Gut microbial substrate switch to improve metabolic health

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The objective of this proposal is to test in a proof-of-concept manner, whether the dietary fiber product WholeFiberTM yields an optimal gut and circulating SCFA concentration to reverse insulin resistance.

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

Summary

ID

NL-OMON49051

Source
ToetsingOnline

Brief title
WholeFiber Study

Condition

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

Synonym
insulin resistance, overweight

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Stichting Life Science -TKI;tradename Health Holland,EFSD/Lilly European Diabetes Research Programme

Intervention

Keyword: dietary fibers, gut microbiota, insulin sensitivity, short-chain fatty acids

Outcome measures

Primary outcome

Insulin sensitivity as assessed by a hyperinsulinemic euglycemic clamp

Secondary outcome

- energy expenditure and substrate oxidation (indirect calorimetry)

- adipose tissue and skeletal muscle gene/protein expression

- faecal and circulating SCFA

- faecal microbiota composition

- circulating incretins, metabolites and inflammatory parameters

- body weight, BMI and body composition (DEXA scan)

- Three-day food record and physical activity questionnaires

A three-day food record will be completed three days prior to each CID.

- Gastrointestinal Symptom Rating Scale (GSRS) questionnaire.

- Proton magnetic resonance spectrometry to assess liver fat content

Study description

Background summary

In the last 15 years, the connection between the gut microbiota and obesity-related cardiometabolic disorders is increasingly recognized. Our gut microbiota affect the cardiometabolic phenotype by fermenting indigestible dietary components, such as dietary fibers, which are coupled to production of short-chain fatty acids (SCFA). These SCFA can affect adipose tissue function and ectopic fat storage thereby modulating host insulin resistance. Our recent findings, using a unique design to administer SCFA in the proximal and distal colon, show that distal colonic SCFA administration, in amounts achieved by a

high fiber diet, has pronounced effects on lipolysis, fat oxidation and inflammatory profile in healthy overweight volunteers. Based on this, we hypothesize that slowly fermentable fibers with a high degree of polymerization that increase SCFA specifically in the distal colon are expected to have higher potential for influencing host metabolism and metabolic health by improving adipose tissue function, preventing lipid overflow and skeletal muscle fat accumulation thereby improving insulin sensitivity.

Study objective

The objective of this proposal is to test in a proof-of-concept manner, whether the dietary fiber product WholeFiberTM yields an optimal gut and circulating SCFA concentration to reverse insulin resistance.

Study design

Double blind, placebo-controlled, randomized, parallel design.

Intervention

In this study there will be two different intervention groups:
1. WholeFiberTM product (First two weeks: 2x 7.5g per day, last ten weeks: 2x 15g per day)
2. Placebo: Puffed Millet (First two weeks 2 x 3.9g per day, last ten weeks: 2x 7.8g per day), isocaloric
The intervention period will be at least 12 weeks (84 days) with a maximum of 90 days intervention due to practical reasons.
The type of treatment will be blinded for both the volunteers and the researchers.

Study burden and risks

All participants will be screened before participation and thereby receive information about their health status. In the future there can be general health benefits for the public, but the volunteers receiving placebo will not have a personal benefits by participating in the study. Participants receiving the dietary fibers may have personal health benefits if intervention effects are according to expectations. The general interest of this study is to investigate how manipulating the gut microbiota, increasing SCFA production and shifting colonic SCFA ratios by the intake of dietary fiber mixtures will influence human peripheral insulin sensitivity and substrate and energy metabolism.
Burdens that volunteers can experience, such as the time spent with the study and the dietary and healthy regimen they have to follow. Also the collection of faecal samples can be experienced as a burden, because they have to handle them themselves and have to store them at home. Also the 12-week

intake of the dietary fiber can be seen as a burden for the participants.
During the CIDs, blood will be collected via a venous catheter.
Venepunctures can occasionally cause a local hematoma or bruise to occur. Some participants report pain during venepuncture. During CID 1 and 2 the total amount of blood sampled is 205ml per CID, totaling 445ml (35ml screening) during the whole test period. During CID 1 and 2, adipose tissue and skeletal muscle biopsies will be taken. The adipose tissue biopsy might cause local hematoma as well. After the muscle biopsy, some participants report pain, which is experienced as muscle pain. More often the muscle feels stiff for a couple of days after the biopsy. To minimize the risk for a hematoma, the biopsy place will be compressed for approximately 5 minutes after biopsy. The place of incision will leave a small scar (* 3 mm for adipose tissue biopsy and * 8 mm for skeletal muscle biopsy). To promote good wound healing, the incision will be sealed with sterile steristrips and a waterproof band-aid. The site of the muscle biopsy will, in addition, be sealed with a compression bandage. During the hyperinsulinaemic-euglycemic clamp there is a small risk of hypo- or hyperglycemia. However, from our own extensive experience, these conditions do not occur very often and can be reversed immediately. A medical doctor is always available during the clamp. Concerning the other study procedures (oral glucose tolerance test (OGTT) (screening), and indirect calorimetry), there are no known risks (in literature and own extensive experience), and these measurements are routinely applied in human biology research. SOPs for each measurement are available in the Human Biology Department*s database.

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

Overweight/obese (BMI >= 28 kg/m2 < 35 kg/m2) with insulin resistance (HOMA-IR>2.2) and/or impaired glucose tolerance (IGT: 2h plasma glucose during 75g OGTT 7.8-11.1 mmol/l) and/or impaired fasting glucose (IFG: plasma glucose >= 5.6 mmol/l) aged 45-70 years

Exclusion criteria

- diabetes mellitus
- gastroenterological diseases or major abdominal surgery (allowed i.e.: appendectomy, cholecystectomy)
- lactose intolerance and other digestive disorders
- cardiovascular disease, cancer, liver or kidney malfunction (determined based on ALAT and creatinine levels,
respectively)
- disease with a life expectancy shorter than 5 years
- abuse of products (alcohol consumption > 15 units/week, or any drugs)
- excessive nicotine use defined as >20 cigarettes per day
- plans to lose weight or follow a hypocaloric diet
- regular supplement of pre- or probiotic products
- intensive exercise more than three hours a week
- - use of any medication that influences glucose or fat metabolism and inflammation, like i.e. lipid
lowering-drugs (e.g. PPAR γ or PPARα (fibrates) agonists), glucose-lowering agents (including all
sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, repaglinide, nateglinide and insulin),
anti-oxidants or chronic corticosteroids treatment.
- use of laxation products in the last three months or during the study period

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-02-2021
Enrollment:	42
Type:	Actual

Ethics review

Approved WMO Date:	08-06-2020
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-01-2021
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	NL72483.068.20