Skeletal muscle mitochondrial (dys)function in humans: Relating macroscopic in vivo observations to mechanistic understanding at molecular scale

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

Summary

ID

NL-OMON39110

Source
ToetsingOnline

Brief title
systems biology of mitochondrial dysfunction

Condition

- Other condition
- Diabetic complications

Synonym
aging, diabetes

Health condition

veroudering, mitochondriële myopathie

Research involving
Human

Sponsors and support

Primary sponsor: Maxima Medisch Centrum
Source(s) of monetary or material Support: CTMM (center for translational molecular medicine) project: predicct (Prediction and Early Diagnosis of Diabetes and Diabetes-related Cardiovascular Complications)

Intervention

Keyword: energy metabolism, mitochondrial dysfunction, skeletal muscle, systems biology

Outcome measures

Primary outcome

Mitochondrial function will be assessed by 31P magnetic resonance spectroscopy

(rate of PCr recovery after submaximal exercise) in M. vastus lateralis.

Differences in molecular phenotype of the muscle cells will be obtained by

analysis of muscle biopsy samples for:

- State 3, 4, U respiration

- Complex I, II, III, IV, ATPase, ANT, UCP3 content

- Mitochondrial DNA copy number

- Fiber type composition, muscle vascularisation

Secondary outcome

- VO2max en Qmax determined on calibrated bicycle ergometer

- Relation between oxygen consumption and power output determined on calibrated

bicycle ergometer

Study description

Background summary

Mitochondrial dysfunction in skeletal muscle has been associated with metabolic diseases and aging. We want to investigate the molecular mechanisms underlying mitochondrial dysfunction in several patients / subject groups: i.e. mitochondrial myotpathy, type 2 diabetes and elderly with a sedentary or active lifestyle. At the moment, it is possible to measure mitochondrial function in vivo by 31P MRS. Differences in the molecular make-up of muscle cells can be detected by analysis of muscle biopsy samples. What has been lacking is methodology for relating the changes in molecular make-up of the muscle to the observed dysfunction in vivo in a quantitative and mechanistic manner. To overcome this limitation a mathematical model of skeletal muscle energy metabolism is being developed at Eindhoven University of Technology (BioModeling and Bioinformatics, BioMedical NMR group). In the present study we want to apply the mathematical model to relate mitochondrial dysfunction as observed in vivo to mechanisms at molecular scale. By combining the mathematical model and an extensive newly obtained dataset it is expected we will gain novel insight in the origin of mitochondrial dysfunction in type 2 diabetes and aging. This knowledge may eventually be useful for the identification of biomarkers, molecular intervention targets and personalized medicine.

Study objective

The main objective of the study is to quantify mitochondrial dysfunction in vivo and obtain information of molecular scale adaptations of the muscle cells that potentially underlie the observed dysfunction. The mathematical model will be applied to relate in vivo measurements to the results of the muscle biopsy analysis. Model simulations will provide the link between the macroscopic in vivo measurements and the results from the muscle biopsy analysis. Secondary objective is to test if supplementation of 500mL/day of beetroot juice to normal diet improves exercise performance in patients with mitochondrial myopathy.

Study design

case - control study

Study burden and risks

Subjects will visit Máxima Medical Center, Erasmus Medical Center or Eindhoven University of Technology 3 or 4 times in a period of 3 or 4 weeks. During these visits the subjects will undergo a VO2max test on a bicycle ergometer, the collection of a blood sample in fastened state, assessment of mitochondrial function by means of 31P magnetic resonance spectroscopy and the collection of a muscle biopsy sample. In addition, all subjects are asked to fill in a

questionnaire quantifying their daily activity.
The VO2max test and blood sample collection are routinely performed in the clinic and the associated risks are considered to be very low. 31P MRS spectroscopy is less frequently applied, however the risks associated with this technology are also considered to be very low [34]. The muscle biopsy can, in some cases, be painful. Infections and bleeding afterwards are possible, but rare.
Yet, the data acquired from these experiments will contribute to an improved understanding of the molecular mechanisms underlying mitochondrial dysfunction in humans. . This knowledge is expected to be useful for the identification of biomarkers, molecular intervention targets and personalized medicine.

The subjects diagnosed with mitochondrial myopathy and the healthy controls will receive 8 days of dietary inorganic nitrate supplementation to their normal diet and will visit the clinic on 3 more days to undergo additional exercise test on a hometrainer (50%Wmax), 31P magnetic resonance spectroscopy scan and muscle biopsy collection.
The oral ingestion of 8.5 mg/kg body wt/day dietary inorganic nitrate is reported to be without additional risks. The expected benefit of inorganic nitrate intake will be a reduction in the O2 cost of exercise thereby improving the exercise tolerance and quality of life of these patients.

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

All subjects:
- written informed consent;Mitochondrial myopathy:
- patients diagnosed with mitochondrial myopathy
- Age: 18+;Type 2 diabetes:
- patients diagnosed with Type 2 diabetes for at least 2 years
- age: 18+
- BMI 26 - 42 kg/m2
- sedentary behaviour as confirmed by a questionnaire asking about physical activity levels
- sex: male

Elderly with sedentary lifestyle:
- Age: 50 - 75 yrs
- sedentary lifestyle as confirmed by a questionnaire asking about physical activity levels
- sex: male ;Elderly with active lifestyle:
- Age: 50 - 75 yrs
- active lifestyle as confirmed by a questionnaire asking about physical activity levels
- sex: male

Control subjects:
- Age: 20 - 30 yrs
- BMI: 20 - 25
- Normally active lifestyle as confirmed by a questionnaire asking about physical activity levels
- sex: male

Exclusion criteria

All subjects:
- pacemaker / implantable cardioverter defibrillator (ICD)
- metal prostheses
- implanted devices
- vascular clips
- profession (current of in the past) as welder or metalworker (risk of small metal fragments in eyes);- claustrophobia
- use of oral anti-coagulants

- use of inorganic nitrate
- cardio-vascular disease (decompensatio cordis, agina pectoris, myocardial infarction of positive signs of cardiac ischaemia on the ECG during the incremental exercise test on the bicycle ergometer)
- cerebro-vascular disease (CVA)
- neurological diseases of deficits
- vascular complications

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:	Recruitment stopped
Start date (anticipated):	09-03-2012
Enrollment:	52
Type:	Actual

Ethics review

Approved WMO Date:	16-11-2011
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	11-04-2012
Application type:	Amendment

Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	06-03-2013
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26686
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL36927.015.11
OMON	NL-OMON26686