'VEMA-trial: MRS based NAD+ quantification. Responsibility of a novel MRS-based method quantifying NAD+ in vivo'

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27957

Source
Nationaal Trial Register

Brief title
VEMA

Health condition

Type 2 diabetes mellitusy / overweight and obesity

Sponsors and support

Primary sponsor: ERC grant
Source(s) of monetary or material Support: ERC grant

Intervention

Outcome measures

Primary outcome

Levels of NAD+ and NADH measured by 31P-MRS.

Secondary outcome

Concentrations of NAD+ and NADH, measured in biopsies.

Study description

Background summary

Rationale: With increasing prevalence of cardiometabolic disease, the challenge of the coming years is to intervene at an earlier stage in the pathogenesis of such disease and discover new therapeutic targets. To identify and monitor the mechanisms responsible for blunted cardiometabolic health in humans, and progression to metabolic disease such as diabetes, non-invasive imaging methods are needed to investigate metabolism dynamically. Standard Magnetic Resonance Spectroscopy (MRS) methodology is nowadays commonly used to examine readily detectable biochemical compounds (like ectopic lipids). However, by dedicated design of novel MRS sequences, more unique metabolites key in the development of metabolic disorders, can be visualized and quantified non-invasively. Animal studies indicate that Nicotinamide Adenine Dinucleotide (NAD+), by being an activator of many intracellular enzymes and a co-regulator of mitochondrial function and biogenesis, may well play a role in regulating metabolic health. Human data on the relevance of NAD+ is still very scarce because investigation in humans requires rapidly processed tissue samples obtained via invasive procedures (muscle biopsies). Consequently, kinetic information is particularly difficult to obtain. 31P-MRS at high magnetic field (7T) was used to quantify NAD+ and NADH in the brain (Zhu, Lu et al. 2015). But at clinical field strength (3T), the spectral resolution is lower, resulting in overlapping peaks of NAD+, NADH and ATP signals. Therefore, to ensure robust quantification in muscle, design of tailored sequences for NAD+ detection are warranted in order to achieve the simultaneous suppression of ATP signals that are overlapping with NAD and enable quantification at clinical field strength.

Objective: The objective of this study is to investigate whether differences over time are able to determine with a novel MRS-based method to quantify NAD+ by selectively suppressing the coupled α-ATP spin system, which is overlapping with the NAD+/NADH signals in vivo. For NAD+/NADH quantification to be valuable in metabolic research, it should be possible to pick up changes in response to physiological stimuli. It is well known that NAD+ is increased upon fasting, exercise and ischemia. Therefore, in the current protocol, the measurement of NAD+ will be applied after such interventions. Furthermore, the in vivo measurements will be compared to NAD+ and NADH quantification in muscle biopsies to explorative investigate whether similar results are found as in vivo.

Study design: Proof of principle study with two short interventions making use of pre/post design.

Study population: Two groups of respectively 8 and 12 healthy young lean subjects will be included.

Intervention (if applicable): One group with 8 subjects will undergo an ischemia protocol during a MRS measurement. The other group will consist of 12 subjects who will remain fasted for 36 hours and MRS will be performed before, during and after the fasting period. Before/after intervention, also muscle biopsies will be taken.

Main study parameters/endpoints: NAD+ concentration as measured by 31P-MRS before/after intervention. Secondary endpoint is NAD+ as determined in muscle biopsies.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This study carries no benefits for the subjects and carries minor risks for the subjects. The major burdens consist of a moderate time commitment, staying fasted for a prolonged time and multiple muscle biopsies and blood sampling.

Study objective

Primary Objective:
The primary objective of this study is to determine whether the physiological increase of NAD+ induced by either ischemia or prolonged fasting can be measured with 31P-MRS in healthy lean subjects.

Exploratory Objective(s):
An exploratory objective of this study is to investigate whether the NAD+ levels measured in vivo with 31P-MRS are comparable with the ex vivo blood and muscle NAD+ levels.

Study design

Ischemia-part: 1 day, 4 hours
Fasting-part: 1.5 day, 36 hours

Intervention

One of the two subject groups will undergo a ischemia protocol combined with MRS measurements (“ischemia” group).
The other group will be included to investigate whether differences over time are able to determine with the MRS-method by monitoring the fasting-induced increase in NAD+ concentration (“fasting” group). MRS measurements will be performed at 4 time points, at the start of the fasting period and after 12-, 24- and 36 hours of fasting. After every MRS measurement, blood will be drawn. After the first and after the last MRS measurement, a muscle biopsy will be taken.

Ischemia group:
In order to increase NAD+ concentrations, a MRI compatible blood pressure cuff will be secured around the thigh of the subject for rapid inflation (ischemia) and subsequently deflation during a MRS measurement to quantify NAD+ levels. Inflation of the cuff will be performed for 8 minutes (cuff pressure inflated to 50 mmHg above resting systolic pressure determined prior to the start of the measurement). The two days before the test days, volunteers will refrain from strenuous exercise and food intake will be standardized by

providing a standardized breakfast and lunch.

Fasting group:
Furthermore, twelve young lean subjects will be included to investigate whether differences over time are able to determine with the MRS-method by monitoring the fasting-induced increase in NAD+ concentrations. For very controlled conditions and to monitor substrate oxidation by indirect calorimetry, subjects will enter so-called respiration chambers in the evening of day 1. Until the morning of day 3, subjects will stay in the chamber and only consume water. MRS measurements will be performed every 12 hours (evening before entering the respiration chamber, morning of day 2, late afternoon of day 2 and morning of day 3 (before breakfast)). In the evening of day 1 and the morning of day 3, a muscle biopsy will be taken to exploratively investigate whether similar results are found as in vivo, see figure 3 for scheme of tests. The day before the test days, volunteers will refrain from strenuous exercise. Food intake will be standardized by asking subjects to consume a light lunch and stay fasted thereafter until they come to the university at 17.30. After the evening meal (provided at the university) subjects will stay fasted overnight and the following day and night.

Note: due to the outbreak of the COVID-19 pandemic the fasting group was not performed in this study.

Contacts

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Eligibility criteria

Inclusion criteria

Age: 18-40 years
BMI: 18-25 kg/m2
Generally healthy

Exclusion criteria

Excessive alcohol consumption (men > 4 units per day; women > 3 units per day)
Use of anti-coagulants or other medication known to hamper blood coagulation
Contraindications for MRI scans
Participation in other (intervention) studies within 1 month before the start of this study
Subjects who do not want to be informed about unexpected medical findings, or do not wish that their physician be informed cannot participate in the study
Any condition, disease, abnormal laboratory test result (such as plasma parameters) or medication that, in the opinion of the investigator or the dependent physician, would in-terfere with the study outcome, affect trial participation or put the subject at undue risk
For the fasting study (as stay in the respiration chamber is part of the experiments): regular (every day more than three cigarettes) smoking is an exclusion criterion. Par-ticipants who smoke by occasion (for instance during a party) but not daily are not ex-cluded from participation

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2020
Enrollment:	20
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	09-09-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 49618
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL8888
CCMO	NL66905.068.19
OMON	NL-OMON49618

Study results