Prevention of diabetes with a novel butyrate-enriched triglyceride

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Primary Objective:The main goal of the study is to investigate the effects of a chronic increase in the gut microbial metabolite butyrate and hexanoate in the systemic circulation on peripheral insulin sensitivity in individuals with overweight/...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56880

Source
ToetsingOnline

Brief title
Preventing Diabetes with Butyrate-Triglyceride

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: AAK,Stichting LSH-TKI

Intervention

Keyword: Butyrate, Glucose homeostasis, Inflammation, Obesity

Outcome measures

Primary outcome

The main endpoint is the difference in change in peripheral insulin sensitivity between intervention and control group, measured by hyperinsulinemic-euglycemic clamp.

Secondary outcome

Differences 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, carbohydrates and fat oxidation)
- Body weight, composition and body fat distribution (anthropometrics, DEXA)
- Plasma and faecal concentrations of butyrate, propionate and acetate (SCFA)
- Plasma concentrations of inflammatory markers (C-Reactive Protein (CRP), Interleukin-10 (IL-10), Tumornecrosefactor-α (TNF-α), Interferon- γ (INF-γ), circulating metabolites (glucose, triglycerides, FFAs) and hormones (insulin, GLP-1, PYY, glucagon)
- Gut permeability
- Faecal microbiota composition and functionality (Metagenome and

-transcriptome sequencing)

- Gastrointestinal side effects (GRGS)

- Expression of gene and protein expression in adipose tissue

Other study parameters (if applicable)

- Plasma HbA1c over the different timepoints; screening, CID1, visit week 12

and CID2

- Three-day food record: completed before CID1 and CID2 and the visit week 12

- Physical activity questionnaire: completed before CID1 and CID2 and visit

week 12 (SQUASH)

- Questionnaires on general wellbeing/quality of life and stress

Study description

Background summary

Obesity has become a serious global health and socioeconomic problem of the twenty-first century due to the easy availability of energy-dens meals and increasingly sedentary lifestyles. Currently, one-third of the world*s population is overweight, with 10% of the population being obese. It is even expected that by 2030, half of the world's population will be overweight or obese. Obesity is also an economic burden, with costs doubling every decade, reaching $860 to $956 by 2030. Moreover, obesity increases the risk to develop metabolic disorders such as type 2 diabetes (T2D). Individuals with overweight/obesity have an increased risk of at least sixfold to develop T2D compared to normal-weight individuals. The primary cause of T2D is obesity-driven insulin resistance (IR) in adipose tissue (AT), liver, and skeletal muscle. This results in the first phase of pancreatic insulin over secretion to overcome this resistance. As a result, the pancreas become exhausted and the β-cells undergo apoptosis. It has been estimated that more than 300 million people are predicted to have T2D as a consequence of obesity by 2025.

The Western diet (WD) has been linked to the worldwide rise in obesity,

obesity-related T2D and IR. The typical WD is rich in high-glycaemic/insulinemic carbohydrates, dairy products, and fat while being low in fibres. Food survey data show that the daily intake of fibres for people living in countries of the Western World is one-third below the recommend level. Dietary fibres are the preferred energy source of the gut microbiota. In individuals with metabolic disorders show indeed altered gut microbial profiles have been reported, resulting in decreased functioning of the microbiota. Hence, targeting the gut microbiota could be one potential therapeutical strategy to combat the obesity and obesity related T2D pandemic since accumulating research suggest that the microbiome may play a crucial role in the aetiology of obesity, IR and T2D.

Over the past years, the gut microbiota has emerged as a critical regulator of host energy and substrate metabolism. One of the essential roles of the gut microbiota is the fermentation of indigestible carbohydrates, such as dietary fibres, into short-chain fatty acids (SCFA). The most abundant SCFA in the gut are acetate, butyrate and propionate. They are important regulators of both the gut and host homeostasis. SCFA regulate many metabolic processes including insulin sensitivity, energy balance, inflammation, glucose homeostasis en lips metabolism by activating the G-protein coupled cell surface receptors (GPR) expressed in the gut, AT, skeletal muscle and liver.

A body of animal studies as well as observational studies in humans demonstrated that butyrate is one SCFA that has pronounced positive effects on body weight control, inflammation, and insulin resistance. We have previously demonstrated that increased concentrations of butyrate in the systemic circulation after one-day dietary fibre supplementation are linked to improvements in postprandial insulin sensitivity. Recently, we showed that a novel butyrate/hexanoate-enriched triglyceride oil temporarily enhanced systemic butyrate and hexanoate concentrations. While butyrate has attracted a lot of scientific interest, the SCFA hexanoate has also been proposed to poses anti-inflammatory effects. However, hexanoate remains a metabolite that has been scarcely investigated, and there have been no reported human clinical studies involved with hexanoate thus far. The increased postprandial circulating butyrate showed no effect on metabolic markers in overweight/obese males, but the intervention was short term. Therefore, the long-term effect of increased systemic butyrate on insulin sensitivity and other markers of metabolic health has never been studied before in humans.

