Effect of simvastatin on myocardial triglyceride accumulation, cardiac function and al vessel wall thickness in patients with type 2 diabetes mellitus

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To study the possible beneficial effect of simvastatin on accumulation of triglycerides in the myocardium of patients with DM2 and the effect on vessel wall thickness using magnetic resonance imaging and spectroscopy

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON32611

Source
ToetsingOnline

Brief title
SIMTAC

Condition

- Heart failures
- Diabetic complications
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
diabetes mellitus complications

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: heart function, myocardial triglyceride accumulation, simvastatine, vessel wall thickness

Outcome measures

Primary outcome

Primary endpoints:

• Myocardial triglyceride content

• Heart dimensions

• Heart function: systolic and diastolic

Secondary outcome

Secondary endpoints:

• Aortic distensibility and pulse wave velocity

• Total vessel wall area and thickness

• Liver triglyceride content

• Body fat distribution

Study description

Background summary

Patients with type 2 diabetes mellitus (DM2) have a considerably higher risk to develop heart failure than can be accounted for by hypertension and coronary artery disease. Diabetes-related alterations in cardiac metabolism are thought to play a causal role in the development of non-ischemic cardiomyopathy.
In DM2, insulin resistance and central obesity lead to increased lipolysis with high flux of free fatty acids (FFA) from adipose tissue and elevated production

of triglyceride (TG)-rich particles. Exposure to high levels of FFA causes accumulation of TG in non-adipose tissues such as pancreas, liver and the myocardium. Animal studies have provided consistent evidence that access accumulation of TG within cardiomyocytes is associated with contractile dysfunction. This excessive accumulation of TG and its by-product ceramide induces activation of nonoxidative metabolic pathways that leads to cell dysfunction and accelerated cell death (apoptosis). In this way, lipid accumulation in the myocardium could be directly cardiotoxic.
Recently, ^{1}H-magnetic resonance spectroscopy (MRS) has been developed and validated for measuring intracellular lipid content in humans in vivo. Recent studies in healthy individuals and patients with heart failure reveal that myocardial lipid content is associated with body mass index (BMI) and age and may contribute to adverse structural and functional cardiac adaptations.
Large clinical trials showed that statin therapy was effective for the prevention of cardiovascular events in patients with diabetes mellitus. Although these studies proved that there was a linear relation between lowering LDL cholesterol and cardiovascular events, the effect of statins on cardiovascular mortality is greater than expected from the changes in serum lipids, leading to the proposal that statins have pleiotropic effects. In a recent cross sectional study we observed that patients with DM2 who were taking statins had lower myocardial triglyceride contents compared to patients without a statin.

Study objective

To study the possible beneficial effect of simvastatin on accumulation of triglycerides in the myocardium of patients with DM2 and the effect on vessel wall thickness using magnetic resonance imaging and spectroscopy

Study design

Double blind randomized placebo controlled intervention study

Study procedure:

All patients will be screened in our outpatient clinic. If the patient meets all the inclusion criteria, and gives signed informed consent, he/she will be included. All patients will be asked not to make any changes in their usual diets and physical activities during the whole study. Patients will have three study days. At day 0, an intravenous (iv) cannula will be inserted for gadoteric acid (Gd) contrast and bloodsampling. Subsequently, a baseline MRI with spectroscopy will be performed on a 1.5 Tesla (T) scanner to measure cardiac function and myocardial/ hepatic triglyceride content. Gd-contrast will be given iv for delayed enhancement scans. Vessel wall imaging will be performed during a separate session using a 3T scanner. Afterwards each patient will start with simvastatin 40 mg or placebo once daily. All participants will

undergo safety and efficacy measurements during follow up visits after 2 and 6 weeks. During the follow up visits, tolerance, safety measures and compliance with therapy will be assessed.
After 12 weeks, blood sampling, MR imaging and MR spectroscopy will be repeated as described above except for the delayed enhancement scans. Afterwards (at 12 weeks of treatment) the randomization code will be broken. In the placebo arm, the placebo will be replaced by simvastatin 40 mg and the simvastatin arm will continue medication at the same dose.
A follow up MRI assessment will be performed as described above in both groups one year after starting simvastatin.

Intervention

treatment with simvastatin 40 mg or placebo for 12 weeks, followed by simvastatin 40 mg for 1 year (in total)

Study burden and risks

The risks associated with participation are small; simvastatin is a safe and efficacious drug which is widely used. Placebo is a capsule of wich no side effects are expected to occur, since it does not contain any active substances. Contrast nephropathy and nephrogenic systemic fibrosis induced by Gadoteric acid contrast are very rare and predominantly occur in patients with pre-existing renal insufficiency, who will be excluded from this study.
There are no known hazards from MRI/MR spectroscopy when MR exclusion criteria have been checked.
Six visits, including screening, follow up visits, begin and endpoint assessments are applicable to all subjects. At screening and before each MRI scan blood samples will be taken via venous puncture or iv cannula. Total amount of blood taken from the patient for the entire protocol is maximally 150 ml.
Total examination time for MRI may be 120 and subsequently 90 minutes at maximum. During that time period patients have to lie still inside the small bore of the MRI machine. This may cause some discomfort.
Participants will benefit from this study, since the will be screened for cardiac dysfunction using MRI and the will use simvastatin which will reduce the risk on cardiovascular disease.

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

• Informed consent
• DM2 treated with metformin or metformin in combination with SU- derivate
• HbA1c<8.5 %
• BMI> 20kg/m2 and <35 kg/m2
• Well regulated blood pressure (i.e. RR<140/90)

Exclusion criteria

• Use of insulin or thiazolidinediones (TZD)
• Use of fibrates or statins one year prior to study
• Hereditary lipoprotein disease
• Psychiatric disorders and/or use of antipsychotic or antidepressant drugs at present or in the past
• Renal disease (plasma creatinine levels>100µmol or clearance <= 60 ml/min) hepatic disease (ASAT/ALAT > 2 times reference values) or other endocrine disease
• Any significant chronic disease
• Any significant abnormal laboratory results found during the medical screening procedure
• Pregnancy/ lactation

• Allergy to intravenous contrast
• Claustrophobia
• Metal implants or other contraindications for MRI
• Recent participation in other research projects within the last 3 months or participation in 2 or more projects in one year

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2009
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	simvastatine
Generic name:	HMG-CoA reductase inhibitor
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	11-08-2008

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-12-2008
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2008-004853-13-NL
CCMO	NL24424.058.08