Using a complex carbohydrate mixture added to a high-protein DIet to STeer fermentation to improve metabolic, gut and brain heALth

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Primary Objective: The main goal of this study is to provide evidence that steering saccharolytic/proteolytic fermentation by a specific indigestible fibre mixture supplemented against the background of a high-protein diet optimizes beneficial and…

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

Summary

ID

NL-OMON51442

Source
ToetsingOnline

Brief title
DISTAL-study

Condition

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

Synonym
Insulin resistance, prediabetes

Health condition

Obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support:
NWO,Avebe,Nuscience,Nuscience;Avebe;Sensus,Sensus

Intervention

Keyword: Fermentation, Fibres, Obesity, Short-chain fatty acids

Outcome measures

Primary outcome

The main endpoint is the difference in change in peripheral muscle insulin

between intervention and control group, measured by hyperinsulinemic-euglycemic

clamp.

Secondary outcome

Difference in changes in pre- and posttreatment values between intervention and

control group, regarding the following parameters/endpoints:

- Hepatic and adipose tissue insulin sensitivity

- Energy and substrate metabolism (energy harvest, intake, expenditure,

carbohydrate and fat oxidation)

- Body weight, composition and body fat distribution (anthropometrics, DEXA)

- Plasma and faecal concentrations of butyrate, propionate and acetate (SCFA)

and proteolytic substrates (BCFA, indoles, ammonia)

- Plasma concentrations of inflammatory markers (IL-6, TNF-α, IL-1),

circulating metabolites (glucose, triglycerides, FFAs) and hormones (insulin,

GLP1, PYY) and blood lipid spectrum (total cholesterol, HDL, triglycerides/TAG)

- Brain health: food reward related brain activation and cognitive function

(CANTAB, fMRI)

- Gut permeability

- Faecal microbiota composition and functionality (Metagenome and

-transcriptome sequencing)

- Gastrointestinal side effects (GRGS / BSS)

- Expression of gene and protein expression in adipose and muscle tissue

Other study parameters (if applicable)

- Three day food record: completed before CID 1 and 3 and the visit in week 2.

- Physical activity questionnaire: completed before CID 1 and 3 and visit in

week 6 (SQUASH)

- Questionnaires on general wellbeing and quality of life, (family) medical

history, stress, sleeping habits and fatigue, mood, satiety

Study description

Background summary

The worldwide prevalence of obesity has nearly tripled in the past 40 years, totalling up to over 650 million adults in 2016. Obesity is related to the onset of metabolic disorders, such as metabolic syndrome, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD). These diseases are associated with a high morbidity and mortality, making T2DM the ninth leading cause of death worldwide. Apart from causing a high burden on a patients wellbeing, this also leads to a global health and socio-economic burden.

The human diet plays an important role in (metabolic) health and can be a major component in the aetiology of obesity, T2DM and NAFLD. The western diet, being energy and relatively low in fibres, is seen as a major contributor to the

development of these diseases. However, diet composition may affect food digestion and fermentation, which may have either a beneficial or detrimental effect on human metabolism and health. The gut microbiome, consisting of trillions of microbes and being responsible for the fermentation of indigestible food components, is being more and more thoroughly understood, and is recognized for its important role in gut health, mucosal immunity and integrity, and in metabolic and psychological health of its host.

The microbiome is able to ferment indigestible food components, such as prebiotics, dietary fibres and resistant starches. Fermentation of these carbohydrates, called saccharolytic fermentation, occurs mainly in the proximal colon and produces short-chain fatty acids (SCFA), of which acetate, propionate and butyrate are the most common. These SCFA, which are the main fuel for colonocytes, are absorbed quickly, leading to an almost absolute absence of SCFA in the transverse colon. In absence of indigestible carbohydrates, the microbiome shifts to proteolytic fermentation in the transverse and distal colon, producing numerous substrates, such as indoles, tryptophane, ammonia and hydrogen sulphide.

In general, SCFA have a beneficial effect on human health. They improve gut health by improving epithelial function, intestinal barrier function and mucosal quality, and reducing gut permeability. SCFA also have a positive impact on metabolic health by reducing body weight, increasing energy expenditure, satiety, insulin sensitivity and adipose tissue lipid buffering capacity, and preventing low-grade inflammation and ectopic lipid accumulation. Furthermore, evidence shows that an increase in circulating SCFA reduces inflammation in the gut, pancreas and throughout the body, including the brain, by reducing cytotoxic T cell activity and increasing anti-inflammatory regulatory T-cells. Lastly, SCFA are found to reduce stress in rodents, as a result of SCFA-induced reduced release of corticotropin-releasing hormone and downregulation of mineralocorticoid receptor expression.

