The effects of statins on skeletal muscle mitochondria:a pilot study?

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Primary Objectives: To investigate whether differences exist in the mitochondrial energy generating capacity of skeletal muscle of statin users with SAMS compared to statin users without SAMS and controls (non-statin users).Secondary objectives:2A....

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

Summary

ID

NL-OMON42199

Source
ToetsingOnline

Brief title
Statins and mitochondria

Condition

- Other condition
- Muscle disorders

Synonym
the effects of statins on musle mitochondrial function, the effects of statins on the aerobic energy metabolism

Health condition

skeletspier mitochondriale functie, algemene spierfunctie en fitheid

Research involving
Human

Sponsors and support

Primary sponsor: Integrative fysiologie
Source(s) of monetary or material Support: NWO ZONMW veni

Intervention

Keyword: mitochondrial energy metabolism, skeletal muscle, statins

Outcome measures

Primary outcome

The main study outcome paramters are:

1.the energy generating capacity of muscle mitochondria,

2. muscle function (muscle strength, muscle contraction efficiency,muscle fatigability),

3. maximal aerobic capacity

These parameters shall be compared between the three study groups

Secondary outcome

1. Mitochondrial number (in muscle biopsy),

2. Blood paramters: Lipid profile (Total cholesterol, HDL-, LDL-cholesterol, triglycerides), liver enzymes (ASAT, ALAT, gamma-GT), creatine kinase, pyruvate, lactate

3. statin concentrations in muscle and blood

4. Questionnaires on muscle complaints (Short-form McGill pain questionnaire and Short-form Brief Pain Inventory)

Study description

Background summary

Statins are among the most widely prescribed medications in developed countries. They markedly reduce the incidence of ischemic heart disease and stroke by lowering low-density lipoprotein (LDL) cholesterol. Although statins have demonstrated remarkable clinical safety, muscle toxicity is a frequent limiting factor in the administration of statin therapy. Statin-associated muscle symptoms (SAMS) exist in a spectrum from mild muscle symptoms (e.g. fatigue, myalgia, cramps, weakness, reported in 9-27% of patients) to rare life-threatening rhabdomyolysis. The occurrence of diffuse muscle aches significantly limits quality of life and prompts many patients to quit this life-saving medication. As lipid-lowering treatments are intended for long-term use, statin non-adherence has a marked impact on cardiovascular risk management an increases mortality risk.

The mechanisms underlying statin-induced muscular side effects remain incompletely understood. Both in vivo and ex vivo evidence is present for an impaired mitochondrial oxidative capacity in skeletal muscle of patients on statin therapy. Recently, Prof. Frans Russel from the department of Pharmacology and Toxicology at the Radboudumc examined muscle biopsies of subjects with SAMS and found that statins can in fact accumulate in skeletal muscle and specifically bind to and inhibit the activity of complex III of the mitochondrial respiratory chain (Schirris, Smeitink, Russel, Cell Metabolism accepted). These novel data strongly support an inhibitory role of statins on mitochondrial function. Unfortunately no comparison was made with individuals on statins without complaints nor with subjects that do not use statins. Therefore, the first aim of this study is to investigate whether we can detect differences in the mitochondrial energy generating capacity of skeletal muscle between 1. statin users with SAMS compared to 2. statin users without SAMS and compared to 3. controls (non-statin users). The three groups will be matched for age and sex.

Statin-induced effects on skeletal muscle cause a decrease in aerobic capacity. The fact that aerobic fitness is a strong predictor for all-cause mortality but also diabetes risk - which has recently been coupled to statin use-, emphasizes the need to clarify the interaction between statins and skeletal muscle function. There are only a limited number of studies that examined the effects of statins on muscle performance, muscle function and on aerobic capacity. Therefore, the secondary aim of this study is (A). to investigate if statin users with SAMS have an altered muscle function and cardiorespiratory fitness compared to statin users without SAMS and controls (non-statin users) and (B). if this relates to the mitochondrial energy generating capacity of the muscle.

Study objective

Primary Objectives:
To investigate whether differences exist in the mitochondrial energy generating capacity of skeletal muscle of statin users with SAMS compared to statin users without SAMS and controls (non-statin users).

Secondary objectives:
2A. To investigate if statin users with SAMS have an altered muscle function and cardiorespiratory fitness compared to statin users without SAMS and controls (non-statin users)

2B To investigate if altered muscle function and cardiorespiratory fitness in statin users relates to the mitochondrial energy generating capacity of the muscle.

Study design

A cross-sectional study will allow comparison of the energy generating capacity of the mitochondria, muscle function and cardiorespiratory fitness between the different study groups.

Intervention

symptomatic + asymptomatic statin users
placebo intake for a period of 12 weeks in a singleblind fashion

Study burden and risks

During this study, patients using statins will not be exposed to a major risk, as standard care will not be withheld, as patients will not be taken of their medication and will carefully screened.
Performance of a muscle biopsy is not associated with an important health risk. Complications include infection, bleeding and hematoma formation (<2%), whilst these complications will resolve within 2 weeks. The biopsy procedures do not induce discomfort and/or functional impairment. The contra-indications for a muscle biopsy (e.g. use of anticoagulants) will be carefully checked by an experienced physician during the medical screening procedure. After the muscle biopsy, participants will receive written instructions (Sectie E.4 voorlichtingsmateriaal) to which they should adhere and pay attention to (e.g. not perform any exercise of heavy labour immediately after the biopsy, not to take a both for 48h, etc.). Venous blood withdrawal can induce a local hematoma (<5%). However, this is completely reversible within 2 weeks and will not induce permanent damage. Taken together, the nature and extent of burden and risks associated with the different measurements are modest.

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

o Age: 18-70 years old
o Current statin user: (group 1-2) for at least three months
o Mentally able/ allowed to give informed consent

Exclusion criteria

o familial hypercholesterolemia
o history of a cardiovascular event within 1 year of study participatie
o impaired liver function (ALAT, ASAT, gamma-GT > 3x ULN)
o known hereditary muscle defect; creatine kinase > 5x ULN
known mitochondrial disorder

o Medication known to potentially interfere with muscle metabolism (fibrates, Beta blockers, laxatives, diuretics, bronchodilatators)
o Impaired kidney function: creatinin <50 or >100 umol/l
o Diabetes mellitus
o Engagement in exercise for more than two hours per week
o contraindications for the exercise test (as explained in the protocol and the SOP) or muscle biopsy (see SOP)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-11-2015
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	12-06-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-09-2015
Application type:	First submission

Review commission: CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2015-000462-62-NL
CCMO	NL52337.091.15

Study results

Date completed: 25-03-2016

Actual enrolment: 30