Diabetes Bootcamp; Sport intervention in patients with diabetes type 2 and the association with the gut microbiota.

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Primary Objective: To investigate whether exercise (Diabetes Bootcamp) induces a change in intestinal faecal microbiota (rise of butyrate-producing intestinal microbiota) related to improved glycaemic control (peripheral and hepatic insulin...

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

Summary

ID

NL-OMON45040

Source
ToetsingOnline

Brief title
Diabetes Bootcamp

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes, Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Vidi beurs Max van Nieuwdorp

Intervention

Keyword: Diabetes mellitus type 2, Gut microbiota, Insulin resistance, Lifestyle intervention

Outcome measures

Primary outcome

Main study parameter/endpoint: change in gut microbiota composition

Secondary outcome

* Whole-body Iinsulin sensitivity: by means of hyperinsulinemic-euglycemic clamp

* Muscle microcirculation: Insulin-mediated capillary recruitment by means of contrast-enhanced ultrasound (CEUS),

* Needle skeletal muscle and adipose tissue biopsies to assess: protein and gene expression of insulin signalling proteins, lipid content and PVAT morphology muscle biopsy

* Markers of inflammation: CRP, LPS serum, cytokines (IL1, IL 6, IL-8 and TNF-*)

* Metabolism: Resting energy expenditure (resting metabolic rate) and % oxidation of macronutrients by means of indirect calorimetry (Quark®) (REE), Bio Impedance Analysis (BIA)

* 24 hour urine samples

* Metabolic and humoral biomarkers (plasma glucose, HbA1c, FFA; catecholamines)

* Body anthropometrics (weight, height, BMI, waist and hip circumferences, fat %)

* Physical activity energy expenditure

* Questionnaires: RPE-scale, PACE-score

Study description

Background summary

Diet and exercise are the most beneficial and most frequently advised lifestyle interventions in patients with diabetes mellitus (DM) type 2, causing an increase in glucose tolerance.
One of the mechanisms through which these treatment modalities work might be explained through changes in the gut microbiota. Recent studies show that the chronic inflammatory status causing insulin resistance in DM type 2, is triggered by an increase in circulating bacterial lipopolysaccharide (LPS). Research in mice has shown that a high-fat diet alters the gut microbiota causing an increase in intestinal permeability, resulting in a rise of circulating LPS. Consequently, LPS causes a low-grade inflammation by inducing pro-inflammatory cytokines (TNF-alfa, interleukin (IL)-1, and IL-6). Strict lifestyle intervention (low-fat diet and exercise), so called Diabetes Bootcamp (DB), may manipulate and reverse the alterations in gut microbiota caused by high fat diet, ultimately reducing circulating LPS, resulting in an increase in glucose tolerance.
That the gut microbiota have a causal role in determining insulin sensitivity in humans was made likely by a faecal transplantation of lean donors to male recipients with metabolic syndrome. Six weeks after infusion of microbiota from lean donors, insulin sensitivity of recipients increased along with levels of butyrate-producing intestinal microbiota. Studies in humans however have so far not been able to answer the question whether the beneficial effects of these targeted lifestyle interventions in patients with DM type 2 are due to a change in gut microbiota.
Also exercise increases the microbial diversity as well as bacterial genes involved in protein metabolism. These changes in gut microbiota might also be a cause for increased glucose tolerance.

A second mechanism that has been proposed to attribute to the pathophysiology of insulin resistance lies within impairments of the hemodynamic effects of insulin. In healthy subjects insulin enhances the perfusion of skeletal muscle capillaries by vasodilatation of pre-capillary arterioles. This process is called capillary recruitment. In patients with DM type 2 insulin-mediated vasodilatation of the microcirculation is blunted. Animal research suggests a causal mechanism between decreased microvascular perfusion in skeletal muscle and decreased glucose uptake. However, evidence from human studies is incomplete. A low-dose infusion of iloprost * a stable prostacyclin analogue - is able to increase glucose uptake in type 2 diabetes patients. However, in this study, capillary recruitment was not assessed and enhancement of capillary recruitment may well explain the effects of iloprost on glucose uptake. Furthermore it remains unknown up till now if insulin-mediated microvascular perfusion defects in DM type 2 are reversible by lifestyle interventions and if

improvement of perfusion contributes to lifestyle-dependent control of glucose uptake.
Finally, there appears to be a correlation between capillary recruitment and systemic inflammation. In rats, acute administration of TNF-* in vivo completely blunts the insulin-mediated capillary recruitment and simultaneously reduces insulin-mediated glucose uptake.

In summary, dietary- and exercise can manipulate the gut microbiota and may also restore insulin-mediated microvascular perfusion defects in patients with DM type 2. However, studies in humans have so far not been able to answer the question whether the beneficial effects of these targeted lifestyle interventions in patients with DM type 2 are due to a change in gut microbiota and/or restoration of perfusion defects (capillary recruitment). We thus hypothesize that through exercise we can manipulate the intestinal microbiota in patients with DM type 2, causing a reduction in LPS exposure and therefore pro-inflammatory cytokines. By observing the dynamical changes of the microbiota during exercise, we will gain more insight in to the complex relationship between DM type 2, the gut microbiota and lifestyle interventions.

Study objective

Primary Objective:
To investigate whether exercise (Diabetes Bootcamp) induces a change in intestinal faecal microbiota (rise of butyrate-producing intestinal microbiota) related to improved glycaemic control (peripheral and hepatic insulin sensitivity) in patients with DM type 2.