Proteolytic fermentation, more prevalent in the transverse and distal colon, produces substrates, such as branched-chain fatty acids, ammonia and phenols, that can have detrimental health effects. On the other hand, there are also indications that substrates of proteolytic digestion may have positive health effects. Proteolytic digestion, and especially digestion of tryptophan rich proteins, in the small intestine is associated with reduced inflammation and improved gut barrier function and increased satiety and weight loss/maintenance. Overall, the balance between saccharolytic and proteolytic fermentation products in different parts of the gut may be an important determinant of metabolic health.

Our recent studies have shown that delivering SCFA, acetate in particular, specifically to the distal colon yields beneficial health effects, such as increased fat oxidation, reduced lipolysis, increased satiety hormone concentrations and reduced inflammatory cytokines (TNF-α). Apart from this,

other studies have shown that delivering SCFA directly to the distal colon improves human metabolism and increases levels of satiety hormones and energy expenditure, which may be partly due to SCFA bypassing the liver and increasing peripheral SCFA concentrations. These effects were not present when acetate was administered to the proximal colon. We therefore hypothesize that an increased delivery of indigestible carbohydrates throughout the entire colon may have the most pronounced health effects by increasing distal saccharolytic fermentation and SCFA production, and thereby inhibiting proteolytic fermentation.

Increasing the SCFA concentration in the distal colon can be achieved by using complex carbohydrates, such as resistant starches or dietary fibres. These complex, indigestible carbohydrates escape fermentation in the small intestine, since the composition of the small intestinal microbiome differs from the colonic microbiome, lacking specific bacteria that are capable of fermenting these carbohydrates.

Many previous studies regarding manipulation of intestinal digestion and fermentation are performed on rodents, while evidence in humans is lacking. The few available human trials mainly describe acute interventions and present inconsistent data. Furthermore, the beneficial effects of SCFA on glucose homeostasis and insulin sensitivity are mainly found in lean individuals, and not in obese/(pre)diabetic adults.
The few human trials on long term effects of introduction of SCFA in the colon are mostly conducted in healthy adults, and results were not consistent. This may be related to interindividual variation in response. We hypothesize that this is partly due to a different composition of initial microbiome, as well as differences in metabolic phenotypes (i.e. being insulin resistant or having prediabetes).

To this end, the aim of the present project is to determine the long-term effects (12 weeks) of an optimal balance between saccharolytic and proteolytic fermentation products on gut health, human metabolism and psychological state in humans with prediabetes and overweight. The present study might give rise to new possible preventative and therapeutic measures to reduce obesity and its related metabolic disorders, including insulin resistance, metabolic syndrome, type 2 diabetes mellitus and non-alcoholic fatty liver disease. Additionally, we expect that improving microbial composition and functionality may also improve brain health by supporting cognitive functioning and appetite regulation, altering reactions to food cues and reducing experienced stress.

Study objective

Primary Objective:
The main goal of this study is to provide evidence that steering saccharolytic/proteolytic fermentation by a specific indigestible fibre mixture supplemented against the background of a high-protein diet optimizes beneficial and minimizes detrimental substrate production. Most importantly, we will be

looking into changes in peripheral insulin sensitivity.

Secondary Objectives:
Apart from determining possible effects on insulin sensitivity, we will also investigate the following parameters and analyse whether steering fermentation can influence the following secondary outcomes:
1. Hepatic and adipose tissue insulin sensitivity
2. Energy and substrate metabolism (energy harvest, energy intake, energy expenditure, fat and carbohydrate oxidation).
3. Circulating metabolites, inflammatory factors and blood lipid spectrum
4. Gut permeability
5. Brain health (neurocognitive functioning and food reward-related brain activity)
6. Adipose tissue and skeletal muscle metabolism
7. Composition and functionality of microbiome
8. Gastro-intestinal side-effects of provided dietary supplement against the background of a high-protein diet

Additionally, we will explore possible correlations in the gathered data, including anthropometric measurements, physical activity, dietary intake, glucose sensitivity, composition of gut microbiota, etc.

