Skeletal Muscle Metabolism during Rest, Exercise and Recovery in Patients with VLCADD and healthy controls

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To investigate whether patients with VLCADD have a different energy metabolism compared to healthy controls.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Inborn errors of metabolism
Study type	Observational invasive

Summary

ID

NL-OMON37550

Source
ToetsingOnline

Brief title
VLCADD muscle metabolism

Condition

- Inborn errors of metabolism
- Muscle disorders

Synonym
Beta-oxidation disturbance; fatty-acid oxidation disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Roorda foundation

Intervention

Keyword: metabolism, MRS, muscle, VLCADD

Outcome measures

Primary outcome

o Blood parameters: glucose, lactaat, creatine kinase (CK)

o Resting, and FATMAX exercise phoscreatine (PCr)

o Resting, and FATMAX Inorganic phosphorus (Pi)

o Resting, and FATMAX pH

o Resting and FATMAX phosphate potential (delta GP)

o Resting, and FATMAX hexose monophosphates (HMP)

o Resting, and FATMAX IMCL content

o Stroke volume

o Urine: myoglobine

Secondary outcome

o Peak workload (Wpeak)

o Resting and peak oxygen uptake (VO2peak/kg (ml/min/kg))

o Resting and peak minute ventilation (VEpeak) (L/min)

o Resting and peak respiratory exchange ratio (RER = VCO2/VO2)

o Resting and peak heart rate (HR; bpm)

Study description

Background summary

VLCADD is a rare disorder affecting the mitochondrial beta-oxidation of long-chain fatty acids. Clinical symptoms such as hypoglycaemia and

(cardio)myopathy arise, or are exacerbated during catabolic situations e.g. during illness or fasting. Age at onset, manifestation patterns and clinical severity differ between patients. Dietary treatment -the only therapeutic option- will prevent hypoglycaemic episodes, however it does not reduce myopathy. One of the most prominent symptoms of patients with VLCADD is myopathy induced by the breakdown of myocytes (rhabdomyolysis). Rhabdomyolysis is provoked by fasting, fever, cold, medication, and exercise from infancy to adulthood. The pathophysiology of these episodes of rhabdomyolysis is not completely understood. The symptoms might be caused by 1) an energy shortage due to the fatty acid oxidation (FAO) defect and/or 2) toxicity caused by the accumulation of FAO intermediates, or 3) by meta-flammation: inflammation caused by abnormal metabolites. Insight into the pathophysiology of muscle metabolism in patients with VLCADD can be used to understand and (eventually) treat myopathy that accompanies this disease.
Recently, 31 Posphate and 1 Proton magnetic resonance spectroscopy (31P/1H MRS)has been shown to non-invasively assess muscle metabolism in-vivo during rest, but also during exercise and recovery. In the proposed study, 31P MRS and 1Proton MRS measurements will be combined with a cardiopulmonary exercise test (CPET) on a cycle ergometer.

Study objective

To investigate whether patients with VLCADD have a different energy metabolism compared to healthy controls.

Study design

A case-controlled study using a novel MRS technique.

Study burden and risks

In clinical practice, many parents wonder to which extent their children will be able to perform exercise. The same applies to adults. This study will gain insight into physical abilities and inabilities of children and adults with VLCADD. This insight will be used to advice patients to what extent they can participate in physical activities and at what intensity. In addition, more rhabdomyolytic episodes have been observed in children with VLCADD opposed to adult patients. As the metabolic response to exercise of children with VLCADD might be different compared to adult patients, it is also important to perform these exercise tests in patients between 12 and 18 years of age when studying the muscle metabolism during rest, exercise and recovery (group relatedness). Participation in the first test will take in total 45 minutes, including a 8-12 min maximal exercise test. To provide the shortest possible exercise duration, step rates on the bicycle are individualised to yield test durations of approximately 10 minutes for each volunteer. The second test will take 270 min, including a 45 min submaximal (~30% of max.) exercise test and recovery time

after the test. Both tests will be performed during two separate test sessions on two different days.
Since the maximum exercise test will use anaerobic derived energy and the endurance test will be at a submaximal level (30% of max.), the burden for controls is very small. No muscle pain is expected. As patients with VLCADD do not have a problem with anaerobic glycolysis, the burden for the maximal exercise test will also be very small. The endurance test at submaximal level might induce muscle pain temporarily, becasue the aerobic system is affected in VLCADD patients. We therefore classify the burden for patients as minimal and will monitor these patients accordingly during the study period. Blood will be drawn intravenously from patients between 12 and 45 years of age. This implies a minimal burden. To minimize the burden for young controls, blood will only be drawn from adult controls.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

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

Inclusion criteria

Patients with VLCADD
- diagnosis confirmed by enzyme assay and mutation analysis
- between 12 and 45 years
Healthy controls:
- between 12 and 45 years
- free from constraints in performing a maximal exercise test

Exclusion criteria

Patients with VLCADD:
- ineligible to perform an exercise test
- pregnancy
- myopathic exacerbation at time of investigation
- with severe complications due to cardiomyopathy/arrythmia
- with severe complications due to epilepsia
- not familiar with the Dutch language
- presence of contra-indications for 31P/1H MRS measurements (assessed by standardised questionnaire as previously used in METC 08-267/K; see section F METC documents)
Healthy controls:
- ineligible to perform an exercise test (assessed by a standardised questionnaire as previously used in METC 10-468)
- not familiar with the Dutch language
- presence of contra-indications for 31P/1H MRS measurements (assessed by a standardised questionnaire as previously used in METC 08-267/K)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-11-2012
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO

Date:	18-10-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL38965.041.12