Secondary Objective(s):
1. To investigate whether changes in gut microbiota induced by an exercise regimen are associated with changes in plasma markers of systemic inflammation (CRP/cytokines/LPS), body composition and REE.
2. To demonstrate that an exercise regimen in type 2 diabetic patients results in improved insulin sensitivity and enhancement of insulin-mediated capillary recruitment.
3. To investigate whether an exercise regimen induces a change in insulin-mediated capillary recruitment related to systemic inflammation in patients with DM type 2.
4. To investigate whether infusion of iloprost in type 2 diabetes patients is able to increase glucose uptake and reveals capillary recruitment. To demonstrate that acute infusion of iloprost * a stable prostacyclin analogue * in type 2 diabetic patients results in enhanced improved insulin sensitivity and enhancement of insulin-mediated capillary recruitment.,
5. To investigate whether an iloprost infusion is able to simulate the effects of a exercise regimen on capillary recruitment and insulin sensitivity.
6. Characterization of PVAT morphology, adipokine profile and function before and after an exercise program.
7. To demonstrate the effects of acute iloprost infusion and an exercise

regimen on:
* Adipose tissue and myocardial perfusion.
* RMR, oxidation of macronutrients (Quark®)
* Blood pressure, heart rate, heart rate variability, peripheral vascular resistance and cardiac output.

Study design

Patients with diabetes type 2 will be included in a prospective open-label study.
After screening, patients will participate in a full exercise program (twice a week, one hour), guided by a physiotherapist.
There will be 5 study visits: 2 baseline visits as well as control visits at 7, 12 and 26 weeks. There will be a 3-day deviation for all return visits. All assessments, including clinical evaluation, safety and biomarker measurement, will be performed at each visit. At baseline and week 12 blood samples, fecal analysis, hyperinsulinemic-euglycemic clamp, indirect calorimetry (REE), Bio Impedance Analysis (BIA), muscle biopsy as well as contrast-enhanced ultrasound (CEUS) measurements will be performed. At baseline, all participants visit the research center on 2 consecutive days to undergo a hyperinsulinemic-euglycemic clamp with and without iloprost infusion. The order of the first 2 days will be randomized.

Intervention

During a 12 week period patients will participate in a full exercise program.

Study burden and risks

After screening, patients will participate in a full exercise program during a period of 12 weeks, called Diabetes Bootcamp (DB). The exercise program is twice a week during 1 hour, matched to their own personal capacity.
There will be 5 study visits: 2 baseline visits as well as control visits at 7, 12 and 26 weeks. All assessments, including clinical evaluation, safety and biomarker measurement, will be performed at each visit. At baseline and week 12 blood samples, fecal analysis, an hyperinsulinemic-euglycemic clamp, indirect calorimetry (REE), Bio Impedance Analysis (BIA), muscle biopsy as well as contrast-enhanced ultrasound (CEUS) measurements will be performed. At baseline, all participants visit the research center on 2 consecutive days to undergo a hyperinsulinemic-euglycemic clamp with and without iloprost infusion.

Risks associated with hyperinsulinaemic-euglymic clamps are hypo-or hyperglycemia, which we will prevent by adjusting pump levels. Iloprost infusion is known to have some side effects, but non are severe at a low dose. The placing of the intravenous cannula in our study can be an unpleasant experience for the subjects. There is a low risk of flebitis at the intravenous

injection sites, this is unpleasant, but not harmful, of temporary nature and self-limiting. Muscle and fat biopsies require a local anesthesia, which can give some discomfort to the participants. Also, after the biopsy participants can expect some muscle ache.

We expect great health benefits for the participants, including weight reduction, an increase in exertion and glucose tolerance. This research can be classified as low risk and will hopefully provide mechanistic insight into whether it is the intestinal microbiota are related to human satiety and metabolism, which may help us to develop therapeutic methods to combat obesity and insulin resistance.

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 with type 2 diabetes
2. Male or female (post-menopausal)
3. Age above 45 years and below 70 years
4. BMI >30 kg/m2
5. Metformine monotherapie (no insulin or other glucose lowering medication)
6. Stable medication use
7. Stable tension regulation (with or without medication)
8. Stable body weight during 6 months before enrolment in the study (<2 kg shifts)
9. Subjects should be able to give informed consent
10. HbA1c < 80 mmol/mol or < 8,6%

Exclusion criteria

1. A history of cardiovascular event (Cerebrovascular event, myocardial infarction or pacemaker implantation)
2. Severe-very severe lung emphysema (GOLD stage III-IV)
3. Use of any antibiotics or proton pump inhibitor (PPI) in the past three months
4. Use of any other antidiabetic medication besides metformin (e.g. SU-derivates, insulin)
5. Use of a platelet inhibitor or cumarin derivate during
6. Subjects participated in a lifestyle programme in the past 6 months (diet or exercise)
7. Contraindications of iloprost (ilomedine®): increased risk of bleeding; severe coronary artery disease or instable AP; heart failure (NYHA class II-IV); severe arrhythmias; suspected left decompensation; hypersensitivity to the active substance or to any of the excipients
8. Contraindications of insulin(NovoRapid®): hypersensitivity to the active substance or to any of the excipients

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-05-2016
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	13-11-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL54284.029.15