Study design

The proposed study will be a double-blind, randomized placebo-controlled trial, to evaluate the effect of the dietary supplement on gut, metabolic, immune and brain health by optimizing saccharolytic and proteolytic fermentation.
Individuals aged 30-70 years with overweight or obesity (BMI >= 28 kg/m2 < 40 kg/m2) and prediabetes (defined as fasting glucose 5.6-6.9 mmol/l or HbA1c 42-47 mmol/mol or HOMA-IR >1.85) will be included in the study.
All visits regarding this study will take place at the facilities of the department of human biology or the Metabolism Research Unit Maastricht of Maastricht University, or at the clinical facilities of Maastricht University Medical Center+.

After the application of an individual via (e-)mail or phone, the researcher will contact the potential participant by email or phone to provide additional information regarding the study, answer questions and determine possible eligibility, after which a week of consideration will be given. After a week, the potential participant will be contacted again and, if they are still interested in participating, a screening visit will be planned.

The first visit to our facilities will consist of the following components:
- Providing additional information, answering questions and checking if all information is understood correctly, ensuring participants are still interested in participating
- Signing informed consent

- Checking an individual*s wellbeing, medical history and determining eligibility and safety of participation.
- Measuring vital parameters and body measurements (body weight, length, waist-to-hip ratio, systolic and diastolic blood pressure)
- Taking blood samples to determine eligibility based on specific inclusion criteria (20ml to determine glucose, insulin, ALAT, creatinine, HbA1c)
The participant will visit our facilities after a >10h overnight fasted state.

All eligible participants will be equally randomized over the two arms (dietary supplement vs placebo) with minimisation for age, sex and BMI. The entire trial period after screening and randomization will take 13 weeks, which will be explained in more detail below.

Intervention period
This randomized clinical trial with the primary outcome tissue-specific insulin sensitivity has a placebo-controlled, double blind, randomized parallel design, which allows evaluation of the role of a fibre mixture against the background of a high protein diet on host metabolism in male and female adult volunteers with overweight/obesity and prediabetes.

The approach is as follows:

1. Preceding this human intervention trial, a pilot study already has been performed to screen for the most optimal fibre mixture increasing distal colonic saccharolytic fermentation (and thus SCFA production) and inhibiting proteolytic fermentation. Faeces have been collected in 13 human volunteers with insulin resistance and overweight. The pooled faecal microbiota has been inoculated in TIM-2 to analyse SCFA and BCFA production after addition of different fibres or fiber combinations in a 24-h protocol against the background of a high-plant based protein mixture (which was comparable to the protein ratio as proposed in the human trial). The fibre mixture that resulted in the highest microbial SCFA production in the part of TIM-2 that represented the distal colon in vitro will be supplemented in the in vivo study. The hereby defined fibre mixture is composed out of potato and pectin fibres
2. After randomization, the 12 week impact of the fiber supplement on tissue-specific insulin sensitivity will be determined in a randomized, double blind, parallel designed study.

Before the start of the intervention, participants will visit our facilities for the first clinical investigation days (CID 1 and 2). These days consist of the following test: (see Chapter 8.3 Study procedures for detailed description of the tests)
- Providing stool samples by participant
- Taking skeletal muscle and adipose tissue biopsies
- Performing two-step hyperinsulinemic-euglycemic clamp
- Performing indirect calorimetry during the clamp
- Performing gut permeability tests by intake of specific sugars dissolved in

water and analysis of urine samples
- Conducting Functional Magnetic Resonance Imaging to study food-reward-related brain activity
- Conducting a DEXA scan to determine body composition
- Filling in questionnaires and performing neuropsychological tests
- Food diaries will be filled in prior to CID 1.
- Distributing and explaining of assigned intervention (fiber supplement or placebo)

After CID 1, participants will be provided with a standardized meal. This meal needs to be consumed at home on the evening before CID 2 ad libitum. Afterwards, they should remain fasted until the hyperinsulinemic-euglycemic clamp on CID 2. CID 2 will take place at least 2 days and preferably within 2 weeks after CID 1.

After the 12 weeks of intervention, two additional CIDs (CID 3+4) will take place, which are similar to CID 1+2, respectively.

After completing the screening and CID 1+2, the intervention will consist of either a dietary supplement or a placebo which will have to be taken once daily during 12 consecutive weeks. Furthermore, all participants will receive a background diet high in protein 25EN% protein mixture, 30EN% fat, and 45EN% carbohydrates. Protein content will consists for 45-50% out of plant-based protein and for 50-55% out of animal-based proteins. The protein-rich products will be consumed during breakfast and dinner. The fibre mixtures and control product can be easily consumed with a high-protein diet. The exact diet composition will be discussed individually to establish a diet suited to the participants* needs and taste. The energy requirements for this diet will be estimated using indirect calorimetry based on resting energy expenditure and an activity factor.
Both the participants and investigators will be blinded to the treatment. The study is designed to study the dietary fibre effects against the background of a high protein diet independent of any diet or exercise intervention.

