Effect of 12 weeks training on muscular lipid handling in relation to type 2 diabetes mellitus.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON30235

Source
ToetsingOnline

Brief title
Training and lipid handling

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
sugar, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO

Intervention

Keyword: ATGL, DAG mass, Physical exercise, Type 2 diabetes

Outcome measures

Primary outcome

DAG levels, ATGL protein content, insulin sensitivity, lipid accumulation and

mitochondrial functioning in cardiac muscle and skeletal muscle.

Secondary outcome

Plasma free fatty acids, basal glucose level, body composition, VO2max.

Study description

Background summary

A key feature in the pathogenesis of type 2 diabetes mellitus is a decreased ability of insulin to stimulate glucose uptake in peripheral tissues, i.e. insulin resistance. Skeletal muscle plays a major role in the development of (whole body) insulin resistance. However the mechanism behind the development of skeletal muscle insulin resistance is still poorly understood. Nevertheless, there is compelling evidence that the accumulation of fat in non-adipose tissues is involved and that intracellular fatty acid metabolites of this IMCL, such as diacylglycerol (DAG), long-chain fatty acyl CoA (LCFACoA) and ceramide, can cause insulin-resistance. This is probably due to the fact, that patients suffering from type 2 diabetes are characterized by a decreased fat oxidative capacity and that DAG may accumulate if lipase activity results in hydrolysis of primarily triacylglycerols (TAG) and not diacylglycerols. Recently, the main triacylglycerol lipase responsible for hydrolysis of TAG to DAG, AdiposeTriGlycerideLipase (ATGL), was identified. Increased ATGL expression/activity in type 2 diabetes potentially contributes to chronically elevated DAG levels and the development of type 2 diabetes. Next to ATGL, other lipases and lipid-coating proteins are involved in regulating intramuscular triglyceride lipolysis. In addition, it is well known that type 2 diabetic patients have an increased risk for cardiovascular diseases, including heart-failure. Therefore it is tempting to suggest that type 2 diabetes mellitus is, next to increased skeletal muscle fat accumulation, also characterized by increased cardiac fat accumulation and mitochondrial dysfunction.

Study objective

The central goal therefore, is to identify mechanisms contributing to an improved mitochondrial fat oxidative capacity after physical activity and consequently identify the mechanisms which are responsible for the development of clinically overt type 2 diabetes. The first aim of the study is to investigate whether proteins, involved in muscular lipid handling, are altered in persons with type 2 diabetes, compared to healthy control subjects, and whether this leads to elevated fatty acid metabolite levels. Since several investigations show a reduction in the incidence of diabetes after the performance of physical exercise in persons of high risk, our second aim is to examine whether lipid content in cardiac and skeletal muscle of type 2 diabetes patients is increased and whether this is associated with impaired oxidative capacity compared to healthy control subjects. Finally, the effect of a 12-week physical activity training program on fatty acid metabolism in skeletal muscle and on lipid accumulation and oxidative capacity in cardiac and skeletal muscle in type 2 diabetic patients compared to healthy controls will be examined.

Study design

The subjects will be invited for screeningstests. These tests include a medical examination, physical investigation, ECG, Oral Glucose Tolerance Test (OGTT), control of laboratory parameters. In addition, the followings tests will be done, before and after the training program: body composition, muscle- and fat biopts, maximal cycling test, fat accumulation and mitochondrial functioning of the heart muscle and the skeletal muscle, and a hyperinsulinemic-euglycemic clamp.

Study burden and risks

Blood samples, infusions and muscle biopts might cause bruisings; participation of the trainings program can possibly cause muscle stiffness or muscle pain.

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

All subjects:
- Male sex
- Age 50-65 years
- BMI 27-35 kg/m2
- Stable dietary habits and physical activity levels;For diabetic patients only:
- Must be on sulphonylurea- or metformin therapy for at least six months with a constant dose for at least two months, or on dietary treatment for at least six months
- Well-controlled diabetes: fasting plasma glucose concentration must be <10.0 mmol/l at the time of screening.;For healthy controls only:
- normoglycemic according to WHO criteria
- no family history of diabetes

Exclusion criteria

- Female sex
- Unstable body weight (weight gain or loss > 3 kg in the past three months)
- Participation in an intensive weight-loss program or vigorous exercise program during the last year before the start of the study
- Active cardiovascular disease
- liver disease of liver dysfunction (ALAT>2.5 x increased)
- renal dysfunction
- systolic blood pressure >160 mmHg or diastolic blood pressure > 100 mmHg

- haemoglobin < 7.5 mmol/l (anaemia)
- use of medications know to interfere with glucose homeostasis (i.e. corticosteroids)
- abuse of drugs and/or alcohol
- participation in another biomedical study within 1 month before the first screening visit
- severe diabetes which requires application of insulin or patients with diabetes-related complications

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-07-2006
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	28-07-2006
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL11297.068.06