Carnitine supplementation as a therapy to improve insulin sensitivity in Type 2 diabetic patients with low carnitine status

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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-OMON48695

Source
ToetsingOnline

Brief title
Carnitine supplementation in type 2 diabetic patients

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
non insulin dependant diabetes, 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: Carnitine supplementation, Insulin sensitivity, Metabolic flexibility

Outcome measures

Primary outcome

The primary study endpoints are insulin sensitivity and metabolic flexibility,

measured by the hyperinsulinemic-euglycemic clamp.

Secondary outcome

Secondary endpoints are maximal acetylcarnitine concentrations after exercise,

Intrahepatic lipid content, body composition, metabolites in the blood before

(i.e. glucose, free fatty acids, triglycerides, cholesterol, insulin), CrAT

activity, acylcarnitine profiles, lipid and lipid intermediates, functional

markers of physical performance, quality of life and quality of sleep.

Study description

Background summary

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. In humans, carnitine supplementation is sometimes also beneficial, but not in everyone. Here we aim to test the hypothesis that carnitine supplementation in type 2 diabetic patients with initially low carnitine status enhances metabolic flexibility and insulin sensitivity to a greater extent than in subjects with an initially high carnitine status. Our novel non-invasive

MRI-based method to determine acetylcarnitine in muscle provides the opportunity for a priori identification of patients with low acetylcarnitine status in muscle.

Study objective

The primary objectives are to investigate which determinants (primarily carnitine status) determine the effect of carnitine supplementation on metabolic flexibility and insulin sensitivity in patients with type 2 diabetes. Furthermore, a secondary objective is to examine the molecular pathways of carnitine and acetylcarnitine, responsible for muscle insulin sensitivity and metabolic flexibility as well as the effects of carnitine supplementation in patients with type 2 diabetes with an initially low carnitine status on intrahepatic lipid content, acetylcarnitine formation, blood plasma metabolites, body composition, physical performance and quality of life.

Study design

The current study is an intervention study. Subjects will not be blinded for the intervention since all subjects will receive oral carnitine supplementation

Intervention

Participants will be asked to take three chewing tablets of L-carnitine (330mg), three times a day (breakfast, lunch and dinner), for 96 days.

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 enter the study and visit the university for a maximal cycling test (visit 1: 30 minutes). All subjects assigned to the study willl undergo baseline measurements and subsequently receive oral carnitine supplementation for a period of 96 days including 3 measurement days in the last week of the supplementation period. Baseline and post supplementation measurements are identical and include 1H-MRS for acetylcarnitine determination, questionnaires, physical performance testing and body composition measurements. Insulin sensitivity and metabolic flexibility will be determined via a 2-step hyperinsulinemic euglycemic clamp. Before the clamp intrahepatic lipid content will be determined. Furthermore, at the beginning and end of the clamp, a muscle biopsy will be obtained. For these visits, subjects have to report to the university in the morning in the fasted state. 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 392ml blood during the entire study period. During each of the three intervention trial we draw a maximum of 169 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

• Men and woman
• Age: 40-75 years
• Woman should be postmenopausal
• BMI: 25-38 kg/m2
• Stable dietary habits
• No use of medication interfering with investigated study parameters (as determined by responsible physician)

Exclusion criteria

• Haemoglobin levels < 7.8 mmol/L
• Uncontrolled hypertension
• Use of anticoagulants
epilepsy
• Insulin dependent type 2 diabetic patients.
• Signs of active liver or kidney malfunction.
• Engagement in exercise > 3 hours a week
• Being vegetarian or vegan (because of altered whole body carnitine status)
• 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
• 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
• Signs of clinical relevant diabetes-related co-morbidities like active cardiovascular diseases, active diabetic foot, polyneuropathy or retinopathy

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2018
Enrollment:	62
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:	29-08-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-01-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-04-2019
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	EUCTR2017-003124-73-NL
ClinicalTrials.gov	NCT03230812
CCMO	NL62791.068.17