Lowering BCAA as a new strategy to improve insulin sensitivity

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Primary objective is the delta change in whole body insulin sensitivity upon Na-PB vs. placebo treatment. Secondary objectives are muscle mitochondrial oxidative capacity, muscle and liver fat content and energy metabolism.

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

Summary

ID

NL-OMON48748

Source
ToetsingOnline

Brief title
The increase in amino acid metabolism in humans with diabetes

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, insulin resistance

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: diabetes fonds Nederland

Intervention

Keyword: BCAA, insulin sensitivity, mitochondrial function, sodium phenylbutyrate

Outcome measures

Primary outcome

Whole-body insulin sensitivity measured upon both treatment periods. Insulin sensitivity will be expressed as the change of insulin-stimulated rate of glucose disappearance (ΔRd).

Secondary outcome

• muscle mitochondrial function

• whole-body energy metabolism

• fat accumulation in muscle and the liver

Study description

Background summary

Insulin resistance is the most important risk factor in Type 2 Diabetes (T2D). Several studies identified branched-chain amino acids (BCAA; leucine, isoleucine and valine) to be substantially elevated in people with T2D. Recently, I confirmed the finding of higher BCAA in people with T2D. Furthermore, I found strong associations between BCAA and key metabolic disarrangements seen in T2D at the level of mitochondrial function, liver fat, insulin resistance and metabolic flexibility. Importantly, data showed lower whole body leucine oxidation in patients with T2DM vs. control humans. Here, I want to use the FDA approved drug Pheburane containing sodium-phenylbutyrate (NaPB) -a drug known to lower plasma BCAA in humans via accelerated BCAA oxidation- in patients with T2DM as strategy to enhance BCAA metabolism. This project aims to investigate whether Na-PB-enhanced BCAA oxidation would be a potential strategy in people with T2D to improve metabolic health.

Study objective

Primary objective is the delta change in whole body insulin sensitivity upon Na-PB vs. placebo treatment. Secondary objectives are muscle mitochondrial

oxidative capacity, muscle and liver fat content and energy metabolism.

Study design

2 week clinical randomized controlled trial (RCT) with a double blinded, placebo-controlled, cross-over design, including a wash-out period of 6 weeks.

Intervention

2 weeks oral administration of 4.8 g/m2/day Pheburane or placebo per day, depending on body surface area. The dose will be spread over the day in 3 times taken with a meal.

Study burden and risks

No direct health benefits for the participants are expected. Burdens: time investment with study visits and administration of study drug.

risks study drug:
• excess urinary loss of nitrogen and a related negative nitrogen balance: if indicated, nitrogen balance will be restored with supplementation.
• adverse reactions like loss of appetite and changed body odor: this can be caused by phenylacetate and reduced taste perception has been described for 3-4% of all patients with prolonged prescription. These reactions could compromise compliance, therefore, a dropout of ~20% is anticipated.
• amino acid deficiency: participants will be advised to keep their normal dietary habits, to exclude this risk.

risks measurements:
low risk for hypoglycaemia during the clamp, hematomas and inflammation upon muscle biopsies.

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

1. Patients are able to provide signed and dated written informed consent prior to any study specific procedures
2. Women are post-menopausal (defined as at least 1 year post cessation of menses) and aged >= 45 and <= 75 years. Males are aged >= 40 years and <= 75 years
3. Patients should have suitable veins for cannulation or repeated venipuncture
4. Caucasians
5. BMI: 25-38 kg/m2
6. Diagnosed with T2D at least 1.5 years before the start of the study
7. Relatively well-controlled T2D: HbA1c < 8.5%
8. Oral glucose lowering medication: metformin only or in combination with sulfonylurea agents and/or on stable dose of a DPPIV inhibitor treatment for at least the last 3 months
9. No signs of active diabetes-related co-morbidities like active cardiovascular diseases, active diabetic foot, polyneuropathy or retinopathy
10. No signs of active liver or kidney malfunction

Exclusion criteria

1. Previous enrolment in a clinical study with an investigational product during the last 3 months or as judged by the Investigator
2. Participate in physical activity more than 3 times a week
3. Unstable body weight (weight gain or loss > 5 kg in the last three months)
4. Insulin dependent T2D
5. Patients with congestive heart failure and and/or severe renal and or liver insufficiency or known sodium retention with oedema

6. Patients using Probalan (probenecid), Haldol (haloperidol), Depakene (valproate) or medical products containing corticosteroids
7. Men: Hb <8.4 mmol/L, Women: Hb <7.8 mmol/l
8. Any contra-indication MRI scanning. These contra-indications include patients with following devices:
• Central nervous system aneurysm clip
• Implanted neural stimulator
• Implanted cardiac pacemaker of defibrillator
• Cochlear implant
• Metal containing corpora aliena in the eye or brains

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):	02-04-2019
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pheburane
Generic name:	sodium phenylbutyrate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-11-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2019
Application type:	First submission
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	EUCTR2018-003176-13-NL
CCMO	NL67133.068.18

Study results

Summary results
Trial ended prematurely