In week 2, 6 and 9, participants will return for a short interview or will be contacted via telephone to assess their wellbeing and compliance, answer arisen questions and fill in questionnaires. Additionally, a stool sample will be provided in week 2 and a stool and blood sample will be provided in week 6. Questionnaires will mainly be filled in before and after the intervention, with the addition of SQUASH and three-day food diary in week 6, and BSS and GSRS in week 2 and 6.

To screen their food intake and physical activity (SQUASH), participants will fill in a three-day food diary before each CID 1+3 and on week 6. Gastrointestinal Symptom Rating Scale (GSRS) questionnaire will be completed the day before the CID1+3 and on weeks 2 and 6. Therefore, we can screen, whether the participant might experience gastrointestinal discomforts during

the intervention period such as bloating and the outcomes are also relevant for our faecal microbiota analysis.

After completion of the trial, all data will be gathered and analyzed. Participants will receive a financial compensation for their efforts, as well as reimbursements of their travel expenses.
The total amount of time participants spend at our facilities will be around 40 hours (Screening: 0.5h; CID 1+2: 2 x 9.5h; Interview week 2, 6, 9: 3 x 0.5h; CID 3+4: 2 x 9.5h).

As mentioned before, CID 3 will be planned 12 weeks after the start of the intervention. The dietary supplement/placebo and the protein-rich diet will have to be continued until CID 3, which means that in some cases the intervention period will be not exactly 12 weeks, but a few days longer or shorter, depending on the availability of the participant. Logically, the investigators aim for CID 3 to be planned exactly 12 weeks after the start of the intervent

Intervention

All participants will receive a high-protein diet during the entire trial (12 consecutive weeks in total, starting the day directly after CID 2 until the day prior to CID3). This diet will consist of 25 energy percentage (E%) protein, 30E% fat and 45E% carbohydrates. Proteins will be 45-50% plant-based and 50-55% animal-based, to ensure a resemblance to the current western diet consisting of mainly animal-based proteins, while simultaneously acting on the currently shifting trend in society towards more plant-based diets.

Furthermore, according to randomization, one group will receive the dietary supplement and the remaining participants will receive a placebo.

The fibre supplement, as determined using the TIM-2 model, will consist of a combination of potato and pectin fibre. It can be consumed with each meal.

The participants not receiving the fibre supplement will be provided with a placebo in an isocaloric manner, which will be maltodextrin. Maltodextrin Glucidex IT 12 (Roquette Freres, Lestrem, France) is a fully digestible carbohydrate and will be used as isocaloric compensation to the investigated fibre additive. Furthermore, maltodextrin will be comparable to the fibre in terms of taste, mouthfeel and appearance.

Study burden and risks

In general, obesity and its related diseases bring a high burden to a patients wellbeing and quality of life. Furthermore, these diseases are one of the leading causes of death worldwide, have a high socio-economic impact on

society, and thus increase health care costs. By evaluating possible strategies to improve metabolic, gut and brain health, we want to attribute to a healthier lifestyle, a decrease in obesity and obesity-related diseases and in the socioeconomic impact of said diseases.

By testing the pre-established, possibly beneficial dietary component, we will gain insight in specific metabolic pathways, analyse interactions between food, gut and brain, and find potential ways to steer the human digestive system to provide beneficial substrates and reduce detrimental by-products. Along with the purpose of finding fundamental evidence to support further preventative or therapeutic interventions and studies, participants might benefit individually from the intervention in terms of small short-term improvements in body weight, body composition and carbohydrate and fat metabolism.

Nor the investigated dietary additive, placebo or high-protein diet will pose any risk to general health in participants, since these are natural, commonly used dietary components and possible allergies or intolerances are established and ruled out during the screening visit. However, they might cause mild gastro-intestinal discomfort. Furthermore, adhering to a diet for 12 consecutive weeks, consisting of relatively high-amounts of proteins and the investigated fibre-combination, requires motivation, compliance, time and willingness to change their normal lifestyle behaviour to a temporary lifestyle compliant with the prescribed intervention. This will subsequently pose a burden to participants, which is necessary to be able to evaluate the effects on primary and secondary outcome parameters as stated in chapter 8.

