Personalized microbial substrates to prevent type 2 diabetes

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON50869

Source
ToetsingOnline

Brief title
Personalizedfiber study

Condition

- Diabetic complications
- 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: Diabetes Fond Nederland (DFN)

Intervention

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

Outcome measures

Primary outcome

Peripheral insulin sensitivity as assessed by a hyperinsulinaemic-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 and in vitro microbial activity testing

- circulating incretins, metabolites and inflammatory parameters

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

Study description

Background summary

Evidence is increasing that the gut microbiota is a key player in the aetiology of insulin resistance and type 2 diabetes mellitus (T2DM). The gut microbiota is able to transform fermentable dietary fibres into short-chain fatty acids (SCFA). In previous clinical trials we demonstrated that acute distal colonic SCFA infusions resulted in increased energy expenditure, fat oxidation and satiety hormones, and decreased inflammatory markers and lipolysis in men. These results suggest a beneficial role of increased distal colonic SCFA in insulin sensitivity. A straightforward approach to translate these promising SCFA-related acute effects into long-term metabolic benefits would be the supplementation of specific fermentable fibres. However, well-controlled long-term human studies supplementing one specific fibre (e.g. galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS)) failed to show enhanced microbial SCFA production and did not induce beneficial metabolic effects.

From these studies, it can be concluded that the lack of metabolic effects is mainly caused by (1) the stimulation of only few specific bacteria genera, thereby decreasing the abundance of other essential SCFA-producing microbes, and (2) the lack of these studies to take into account the individual*s initial microbiome and its capacity to produce SCFA.
Therefore, in this project we hypothesize
(1) that a mixture of fermentable fibres, which differ in degree of polymerization and side chains, will stimulate a broad range of SCFA-producing bacterial genera, resulting in enhanced chronic SCFA production with a large variation between individuals; (2) that providing personalized fibre mixtures, selected based on the individuals* initial microbial capacity for SCFA production, is crucial to successfully improve host insulin sensitivity and metabolic health.

Study objective

In this project we intends to study the therapeutic potential of a personalized fibre mixture in individuals at high risk of developing T2DM, and aims to address the following key objectives:
1. To investigate whether a mixture of fermentable fibres, which differ in DP and side chains, will stimulate a broad range of SCFA-producing bacterial genera, resulting in enhanced chronic SCFA production throughout the whole colon with a large variation between individuals;
2. To unravel whether providing personalized fibre mixtures, selected based on the individuals* initial microbiota and capacity for SCFA production is crucial to successfully improve host insulin sensitivity and metabolic health

Study design

Double blind, controlled, randomized, parallel design.

Intervention

First, a fibre mixture that yields the highest amounts of SCFA in the distal colon will be determined for each individual in the in vitro model. Food-grade fibres will be used, which allows me to apply them directly in the human in vivo study. In total 4 fibre mixtures will be tested for each individual microbiota. The fibre mixtures will be a combination of 3 fibres that differ in DP and branching (each 4 g). Each fibre mixture will include a rapidly fermentable oligosaccharide (FOS or GOS), a more complex fibre (resistant starches (RS2)) and slowly fermentable, high DP fibres pectin, corn bran arabinoxylans). The 4 fibre mixtures will contain:
1. 4 g FOS + 4 g RS2 + 4 g pectin
2. 4 g GOS + 4 g RS2 + 4 g pectin
3. 4 g FOS + 4 g RS2 + 4 g corn bran arabinoxylans
4. 4 g GOS + 4 g RS2 + 4 g corn bran arabinoxylans

The individual fibre mixture will then be provided to 22 participants who will receive in the first two weeks of the intervention period 12 g of the fibre mixture daily and thereafter for ten weeks 24 g daily. The control group will receive in the first two weeks 12 g GOS daily and in the last 10 weeks 24 g GOS daily.

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. Participants receiving the personalized 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 (participants will have to invest approximately 14.5 hours in the study, divided among 2 clinical investigation days (CIDs) interim visits for feces collection and questionnaires and a screening visit (see for an overview table 1 and figure 1)). In addition, the participants will fill in diet and physical activity records and will fill in with an intake record of the supplements, which are also time consuming. 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 140 ml per CID, totaling 315 ml (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. In addition, participants will undergo for two times a DEXA scan. Thereby, they will receive a radiation of circa 20 microSievert (calculated by Radiation Experts, Randwyck, Maastricht). The average doses of each person in the Netherlands is 2,5 miliSievert per year

(thus a factor 125 higher), therefore the risk of the radiation is considered negligible.

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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 < 40 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 30-70 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- Suikerziekte heeft;
- Pregnancy

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-11-2022
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	10-06-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-12-2021
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	NL76905.068.21