2 diabetic donors to further characterize muscle function via dietary, pharmacological and genetic

manipulations in vitro.

Study description

Background summary

Type 2 diabetes (T2D) is a global burden disease affecting almost 200 million people and is expected to nearly double by 2030. It is imperative that this disease is kept under control, and that we begin to reverse the direction of its incidence. We propose to start by identifying the physiological and molecular aspects of the problem in all spectrums of the disease (ie from insulin sensitive athletes to sedentary lean and obese individuals and further to overt type 2 diabetics), and focus our efforts on examining the differences and identifying the stages of progression for possible targets of future intervention. The proposed study *Metabolic Phenotyping* is novel in its target populations and innovative in its use of state-of-the-art techniques. We hypothesize that the in vivo differences in metabolic flexibility and mitochondrial function between endurance athletes and type 2 diabetics and their lean and obese controls are retained in vitro and will offer a new model in which to study the underlying mechanisms of the progression of T2D.

Study objective

The aim of the present research proposal is to metabolically phenotype endurance trained athletes, lean and obese sedentary and type 2 diabetic individuals with the following objectives:
(1) To assess metabolic flexibility as measured by a euglycemic-hyperinsulinemic clamp
(2) To measure in vivo mitochondrial function by magnetic resonance spectroscopy (MRS) of phosphocreatine (PCr) recovery
(3) To establish primary myoblast cell lines to correlate with the above in vivo measurements, as well as further explore dietary, pharmacological and genetic manipulations in vitro
(4) To quantify intramyocellular lipid (IMCL) and acetylcarnitine in vivo by magnetic resonance spectroscopy (MRS).
(5) To measure the differences in BAT activity and brown adipocyte recruitment in white adipose tissue ("browning") between endurance atheletes and untrained sedentary lean subjects.

Study design

132 male participants will be recruited to Maastricht University (See Study Population). Eligible participants will undergo a euglycemic-hyperinsulinemic clamp, MRS for PCr recovery and muscle fat content, body composition

measurements and a skeletal muscle biopsy to complete the three study objectives.

After participants send back the informed consent, they will be invited to the University for a screening. During the screening visit participants will be screened to assess eligibility, which will include fasting blood samples, resting blood pressure, body weight and height, a medical history questionnaire, an oral glucose tolerance test (OGTT, only for the type 2 diabetic group), a resting 12-lead electrocardiogram (ECG), a pretest to determine maximal knee extension capacity and a cycling test (VO2max). The total duration of the screening visit will be 1.5 hours. Following determination of eligibility, the participants will return to the University for 2 separate testing days (consecutive if possible) that total 13 hours in duration. Test Day 1 consists of a muscle biopsy and a euglycemic-hyperinsulinemic clamp (10 hours in total). Test Day 2 consists of an MRS scan for intramyocellular lipid and acetylcarnitine content and PCr recovery and a DEXA scan for body composition (3 hours in total).

Study burden and risks

A burden is the time that the participants spend undergoing the study procedures (3 visits, total time 13h). In an effort to limit this burden, all study procedures are only performed once. Blood draws are done through cannulas that are inserted for the euglycemic-hyperinsulinemic clamp. There is risk of pain, swelling of the vein, bleeding, or bruising at the site of the cannula insertion on the arm. Sterile technique and trained personnel minimize these risks. During MRS, kan er ongemak ervaren worden tijdens het uitoefenen van druk met het been tegen de weerstand; dit is echter van korte duur (~5 minuten). Er is een kleine kans op een onverwachte medische bevinding bij de analyse van de MR opnames. In dat geval zal de deelnemer worden geïnformeerd en ook zijn behandelend arts zal op de hoogte gesteld worden. Tijdens de MRS scan kan het lawaai als onplezierig ervaren worden, maar deelnemers krijgen oordoppen en/of een hoofdtelefoon. Er is een minimale hoeveelheid radiatie geassocieerd met de DEXA scan voor lichaamssamenstelling. It is roughly equal to 12 hours of background sun radiation. There is some pain associated with the muscle biopsy; however, this is associated with the injection of xylocaine to desensitize the skin and muscle for the procedure and is thus short in duration (~1 minute). Sterile technique and trained personnel minimize these risks. The primary benefits of participation is knowledge of one*s own ability to switch between oxidation of glucose and fat, as well the ability to resynthesize phosphocreatine after a bout of exercise. Another benefit of participation is monetary compensation (¤150).
For the endurance trained athletes and the lean sedentary group a white biopsy will be taken. There will be a risk for a haemotoma during this procedure. Furthermore, there is a small chance on finding an unexpected medical issue on the PET-CT image. In that case the participant will be informed including his general physician. The total absorbed radiation dose from one FDG-PET/CT-scans