All other conducted tests will not pose a threat to the participants* health, but come with possible side-effects or complications. The physical examination, all questionnaires, collecting and providing of faecal and urine sample, neuropsychological evaluations, MRI and DEXA scan, the gut permeability test and indirect calorimetry will not harm the participants, nor pose a threat to their health. For all these tests, a participant will have to be cooperative and motivated to actively and correctly fulfil all tests and interventions, and will have to be willing to spend a vast amount of time at our facilities (40 hours in total). These tests will not pose a health risk for participants. However, the mental burden posed by these tests may be relevant. Especially the neurocognitive tests may have an impact on mental/psychological wellbeing, in particular when confronted with less optimal test results.However, the mental burden posed by these tests is relevant. Especially the neurocognitive tests can have a significant impact on mental/psychological wellbeing in terms of exhaustion and the possibility of confronting results if these tests are performed inadequately.
The induced radiation during a DEXA scan (<20 µSv) is far less than a Dutch citizen is exposed to on a yearly basis (2.5 mSv). This will not cause any additional health effects.
The MRI is performed in a narrow space and is known to be noisy. Some participants might experience claustrophobia, which will be examined during the

screening visit, and during the scan, participants will be monitored closely.
The invasive tests (i.e. blood samples, tissue biopsies, hyperinsulinemic-euglycemic clamp) might cause more of a burden to a participant. Blood samples and intravenous cannulas will be drawn or inserted on multiple occasions, for which a sharp needle will need to penetrate skin tissue. This might hurt a participant or cause bleeding and hematoma, but is in general of minor relevance/importance/danger.
Tissue biopsies (adipose tissue and skeletal muscle) are the most invasive tests and might cause pain, hematoma, bruising or bleeding to a participant, mainly during and after the skeletal muscle biopsy. Pressure will be applied to the insertion site after the muscle biopsy to reduce the risk of hematoma and will be properly bandaged. The insertion site of both tissue biopsies will leave a small scar (~3mm for scAT and ~8mm for SMT).
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.
All CIDs will be performed at the Metabolic Research Unit Maastricht (MRUM) at Maastricht University. All tests will be performed following general safety and health guidelines and Standard Operating Procedures (SOPs). Strict guidelines in case of emergency are in place. Furthermore, a medical doctor will always be either physically present or reachable via telephone during all tests.

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

Male/female
Age 30-75 year
BMI 28-40 kg/m2 (weight in kg / length in m)

One of the following criteria: Fasting glucose 5.6 - 6.9 mmol/l OR HbA1c 42-47 mmol/mol OR HOMA-IR >1.85

Exclusion criteria

Diabetes mellitus (type 1 or 2)
Cardiovascular disease: Including no history of myocardial infarction, heart failure, arrhythmias (except hypertension (<160/100 or <140/90 mmHg without or with medicinal treatment, respectively)
Pulmonary disease: no history of chronic obstructive pulmonary disease, emphysema, bronchitis, asthma
Kidney disease/failure
Hepatic disease/failure
Gastrointestinal disease or a history of abdominal surgery (except appendectomy and cholecystectomy): No inflammatory bowel disease, irritable bowel syndrome and related diseases.
Any other diseases affecting glucose and/or lipid metabolism
Malignancy (except non-invasive skin cancer)
Auto-immune disease
Major mental disorders preventing correct participation (such as severe depression, psychosis, schizophrenia)
Ongoing (infectious) disease or any disease with a life expectancy <=5 years
Substance abuse (nicotine abuse (including e-cigarettes) defined as >20 cigarettes per day; alcohol abuse defined as >=8 drinks/week for females and >=15 drinks/week for males(38); any drugs)
A change in weight >=3kg over the last 3 months or plans to lose weight or follow a hypocaloric diet during the study period
Pre/pro/antibiotic use in the last 3 months or during the study
Use of medication that influences glucose or fat metabolism and inflammation, such as:
o Use of statins (stable use >=3 months prior to and during study is allowed)

o Use of antidepressants (stable use >=3 months prior to and during study is allowed)
o Use of anticoagulants (acetylsalicylic acid and carbasalate calcium are allowed)
o Use of medication known to interfere with study outcomes
o Use of β-blockers
o Chronic corticosteroid treatment (>7 consecutive days)
Regular use of laxatives 3 months prior to the study or during study period
Change in physical activity or diet during study period
Intensive physical activity (>3h per week)
Pregnancy
Following a vegan or vegetarian diet; presence of food allergies, intolerances or diet restrictions interfering with the study.

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):	03-10-2022
Enrollment:	44
Type:	Actual

Ethics review

Approved WMO

Date:	23-05-2022
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-12-2022
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
ClinicalTrials.gov	NCT05354245
CCMO	NL80459.068.22