Searching for non-invasive Magnetic Resonance-based markers for CrAT activity and carnitine availability

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Primary objective:To investigate the correlation between skeletal muscle phosphocreatine (PCr) on-kinetic at the beginning of exercise and CrAT protein abundance/activity in healthy young males characterized by a wide range of maximal aerobic...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Observational invasive

Summary

ID

NL-OMON48547

Source
ToetsingOnline

Brief title
Markers of CrAT protein activity and carnitine availability

Condition

- Lipid metabolism disorders

Synonym
Phosphocreatine kinetic and exercise metabolism

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Acetylcarnitine, Carnitine, Exercise metabolism, Skeletal muscle

Outcome measures

Primary outcome

- Skeletal muscle phosphocreatine on-kinetic (pmol / kg tissue) at the beggining of exercise measured by MRS technique

- Protein content and activity of carnitine acetyltransferase (CrAT) determined in muscle biopsy

Secondary outcome

- Acetylcarnitine levels in skeletal muscle measured by MRS technique (mmol/kg wet weight) at resting and post exercise condition

- Muscle tissue oxygenation measured by Blood Oxygen level-dependent (BOLD) MRI technique.

- Ex vivo skeletal muscle mitochondrial function expressed as O2 consumption in pmol/mg/min, determined from muscle biopsy sample

- Total carnitine availability and protein content, expression/activity of regulatory enzyme involved in the skeletal muscle acetylcarnitine formation (determined in muscle biopsies)

Study description

Background summary

Previous studies have shown that mitochondrial function is essential at the transitions from rest to steady state exercise, exhibiting a short activation delay to supply ATP for muscle contraction. A delayed mitochondrial activation rate at the onset of exercise is associated with muscle metabolic instability, poor exercise tolerance and early muscle fatigue. As a likely underlying mechanism, it is proposed the existence of an Acetyl group deficiency, referred as metabolic inertia. In this context, acetylcarnitine is pointed out to as a key factor, as acetylcarnitine breakdown (regulated by the action of CrAT protein) may deliver Acetyl-CoA groups to the tricarboxylic acid cycle (TCA cycle) under conditions of high demand; for example at the onset of exercise (Acetylcarnitine on-kinetic). Indeed, increments of acetylcarnitine content in the resting state before exercise modulates the mitochondrial activation speed and CrAT activity may determine the duration of metabolic inertia. To date, the only possibility to get information on CrAT activity is by taking a muscle biopsy and perform enzyme activity assays ex vivo. By dynamic MRS scanning, it might be possible to deduce information that reflects CrAT activity, thereby making the biopsy sampling unnecessary.
It is expected that CrAT protein activity modulates mitochondrial activation during exercise. As phosphocreatine (PCr) kinetic at the beginning of exercise might reflect mitochondrial activation, it is expected that CrAT protein activity is correlated with PCr on-kinetic at the beginning of exercise. Furthermore, another interesting metabolic parameter that can influence mitochondrial activation is muscle tissue oxygenation and intrinsic mitochondrial function. Thus, those parameters will be assessed in the current proposal. We hypothesize that muscle tissue oxygenation correlates with mitochondrial activation. Finally, it will be tested whether CrAT protein activity and carnitine availability in skeletal muscle determines maximal acetylcarnitine formation upon exercise.

Study objective

Primary objective:

To investigate the correlation between skeletal muscle phosphocreatine (PCr) on-kinetic at the beginning of exercise and CrAT protein abundance/activity in healthy young males characterized by a wide range of maximal aerobic capacity.

Secondary objective:

To investigate the correlation of CrAT protein abundance/activity and and muscle tissue oxygenation in healthy young males in a wide range of maximal

aerobic capacity

To investigate whether phosphocreatine (PCr) on-kinetic at the beginning of exercise and CrAT protein abundance/activity is associated with ex vivo skeletal muscle mitochondrial function in healthy young males in a wide range of maximal aerobic capacity.

To explore whether maximal acetylcarnitine formation upon exercise is correlated with CrAT protein activity/content and carnitine availability from muscle biopsies

Study design

In this cross sectional study 13 subjects will visit the University 3 different days, for screening and for the exercise test days.

Screening; to assess eligibility.
-Informed consent
-Medical history questionnaire
-MRI contra-indications form
-Fasted blood samples to determine metabolic health
-Maximal aerobic capacity
- Maximal one-legged extension
- Electrocardiogram at resting

MRS+Exercise test day 1:
- Body composition by Bod pod technique
- Muscle tissue oxygenation before and after one-legged exercise

Exercise test day 2:
-Acetylcarnitine levels at resting and post cycling exercise
- Standardized cycling test 30 minutes total; 10 minutes at 30% Wmax, 10 minutes at 50% Wmax and 10 minutes at 70% Wmax
- PCr kinetic during and post exercise.
- Maximal acetylcarnitine formation upon exercise
- One muscle biopsy before exercise
-Indirect calorimetry throughout cycling test
-4 Blood samples during exercise and 4 blood samples during recovery post exercise (8 blood sample sin total; ~10 ml each sample)

Study burden and risks

The results of this research will provide a novel approach to measure CrAT protein activity and carnitine availability by using a non-invasive Magnetic Resonance-based methodology in humans. Indeed, by measuring the kinetic of phosphocreatine (PCr) during exercise may give us information about

mitochondrial activation, process on which CrAT protein activity might play a pivotal role to determine the exercise tolerance and early muscle fatigue during exercise in humans.

The risk involved in this research are very small. Adverse effects will hardly occur.
The exercise test days comprise non-invasive and invasive measurements. The used techniques are safe, but the muscle biopsies can cause some discomfort and may result in a local bruise or hematoma. Likewise, blood sampling can cause a local hematoma. The risk of infection and or prolonged bleeding is very low due to state of the art technique and sterility measures. Magnetic Resonance Imaging can result in unexpected medical findings.

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

- Males
- Generally healthy (not cardiovascular complications)
- Age 18-40 years old
- BMI 18 - 28 kg/m2
- No medication use that interfere with the aims of the study
- Stable level of daily physical activity or training for at least 6 months

Exclusion criteria

- Regular smokers, drug abuse
- Participation in other studies
- Weight gain/loss > 3 kg in the last 6 months
- Contraindications for MRS scans
- Vegetarian eating behavior
- Females

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-03-2019
Enrollment:	13
Type:	Actual

Ethics review

Approved WMO

Date:	10-10-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC 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	NL63005.068.18