after administration of one time 74 MBq of 18F-FDG is 3.2 mSv, which is considered as a low risk.

Contacts

Public
Selecteer

Universiteitssingel 50
Maastricht 6229ER
NL
Scientific
Selecteer

Universiteitssingel 50
Maastricht 6229ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

General inclusion criteria:
- Male sex
- Generally healthy with specifically no known cardiovascular disease or gastric ulcers, which can affect the study parameters
- Stable dietary habits (no weight loss/gain > 3 kg in the last 6 months);Group 1, type 2 diabetes participants:
- Ages 40-70 years
- BMI > 30 kg/m2

- Non-insulin dependent type 2 diabetes
- Must be on sulphonylurea(SU)- derivate or metformin therapy for at least six months with a constant dose for at least two months, or on dietary treatment for at least six months
- Well-controlled diabetes: HbA1c < 8%
- No diabetes related co-morbidities like cardiovascular diseases, diabetic foot, polyneuropathy, retinopathy
- No other (genetic) diseases that are associated with altered lipid profiles (including familial hypercholesterolemia and familiar combined hyperlipemia);Group 2, obese healthy control participants:
- Ages 40-70 years
- BMI > 30 kg/m2
- A plasma glucose level lower than 6.1 mmol/L
- No family history of diabetes
- No medication use
- Sedentary lifestyle; No participation in any physical activity for at least 2 years
- No other (genetic) diseases that are associated with altered lipid profiles (including familial hypercholesterolemia and familiar combined hyperlipemia);Group 3, endurance trained athletes:
- Ages 18-35 years
- BMI < 25 kg/m2
- No family history of diabetes
- No medication use
- VO2max > 55ml/kg/min
- Active in competitive endurance-exercise activities, 3 times a week for at least 2 years
- Stable level of training for at least 6 months
- No dyslipidemia (including familial hypercholesterolemia and familiar combined hyperlipemia);Group 4, lean healthy sedentary control participants:
- Ages 18-35 years
- BMI < 25 kg/m2
- No family history of diabetes
- No medication use
- VO2max < 55ml/kg/min
- Plasma glucose < 6.1 mmol/L
- Sedentary lifestyle; No participation in physical activity for more than 1 hour per week for at least 2 years
- No dyslipidemia (including familial hypercholesterolemia and familiar combined hyperlipemia)

Exclusion criteria

General exclusion criteria:
- Regular smokers
- Participation in other studies
- Female sex
- Insulin dependent diabetic individuals

- Participants with diabetes related diseases (diabetic foot, diabetic polyneuropathy, diabetic retinopathy etc.)
- Use of Thiazolidines (glitazone/rosiglitazone/pioglitazone/troglitazone)
- Use of anti-coagulants (not trombocyte-aggregation inhibitors)
- Aberrant ECG (with signs of ischemia or cardiac failure or arrythmias)
- Weight gain/loss > 3 kg in the last 6 months
- HbA1c < 7.8 in type 2 diabetic individuals
- Contraindications for MRS scans:
• Electronic implants such as pacemakers or neurostimulator
• Iron-containing foreign bodies in eyes or brain
• Some hearing aids and artificial (heart) valves which are contraindicated for MRS
• Claustrophobia
- Participants, who do not want to be informed about unexpected medical findings, or do not wish that their physician is informed, cannot participate in the study.
- Participants who have been involved in studies (or for medical reasons) with medical radiation (PET-CT scans)

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):	01-07-2011
Enrollment:	132
Type:	Actual

Ethics review

Approved WMO

Date:	04-04-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-08-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

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	NL35178.068.11
Other	pending