Impact of L-Carnitine infusion on Lipid induced Insulin resistance

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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-OMON43461

Source
ToetsingOnline

Brief title
Carnitine infusion and Insulin resistance

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
noninsulin dependant diabetes, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Acetylcarnitine, Carnitine, insulin sensitivity, metabolic flexibility

Outcome measures

Primary outcome

The primary study endpoint is whole body insulin sensitivity, measured by the hyperinsulinemic-euglycemic clamp.

Secondary outcome

Secondary endpoints are maximal acetylcarnitine concentrations after exercise, metabolic compounds in the blood and measurements regarding skeletal muscle metabolism in skeletal muscle tissue obtained by needle biopsies.

Study description

Background summary

Insulin resistant subjects and type 2 diabetic patients are characterized by a decreased metabolic flexibility: a reduced capability to switch from fat oxidation in the basal state to carbohydrate oxidation in the insulin-stimulated state. This metabolic inflexibility is an early hallmark in the development of diabetes. Recent evidence suggests that a low carnitine availability may limit acetylcarnitine formation, thereby reducing metabolic flexibility. Thus, when substrate flux in the muscle is high, acetyl-CoA concentrations increase, leading to inhibition of pyruvate dehydrogenase (PDH) and thereby reducing glucose oxidation. The conversion of acetyl-CoA to acetylcarnitine relieves this acetyl-CoA pressure on PDH. To provide more direct insight into the effect of carnitine in preventing metabolic inflexibility and insulin resistance and to further explore the mechanism of action is the focus of this research. Here, we hypothesize that the capacity to form acetylcarnitine may rescue lipid-induced insulin resistance. To this end, insulin resistance will be induced by lipid infusion in healthy volunteers and it will be tested whether carnitine co-infusion can alleviate insulin resistance.

Study objective

The primary objectives are to investigate whether L-carnitine infusion may rescue lipid-induced insulin resistance and whether L-carnitine infusion is improving metabolic flexibility in the state of lipid-induced insulin resistance. Furthermore, secondary objectives are to examine the molecular pathways of carnitine and acetylcarnitine, responsible for muscle insulin sensitivity and to investigate the effect of L-carnitine infusion on insulin signalling pathways in skeletal muscle

Study design

The current study is an interventional randomized crossover trial in which each subject serves as it owns control. Subjects will be blinded for the intervention.

Intervention

Ten healthy subject will be subjected to the intervention of L-carnitine infusion. To investigate whether L-Carnitine infusion may rescue lipid induced insulin resistance and improve metabolic flexibility three intervention trials are included. The first trial includes lipid infusion combined with L-Carnitine infusion (=LIPID + CAR). In the second trial, L-carnitine infusion will be replaced by placebo infusion in the form of saline (= LIPID + PLAC) in order to investigate the effect of L-Carnitine. During the third trial, lipid infusion will be replaced by infusion of saline and will serve as a control for the lipid infusion (=Saline + PLAC) and is necessary to investigate to what extend L-carnitine can rescue lipid induced insulin resistance. All three trials will be separated by at least two weeks. Subjects will be blinded, so no information about the infused substances will be provided to them. The three different trials will be allocated in a random order.

Study burden and risks

Subjects will first visit the University once for screening purposes during which length, weight and blood pressure will be measured. An ECG will be performed, blood will be drawn and they will fill in 2 questionnaires. If screening was successfully completed, subjects will visit the university in the morning (fasted) for a Bod Pod measurement (body composition measurement) and a maximal cycling test (visit 2: 1 hour). During the third visit subject will come fasted (for 5 hours, from lunch onwards) to the university in the afternoon (5PM) for a 30 minute cycling test with a magnetic resonance spectroscopy (MRS) measurement immediately before and after cycling to determine exercise-induced acetylcarnitine concentration. Subsequently, subjects visit the University for the three intervention trials (LIPID+CAR, LIPID+PLAC, Saline+PLAC). These three days will consist of undergoing a hyperinsulinemic euglycemic clamp combined with either lipid, carnitine or saline (11 hours). Furthermore, at the beginning and end of the clamps, a

muscle biopsy will be obtained. For these visits, subjects have to report to the university in the morning in the fasted state. Three days in advance, subjects fill out a food diary to monitor their food intake. The evenings prior to these three test days, subjects have to eat a standardize meal (macaroni bolognaise). Muscle biopsies lead to mild discomfort and there is a risk of hematoma. During the hyperinsulinemic euglycemic clamp, a risk of hypoglycaemia exists. In summary, we will draw approximately 538 ml blood during the entire study period. During each of the three intervention trial we draw a maximum of 176 ml blood.

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

Caucasian

* Healthy (as determined by responsible physician based on a medical questionnaire)
* Male
* Age: 18-40 years
* Normal BMI: 18-25 kg/m2
* Stable dietary habits
* No use of medication interfering with investigated study parameters (as determined by responsible physician)

Exclusion criteria

* Female
* Haemoglobin levels < 7.8 mmol/L
* Uncontrolled hypertension
* Use of anticoagulants
* Engagement in exercise > 3 hours a week
* Being vegetarian or vegan (because of altered whole body carnitine status)
* Smoking
* Alcohol and/or drug abuse
* Unstable body weight (weight gain or loss > 5kg in the last 3 months)
* Significant food allergies/intolerances (seriously hampering study meals)
* Participation in another biomedical study within 1 month before the first study visit, which would possibly hamper our study results
* Medication use known to hamper subject*s safety during the study procedures
* Medication use known to interfere with investigated study parameters
* Subjects with contra-indications for MRI
* Subjects who intend to donate blood during the intervention or subjects who have donated blood less than three months before the start of the study
* Subjects who do not want to be informed about unexpected medical findings
* Subjects who do not want that their treating physician is informed

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-10-2016
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carnitene
Generic name:	L-Carnitine of levocarnitine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-03-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-07-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-12-2016
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
EudraCT	EUCTR2016-000810-31-NL
ClinicalTrials.gov	NCT02722902
CCMO	NL56319.068.16