The effects of cholesterol-lowering medication on skeletal muscle functioning

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON22168

Source
NTR

Brief title
STATEX

Health condition

Statin associated muscle symptoms
muscle functioning (contraction efficiency, muscle relaxation, muscle fatigue)
whole body aerobic fitness
mitochondrial function

Sponsors and support

Primary sponsor: Radboud University Nijmegen Medical Centre
Source(s) of monetary or material Support: ZonMW Veni

Intervention

Outcome measures

Primary outcome

o Energy generating capacity of muscle mitochondria (in muscle biopsy)

o Muscle function (= muscle force, contractile speed, relaxation and fatigability)

o Cardiorespiratory fitness (incremental cycling test)

Secondary outcome

o Mitochondrial number (in muscle biopsy)

o Blood parameters: lipid profile (total cholesterol, HDL-, LDL-cholesterol, triglycerides), liver enzymes (ASAT, ALAT, gamma-GT), creatine kinase, pyruvate and lactate

o Statin concentrations in the muscle and blood

o 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 [8] 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, sex and physical activity level.

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 aim:

1. 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 aims:

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

The participants will visit the lab two times. On measurement day 1, the medical screening will take place. If subjects are found eliglible, the muscle function measurement will be performed, which will be followed by an incremental cycling test. On day 2, a blood sample will be withdrawn in the overnight fasted state, which will be followed by the collection of a muscle biopsy

Intervention

All study participants will undergo a medical screening session of 1 hour to determine whether they comply with the in- and exclusion criteria. The medical screening will contain an elaborate physical examination and participants are asked to fill out two short questionnaires on muscle complaints (Short-form McGill pain questionnaire and Short-form Brief Pain Inventory). If participants are found eligible for inclusion, we will invite participants to the lab to perform an incremental cycling test and a muscle contractile function test. For these tests, participants are instructed to refrain from strenuous exercise 24h prior to the tests. On a seperate day, in the overnight fasted state, a blood withdrawal will take place to check the lipid profile, liver enzymes and kidney function, creatine kinase, pyruvate, lactate and glucose levels, which will be followed by the collection of a muscle biopsy.

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Eligibility criteria

Inclusion criteria

o Age: 18-70 years old

o Current statin user (group 1-2) for at least 3 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 participation

o Impaired liver function (ALAT, ASAT, gamma-GT > 3x ULN)

o Known hereditary muscle defect, creatine kinase >5 x ULN

o known mitochondrial disease

o Medication known to potentially interfere with muscle metabolism (fibrates, Beta blockers, laxatives, diuretics, bronchodilatators)

o Impaired kidney function (creatinine <50 or > 100 µmol/l)

o Diabetes mellitus

o Engagement in exercise for more than two hours per week

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-10-2015
Enrollment:	30

Type:	Anticipated

Ethics review

Positive opinion Date:	20-10-2015
Application type:	First submission

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
NTR-new	NL5248
NTR-old	NTR5505
Other	: 2015-1836 // NL52337.091.15

Study results