Optimizing the beneficial health effects of exercise for diabetes: focus on the liver!

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

Summary

ID

NL-OMON39037

Source
ToetsingOnline

Brief title
Effect of exercise on liver fat and metabolism

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Hepatic and hepatobiliary disorders
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht

Source(s) of monetary or material Support: Diabetes Fonds

Intervention

Keyword: exercise training, Hepatic ATP and Pi concentration, Hepatic fat, Type 2 diabetes

Outcome measures

Primary outcome

The main study parameters are the differences in values for intrahepatic lipid content and mitochondrial liver function from baseline to endpoint in the same group, as well as the differences in effect of the intervention between the different groups.

Secondary outcome

The secondary objective is to investigate if the beneficial effects of exercise training on metabolic risk markers are dependent on the reduction of liver fat. Furthermore, we will measure if the reduction of liver fat and improvement of liver metabolism correlates with improvement of lipid metabolism in the skeletal muscle.

Study description

Background summary

Due to the western lifestyle, correlated with a high calorie intake and low physical activity, obesity is becoming a major health problem. All over the world obesity reaches epidemic proportions. Obesity is closely linked to type 2 diabetes, a multi-factorial disease that increases the presence of multiple health problems. Until now, exercise and dietary intervention seem to be the single most effective interventions to treat obesity and type 2 diabetes mellitus. In obesity and type 2 diabetes, not only fat accumulation in adipose tissue, but also fat accumulation in the peripheral tissues occurs. Fat accumulation in peripheral tissues has been associated with insulin resistance. Exercise seems to have a positive effect on the accumulation of fat in the

peripheral tissue and on the insulin sensitivity in type 2 diabetic patients.

Study objective

The major objectives are to investigate if a prolonged exercise training program can lower the intrahepatic lipid content and can improve the metabolism of the liver in type 2 diabetic patients and patients with non-alcoholic fatty liver disease, and to examine if this leads to improvements in metabolic risk markers. To this end, we will include investigation of the effect of exercise on adipose tissue (inflammatory markers and adipocyte size) and skeletal muscle (ex vivo lipid metabolism) to incorporate the effect of exercise on liver, muscle and adipose tissue and to clarify the crosstalk between these tissues in the pathophysiology of type 2 diabetes.

Study design

Thirty-eight type 2 diabetic patients, 38 non-alcoholic fatty liver patients and 38 matched controls will follow a 12 weeks exercise-training program. Two times a week they will perform an aerobic cycling training and once a week resistance training. Before onset and after the training period body composition (DEXA), endothelial wall function (RH- PAT), cardiac lipid (1H-MRS), cardiac function (Ultrasound), liver mitochondrial function (MBT), liver metabolism (31P-MRS), maximal aerobic capacity (VO2max), maximal voluntary contraction, intrahepatic lipid (1H-MRS) and insulin sensitivity (hyperinsulinemic- euglycemic clamp) will be measured.

Intervention

Subjects will undergo a 12 weeks exercise intervention, which consist of 2 times a week an aerobic exercise and 1 time per week resistance training.

Study burden and risks

Blood drawing and the placement of several cannulas can cause a bruise. Furthermore, the training-intervention can lead to mild muscle pain and stiffness. There can be coincidental findings due to the MRS measurements (= *toevalsbevindingen*) and there is radiation exposure due to DEXA measurements (0.001 mSv/time).
Three days prior to the clamp diabetic subjects will have to stop their anti-diabetic medication. This may cause an increase in blood glucose levels. Subjects will receive a one-touch blood glucose meter to determine their fasted blood glucose levels in the 3 days before the 3rd post-intervention test day. If their fasted blood glucose levels are higher than 13.0 mmol/l, they will need to contact the principal investigator. He will decide to restart the anti-diabetic medication and to exclude the subjects of the study.
A muscle biopsy can lead to a painful bruise and muscle pain on the place the

biopsy was taken. To limit these risk as much as possible, a bandage will be placed and subjects will have to wear it for at least 24 hours. Intense exercise will be discouraged for the next 24 hours. Bruises disappear after some days. An experienced medical doctor will take muscle biopsies.
Due to local anesthesia, the adipose tissue biopsy is painless. To minimize the risk for a hematoma, the adipose tissue biopsy place will be compressed for approximately 5 minutes after biopsy. The place of incision will leave a small scar (~ 3 mm). To promote good wound healing, the incision will be sealed with sterile steri-strips and a waterproof band-aid.

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 40-70 years
BMI 27-35 kg/m2
Stable dietary habits
sedentary: no participation in any kind of sports for at least 2 years
For diabetic patients only:
Must be on sulphonylurea or metformin therapy for at least 6 months with constant dose for at least 2 months, or on a dietary treatment for at least 6 months
Well-controled diabetes: fasting plasma glucose concentration * 7.0 mmol/l and < 10.0 mmol/l at the time of screening.;For subjects with non-alcoholic fatty liver disease:
Liver fat content * 5,56%
Fasting plasma concentration must be < 7.0 mmol/l ;For control subjects:
Liver fat content < 5,56%
Normoglycemic according to the WHO criteria (OGTT)

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 in a exercise program during the last year before the start of the study.
(Low) physical activity (more than 30 minutes (low) physical activity per week)
Active cardiovascular disease. (This will be determined by quenstionnaires and by screening on medication. Furthermore, all subjects
will undergo a physical examination by a medical doctor).
Chronic renal dysfunction (creatinine > 2 increased (normal values: 64-104 µmol/l))
Use of Beta-blockers
Systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg
Haemoglobin < 7.5 mmol/l (anemia)
Blood donor
Use of medication know to interfere with glucose homeostasis (i.e. corticosteroids), except for diabetics
Use of anti-trombotic medication
Claustrophobia and metal implants (with respect to MRI)
Abuse of drugs
Participation in another biomedical study within 1 month before the first screening visit
Alcohol abuse (> 3 units (1unit = 10 gram ethanol) per day);For diabetic patients:
Severe diabetes which requires application of insulin or patients with diabetes-related complications;For controls:
Liver disease or liver dysfunction (ALAT > 2.5 x increased (normal values: 5 - 60 U/L))

Study design

Design

Study type:	Interventional
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):	02-08-2011
Enrollment:	114
Type:	Actual

Ethics review

Approved WMO Date:	21-04-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-12-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-02-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	10-06-2013
Application type:	Amendment
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
ClinicalTrials.gov	NCT01317576
CCMO	NL34882.068.10