The fate of incomplete amino acid metabolism in type 2 diabetes

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1. to determine whether the oxidation of BCAA (leucine) is impaired in patients with T2DM and in humans at risk to develop T2DM (first degree relatives). 2. to investigate whether an altered leucine oxidation in muscle is associated with insulin...

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

Summary

ID

NL-OMON43574

Source
ToetsingOnline

Brief title
amino acids in type 2 diabetes

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Protein and amino acid metabolism disorders NEC

Synonym
diabetes mellitus type 2, sugar disease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: ZonMw,EFSD

Intervention

Keyword: branched chain amino acids, insulin resistance, mitochondrial function, type 2 diabetes

Outcome measures

Primary outcome

The primary study objectives are:

i) to determine whether T2DM and FDR have lower rate of leucine oxidation (umol

kg-1 min-1) in muscle

ii) to evaluate whether altered leucine oxidation is associated with whole body

and hepatic insulin sensitivity (umol kg-1 min-1)

Secondary outcome

The secondary study objectives are:

i) to evaluate whether altered leucine oxidation is associated with

mitochondrial function (pmol/mg/s)

ii) to evaluate whether altered leucine oxidation is associated with the amount

of liver fat (%)

Study description

Background summary

Recent high impact research identified clusters of circulating branched-chain amino acids (BCAA), aromatic amino acids (AAA) and amino acid-derived short-chain acylcarnitines in insulin resistant humans, as risk factors in the development of type 2 diabetes. The elevated amino acid clusters may derive from elevated amino acid supply or incomplete amino acid catabolism. These findings shed new light in the etiology of diabetes, which for long time was considered to be related only to disturbances in fat and glucose metabolism, underlying the development of insulin resistance and mitochondrial dysfunction. Here, I propose the novel hypothesize that type 2 diabetes (T2DM) is linked to

dysregulated amino acid metabolism, resulting in elevated clusters of BCAA, AAA and acylcarnitines causing insulin resistance. Furthermore, I hypothesize that impaired amino acid metabolism underlies impaired mitochondrial oxidative capacity in T2DM via diminished delivery and flux of amino acid-derived tricarboxylic acid cycle (TCA) intermediates. The experiments presented in this project include metabolic profiling of amino acid metabolism-derived intermediates in plasma and muscle of patients with T2DM and in first-degree relatives, which has never been explored before. Another innovative element of this study is to investigate whether sustained lowering of BCAA availability via a dietary intervention will reverse possible detrimental effects of BCAA in T2DM. The use of labelled glucose and amino acids, hyperinsulinemic-euglycemic clamp and magnetic resonance spectroscopy are state-of-the-art methods applied in this project. To conclude, this research project would reveal the fate of dysregulated amino acid metabolism in T2DM, and could introduce a shift from the recent 'lipotoxic view' towards a focus on amino acid metabolism, finally leading to new strategies to treat diabetes.

Study objective

1. to determine whether the oxidation of BCAA (leucine) is impaired in patients with T2DM and in humans at risk to develop T2DM (first degree relatives).
2. to investigate whether an altered leucine oxidation in muscle is associated with insulin sensitivity, mitochondrial function and the amount of fat in the liver.

Study design

Observational study in which 3 groups will be included: (1) healthy controls, (2) patients with T2DM and (3) first degree relatives. The leucine oxidation will be measured in all groups and the outcome will be related to other metabolic parameters.

Intervention

A randomized, cross-over study in which patients with T2DM and first degree relatives will undergo a 4 week dietary intervention with normal BCAA in the diet or to a 4 week intervention with low BCAA levels in the diet. The two periods will be seperated by a 2 months wash-out period.

Study burden and risks

The risks of the performed measurements for the participants are relatively low. There is a very low risk of complications with the biopsies and with the intravenous catheters. With taken the muscle biopsy a risk exits that a small skin nerve get damaged causing a dull feeling, which will compeltely recover wthin maximal 6-12 months. During the withdrawal of glucose lowering

medication, the patients with T2DM will be carefully monitored to prevent hyperglycemia. Moreover, the experiments as scheduled in this research project are performed at a regular basis at the Maastricht University and performed by a very experienced researcher in the field already for many years. This research project would reveal the fate of dysregulated amino acid metabolism in T2DM, and could introduce a shift from the recent 'lipotoxic view' towards a focus on amino acid metabolism, finally leading to new strategies to treat diabetes. Therefore, the risk and burden for the participants is justified.

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

Overall
* Male en postmenopausal females

* Age 45-70 years
* Body mass index (BMI) < 35 and > 27 kg/m2
* Stable dietary habits (no weight loss/gain >5 kg in the last 3 months)
* Stable physical activity levels for at least 6 months
* Control participants without type 2 diabetes should be normal glucose tolerant (OGTT with fasting plasma glucose <6.1 mmol/l (<110 mg/dl) and 2h glucose of <7.8 mmol/l (<140 mg/dl))
* FDR should have a at least 1 family member with type 2 diabetes (father, mother, sister or brother);Type 2 diabetic patients
* Non-insulin dependent type 2 diabetic patients, diagnosed with type 2 diabetes for at least 2 years using sulphonylurea- or metformin therapy for at least six months with a constant dose for at least two months
* Type 2 diabetic patients should have a HbA1c level <8.5%
* Type 2 diabetic patients will be included when having no active diabetes-related co-morbidities like cardiovascular diseases, diabetic foot, polyneuropathy, retinopathy.

Exclusion criteria

- participants will be excluded when being diagnosed with active cardiovascular disease, diabetic foot, polyneuropathy, retinopathy
- participants will be excluded when having uncontrolled hypertension
- participants following a vegetarian diet or having an allergy against soya
- participants with contra-indication for MRI

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):	21-02-2014

Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	04-12-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-04-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-06-2016
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	NL41586.068.12
Other	TC=4181