To boost amino acid oxidation in diabetes

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28825

Source
Nationaal Trial Register

Brief title
NaPB as tool to boost BCAA oxidation

Health condition

type 2 diabetes
sodium phenyl butyrate
insulin resistance
branched-chain amino acids
mitochondrial function
energy metabolism

Sponsors and support

Primary sponsor: Maastricht UniversityNUTRIMUniversiteitssingel 406229 ER Maastricht+31 43 3881476secretariaat-nutrim@maastrichtuniversity.nl
Source(s) of monetary or material Support: Diabetes Foundation Netherlands and self financing research

Intervention

Outcome measures

Primary outcome

Primary objective is the delta change in whole body insulin sensitivity expressed as glucose disposal rate (µmol/kg/min) upon 2 weeks of Na-PB vs. placebo treatment.

Secondary outcome

• muscle mitochondrial function upon 2 days and 2 weeks treatment periods expressed as O2-flux in pmol/mg/s
• whole-body energy metabolism upon 2 days and 2 weeks treatment periods expressed as respiratory exchange ratio (RER) and kJ/kg/min
• fat accumulation in muscle and the liver expressed as % upon 2 days and 2 weeks treatment periods

Study description

Background summary

Rationale: 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 administer the drug 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.

Objective: Primary objective is the delta change in whole body insulin sensitivity expressed as glucose disposal rate (µmol/kg/min) upon 2 weeks of Na-PB vs. placebo treatment.

Secondary objectives are muscle mitochondrial oxidative capacity (pmol/mg/s), muscle and liver fat content (%) and energy metabolism (respiratory exchange ratio and kJ/kg/min).

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.

Study population: 16 male and (post-menopausal) female participants (50% m/ 50% f) with T2D. Participants will be relatively well-controlled (HbA1C<8.5%), are on oral glucose-lowering medication, are overweight/obese (BMI 25-38 kg/m2) and between 40-75 years old.

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

Main study parameters/endpoints: insulin sensitivity expressed as delta change in µmol/kg/min upon Na-PB treatment versus placebo. The endpoint of study is the measurement of insulin sensitivity of the 15th participant after the second intervention period.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: No direct health benefits for the participants are expected. Burdens: time investment with study visits and administration of study drug. (Low) risks of measurements: hypoglycaemia during the clamp, hematomas and inflammation upon muscle biopsies. Risks with study drug: negative nitrogen balance, loss of appetite, changed body odour (described for 3-4% of all patients using Na-PB with long administration time).

Study objective

Sodium phenylbutyrate administration in patients with T2D would improve whole body insulin sensitivity.

Study design

2 times 2 week intervention period with a washout of 6-8 weeks between the treatment arms. Total duration of the study is 10-12 weeks for each participant

Intervention

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

Contacts

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Eligibility criteria

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 e.g. the following:
• 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
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2019
Enrollment:	16
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	10-08-2018
Application type:	First submission

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
NTR-new	NL7227
NTR-old	NTR7426
Other	METC aZM/UM : ABR_67133

Study results