Effects of resveratrol on insulin sensitivity, brown adipose tissue and metabolic profile in first-degree relatives of type 2 diabetic patients

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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-OMON45176

Source
ToetsingOnline

Brief title
Resveratrol and pre-diabetes

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Lipid metabolism disorders

Synonym
obesitas and sugar disease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Nederlands Diabetes Fonds

Intervention

Keyword: Brown adipose tissue, Metabolism, Mitochondrial Function, Resveratrol, Type 2 Diabetes

Outcome measures

Primary outcome

The main study endpoints are the differences in whole body- and muscle insulin sensitivity, and mitochondrial fat oxidative capacity after 30 days of resveratrol supplementation compared to the placebo trial.

Secondary outcome

Secondary outcome measures are the changes in liver and muscle fat storage after 30 days of resveratrol or placebo supplementation. Also, in 9 subjects we want to determine brown adipose tissue activity on day 33.

Study description

Background summary

There is now a general consensus that the combination of excessive energy intake and a low capacity to oxidize fat will lead to muscular fat accumulation and insulin resistance. It is known for many years that physical activity and diet therapy are the most powerful treatment to combat obesity and insulin resistance, but it is also known that it is difficult to get people to exercise and follow diets. A major breakthrough in this field has come from the nutrition field, with the finding that resveratrol, a natural polyphenolic compound, could serve as an *caloric restriction mimetic*, as a recent study of S. Timmers et al. in Cell metabolims (2011) showed that resveratrol mimicked the effect of caloric restriction in healthy obese man (lowering liver fat accumulation and increasing fat oxidation, thereby improving metabolic health in these subjects). These findings were similar to those found earlier in

animal studies, where it was found that resveratrol protected mice from many detrimental effects of diet-induced obesity. Therefore we would like to investigate if resveratrol has the same effects in humans at increased risk for developing type 2 diabetes (first-degree relatives of type 2 diabetics) as it does in healthy obese man. This information can then be used to develop new treatment of type 2 diabetes especially with respect to preventive strategies. Therefore, we would like to investigate whether ResvidaTM can increase mitochondrial number together with an increased intrinsic activity and whether this will lead to a better insulin sensitivity in first-degree relatives of type 2 diabetic patients.
Besides the recently discovered positive effects of resveratrol on the metabolic complications associated with obesity, resveratrol could also target obesity itself. Since the rediscovery of functional active brown adipose tissue in adult humans this tissue has received strong scientific attention. Recent studies in mice inidcate that the improved metabolism accompanying oral administration of reseveratrol is associated with increased brown adipose tissue thermogenesis and high UCP1 and SIRT1 expression.

Study objective

To examine whether resveratrol supplementation in first-degree relatives of type 2 diabetic patients improves overall and muscle-specific insulin sensitivity by affecting mitochondrial fat oxidative capacity. Furthermore, we are interested is this also affects liver and muscle fat storage and whether brown adipose tissue activity increases after resveratrol administration.

Study design

80 overweight (BMI 27-35 kg/m2) male subjects with family member(s) diagnosed with type 2 diabetes, aged between 40 and 70 years, who are not engaged in regular programmed exercise, with glucose clearance rate <350 ml/kg/min will be recruited of which 24 will be included in a randomized, double blind cross over design. Each subject will participate in two interventions, in random order, and separated by a wash-out period of at least 4 weeks. Each intervention includes a 30 days suppelementation with resveratrol or placebo. Before the start of the study, subjects will be screened to assess eligibility, which will include a medical questionnaire, and a fasted blood sample.
On day 0, subjects will come to the university for withdrawal of a fasted blood sample and a measurement of body weight. Hereafter, heart rate and blood pressure will be checked and an ECG will be made by an experienced physician. Finally a measurement to determine body composition and fat content is executed (DEXA scan).
Thereafter, subjects can go home and they will receive enough capsules for the first week of the intervention. Additional blood samples will be drawn on a weekly basis as well as measurements of body weight (day 7, 14, 21). During these weekly visits, subjects will receive enough capsules for the next week.

