The effects of statins on exercise performance

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Primary Objectives: 1a. To investigate whether differences exist in training response after a 12-week combined endurance- and resistance training program between statin users with and without muscle complaints and a control group (non-statin users)....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON45565

Source
ToetsingOnline

Brief title
Statins and exercise

Condition

- Muscle disorders

Synonym
The effects of statins on exericse performance, the effects of statins on trainingresponse

Research involving
Human

Sponsors and support

Primary sponsor: Integrative fysiologie
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: exercise, mitochondria, muscle function, statins and muscle complaints

Outcome measures

Primary outcome

Aim 1a.

Difference in training response between the 3 groups

Training response is defined as:

* change in aerobic fitness (maximal incremental cycling test)

Aim 1b.

* Exercise-induced change in mitochondrial mass and function

* Exercise-induced change in substrate use

Secondary outcome

Aim 2.

* Exercise-induced change in muscle strength, contractile function and fatigue,

mass (voluntary force: 1 repetition maximum; contractility and fatigue assessed

by electrical stimulation; mass assessed by DEXA scan) (aim 2)

Aim 3.

* Exercise-induced change in pain- and fatigue rating, and quality of life

Study description

Background summary

Adoption of a healthy lifestyle (e.g. physical activity) is an important strategy for cardiovascular risk reduction. However, adopting or maintaining a physically active lifestyle is often not feasible for statin users, as muscle toxicity is the most frequent adverse effect of statins with rates up to 26%. In fact, statin use has been linked to a decreased ability to perform activities of daily living, and increased fall risk in older subjects. Some evidence even suggests that the practice of physical exercise on top of statin treatment can blunt the aerobic training response.

Our colleagues from the department of Pharmacology suggested a pivotal role for mitochondrial dysfunction (complex III inhibition) in statin-induced muscle complaints. Based on these results, we recently investigated (CMO 2015-1836) in a cross-sectional design whether muscle of statin users with muscle complaints has a disturbance in mitochondrial energy production capacity compared to statin users without muscle complaints and controls. As a secondary aim, we also looked at skeletal muscle function and whole body aerobic fitness. Our results (explained in more detail in the introduction and rationale) clearly indicate that muscle mitochondria are affected in statin users with muscle complaints. However, it is currently unknown if the exercise intolerance of statin users with muscle complaints is causally related to disturbances in muscle mitochondrial function.

Therefore, we want to investigate whether: i) differences exist in training response after a 12-week combined endurance- and resistance training program between statin users with and without muscle complaints and a control group (non-statin users) and ii) the size of the training response is depend on the exercise-induced change in mitochondrial mass and function and substrate use in statin users with and without muscle complaints and a control group (non-statin users).

We hypothesize that improving both the quantity and the quality of the mitochondria may counteract the statin-induced myocellular changes, and optimize muscle function and overall aerobic exercise capacity. That is, aerobic exercise specifically targets skeletal muscle mitochondria and hence aerobic capacity and muscle fatigue. This type of training induces mitochondrial biogenesis, which translates into an increase in both mitochondrial content and volume and an induction of numerous enzymes related to respiratory capacity. In addition, resistance training can profoundly stimulate muscle cell hypertrophy by increasing net muscle protein synthesis and is therefore ideally suited to counteract muscle wasting and strength loss. Since exercise improves mitochondrial function and prevents muscle mass wasting, combining aerobic and resistance exercise training may be helpful to combat the statin-induced muscle complaints, while simultaneously improving quality of life and exercise tolerance.

Study objective

Primary Objectives:

1a. To investigate whether differences exist in training response after a 12-week combined endurance- and resistance training program between statin users with and without muscle complaints and a control group (non-statin users).

1b. To investigate whether the size of the training response depends on the exercise-induced change in mitochondrial mass and function and substrate use in statin users with and without muscle complaints and a control group (non-statin users).

Secondary Objectives:

2. To investigate whether differences exist in muscle function after a 12-week combined endurance- and resistance training program between statin users with and without muscle complaints and a control group (non-statin users), and whether the change in muscle function depends on the exercise-induced change in mitochondrial mass and function and substrate use.

3. To investigate the effect of a 12-week combined endurance- and resistance training program on muscle pain, fatigue and quality of life in statin users with and without muscle complaints and a control group (non-statin users).

Study design

Single-centre Intervention study

Intervention

12-week combined endurance- and resistance training program

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 be carefully screened.

Performance of a muscle biopsy is not associated with an important health risk, and my own experience has thought me that if subjects have received a well-explained instruction, 100% of the participants who are found eligible for participation, undergo a successful biopsy. Complications can include infection, bleeding and hematoma formation (<2%), however, these complications will resolve within 2 weeks. The biopsy procedures do not induce discomfort and/or functional impairment and will leave a small scar only (maximal 1 cm). 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 (Section 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 bath or go swimming for 48h, taking a shower is no problem.

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.

The radiation dosage of a whole-body DEXA scan (performed without contrast medium) is 4.2 µSv. This dosage of radiation is not associated with any health risk.

Performance of exercise training in healthy individuals or in those with increased cardiovascular risk is not associated with a health risk. Performance of exercise training at levels of 90% of maximum heart rate is associated with a transient increased risk for sudden cardiac death or myocardial infarction in susceptible subjects. In our protocol training will not be performed at levels of 90% of maximum heart rate or more. Furthermore, supervision during exercise testing is ensured and will be performed according to previous guidelines (described in the *SOP inspanningstest*) and exercise training will be continuously and entirely supervised by a trained researcher.
In addition, we have vast experience with designing and executing training programs in patient populations (e.g. obese subjects CMO2014-1336, patients with heart failure CMO 2010-065). Furthermore, during the medical screening procedure, an experienced physician will check the subject's health status carefully and will check the eligibility of the subject to perform a maximal aerobic exercise test (contra-indications listed in section 4.3 exclusion criteria of this procotol) and the participation in the training program.

Contacts

Public
Selecteer

Geert Grooteplein 10
Nijmegen 6500 HB
NL
Scientific
Selecteer

Geert Grooteplein 10

Nijmegen 6500 HB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

o Age: 40-70 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 Known hereditary muscle defect
o known mitochondrial disease
o Diabetes mellitus
o Contraindication for maximal incremental exercise test
o Contraindication for muscle biopsy

Study design

Design

Study type:	Interventional
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):	15-05-2017
Enrollment:	72
Type:	Actual

Ethics review

Approved WMO

Date:	03-04-2017
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
CCMO	NL59192.091.16