On day 27, subjects will report to the university for a maximal aerobic capacity test under the supervision of a physician. An ECG will be made during the cycling test. On day 29, hart function will be measured by echocardiography, and in vivo mitochondrial function and liver fat content will be measured with MR spectroscopy. Thereafter, subjects will stay in the respiration chamber for 12 hours (evening day 29 and night day 29) during which their energy expenditure and fat oxidation will be measured. On day 30 in the morning, subjects will leave the respiration chamber, and a fasting blood sample will be drawn. An ECG will be made and blood pressure and heart rate will be measured. Then, fat content in the heart will be measured by MR spectroscopy and a muscle biopsy will be taken. Hereafter, the insulin sensitivity measurement will be started to determine overall and muscle and liver specific insulin sensitivity. After the test, a second muscle biopsy will be taken.
9 subjects will also participatie in the brown adipose tissue part op this study. They will recieve resveratrol (or placebo) for 33 days and come to the university on day 33 for a FDG PET/CT scan after mild cold exposure.

Intervention

Subjects will be asked to take two pills of resveratrol 75 mg, or placebo, twice daily (lunch and diner), for 30 days, which will be randomized. Resveratrol (resvidaTM) is a food supplement and is regulated in the body as a food component. ResvidaTM and placebo are provided by DSM Nutritional Products Ltd. For the resveratrol product, the maximal approved daily dose in humans is 150 mg/day. For higher doses the safety concerns are not yet investigated. Therefore, we have chosen to supplement the subjects with a dose of 150 mg/day spread out over two doses of 75 mg twice a day with lunch and diner.

Study burden and risks

Before the start of the study, subjects will be screened to access eligibility which will include a medical questionnaire, measurement of body weight and OGTT wil be executed to determine glucose clearance (as marker for insulin sensitivity). A fasted bloodsample will also be drawn (duration: 3 hours). Thereafter, they will be randomized and undergo two intervention periods of 30 days separated by a wash-out period of at least 4 weeks. The subjects will come to the University 6 times (day 0, 7, 14, 21, 27, 29). During these visits at the University, a bloodsample will be taken weekly as well as a weekly measurement of body weight (day 0, 7, 14, 21). On day 0 also a DEXA scan is executed in order to determine body composition and body fat. A maximal aerobic capacity test will be performed (day 27) and heart function will be measured by echocardiography, in vivo mitochondrial function and liver fat content will be measured with MRS (day 29). In addition, subjects will stay in the respiration chamber for 12 hours (1 evening and night) (day 29-30) after which the fat content of the heart will be measured by MR spectroscopy (day 30), and a muscle

biopsy will be taken (day 30). Hereafter, the insulin sensitivity test will be started (day 30). After this test is finished, a second muscle biopsy will be taken (day 30).

For the subjects that participate in the brown adipose tissue part of the study: On day 33 an FDG PET/CT scan after mild cold exposure takes place. These subjects will come to the university 7 times during 4 weeks (day 0, 7, 14, 21, 27, 29 and 33).

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

* Male sex
* Age: 40-70 years

* BMI 27-35 kg/m2
* Has first-degree relative(s) diagnosed with type 2 diabetes
* Sedentary:
o Not more than 2 hours of sports a week
o No active job that requires strenuous physical activity
* Stable dietary habits: no weight gain or loss > 5kg in the last three months
* Insulin resistant: glucose clearance rate <350 ml/kg/min, as determined using OGIS120
* Willingness to abstain from resveratrol-containing food products
* Subjects will only be included when the dependent medical doctor of this study approves participation after evaluating data obtained during screening

Exclusion criteria

* Use of anticoagulants
* Uncontrolled hypertension
* Haemoglobin <7.8 mmol/l
* In case of an abnormal ECG at rest: this will be discussed with the responsible medical doctor
* HBA1C > 6.5%
* Diagnosed with type 2 diabetes
* Medication use known to interfere with glucose homeostasis/metabolism
* Current alcohol consumption > 20 grams/day
* Subjects who don*t want to be informed about unexpected medical findings during the screening /study, or do not wish that their physician is informed, cannot participate in the study.
* Subjects who intend to donate blood during the intervention or subjects who have donated blood less than three months before the start of the intervention.
* Participation in another biomedical study within 1 month before the screening visit
* Any contra-indication to MRI scanning:
o Central nervous system aneurysm clip
o Implanted neural stimulator
o Implanted cardiac pacemaker of defibrillator
o Cochlear implant
o Insulin pump
o Metal containing corpora aliena in the eye or brains
For the 18F-FDG PET-CT scan:
o Participation in earlier research or medical examinations that included PET/CT scanning

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-05-2014
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	19-03-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-02-2016
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
CCMO	NL47018.068.13

Study results

Date completed: 19-03-2017

Actual enrolment: 30

Summary results
Trial is onging in other countries