We believe that a chronic increase of butyrate and hexanoate in the systemic circulation improves adipose tissue fat storage capacity, oxidative metabolism and inflammatory processes, resulting in decreased chronic low-grade inflammation and ectopic lipid accumulation, thereby improving insulin sensitivity in people with overweight/obesity and a high risk of developing T2D. Combining butyrate and hexanoate could be a potential strategy to treat obesity-related chronic low-grade inflammation and tissue-specific metabolic

dysfunctions because of the features of both SCFA.

Study objective

Primary Objective:
The main goal of the study is to investigate the effects of a chronic increase in the gut microbial metabolite butyrate and hexanoate in the systemic circulation on peripheral insulin sensitivity in individuals with overweight/obesity and a high risk to develop T2D.

Secondary Objective(s):
We will also look at the effect of a chronic increase of systemic butyrate on other metabolic health markers including the following;
1. Hepatic and adipose tissue sensitivity
2. Energy and substrate metabolism (energy harvest, energy intake, energy expenditure, fat and carbohydrate oxidation)
3. Circulating metabolites, hormones and inflammatory factors
4. Gut permeability
5. Composition and functionality of the microbiome
6. Body weight and composition
7. Adipose tissue gene/protein expression
8. Faecal and circulating SCFA

Finally, we will monitor dietary food intake and physical activity, assess gastro-intestinal side-effects and evaluate general well-being and stress.

Study design

The proposed study will be a double-blind, randomized placebo-controlled parallel trial, to evaluate the effect of an increased systemic butyrate concentrations on peripheral insulin sensitivity and other markers of metabolic health and gut functioning. Individuals aged 20-70 years with overweight or obesity (BMI >= 28 kg/m2< 40 kg/m2) and impaired fasting glucose (defined as fasting glucose 5.6-6.9 mmol/L), impaired glucose tolerance (two-hours plasma glucose 7.8-11.1 mmol/L) or insulin resistance (HOMA-IR >2.2) 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+.

Recruitment and screening period
Volunteers will be recruited by means of posters (for example hung up in the hospital and university), advertisements in local newspapers and in social media, as well as from existing co-hort of subjects that have previously approved by the investigator for future studies within our department. Potentially interested participants will be contacted by the researcher via

e-mail or telephone, and will subsequently receive the written information brochure via their e-mail. After this initial contact, the participants will get one week to consider if they are willing to participate. In case the volunteer wants to participate, an appointment for the screening will be made. The screening is the first visit at the University. The participant will visit the University after an overnight fast (>10h) and the screening will consist of the following components;
- Checking an individual*s health, medical history and determining eligibility and safety of participation
- Signing informed consent
- Measuring vital parameters and body measurements (body weight, length, waist-to-hip ratio, systolic blood pressure and diastolic blood pressure)
- Taking blood samples to determine eligibility based on specific inclusion criteria
o 20 mL for fasting glucose, insulin, Alanine Aminotransferase (ALAT), creatinine, Hemoglobin A1c (HbA1c)
o Oral Glucose Tolerance Test (OGTT): 5 mL blood sampling for two hours after a 75 g glucose drink for plasma glucose and insulin

Intervention period
All eligible participants will be equally randomized over the two arms (butyrate/hexanoate-enriched oil vs oil devoted of butyrate/hexanoate) with stratification for age, BMI and sex. This randomized clinical trial with the primary outcome peripheral insulin sensitivity has a placebo controlled, double blind, parallel design which allows the evaluation of the role of a developed oil containing butyrate/hexanoate-enriched triglyceride in human substrate and energy metab-olism in 48 adult volunteers with overweight/obesity and impaired glucose homeostasis.
After initial screening, participants will come to the university for the clinical investigation day (CID) 1 and CID2, along with small follow-up sessions at week 2 and 4.5 months, and a major follow-up visit at week 12 (3rd month). In total, the participants will need to come to the university for at least eight times (screening, CID1, CID2, week 2, week 12 and the 4.5-month visit).

A CID will consist of the following measurements;
- Two-step hyperinsulinemic euglycemic clamp with parallel measurements of indirect calorimetry
- Dual-energy x-ray absorptiometry (DEXA)
- Adipose tissue biopsy
- Multi-sugar permeability test
- Collecting stool samples
- Checking filed in questionnaires about dietary intake, physical activity, general health status (Rand-36), stress (perceived stress scale; PSS) and gastrointestinal symp-toms rate (GSRS) with the Bristol stool scale

Before each CID and for week 12, the food intake, physical activity and

Gastrointestinal Symptom Rating Scale (GSRS) with Bristol stool scale will be filled in. The food intake is recorded by filling out a three-day food questionnaire. Physical activity is measured via the Short questionnaire to Assess Health-enhancing physical activity (SQUASH). The GSRS is used to screen for whether the participant might experience gastrointestinal discomforts during the intervention period such as bloating and the Bristol stool scale for the type of faecal sample. Furthermore, their general health status will be assessed using the Rand-36 questionnaire, and their stress level will be evaluated through the PSS questionnaire. Also, the day before each CID and week 12 visit, the participants will collect a faecal sample for the analysis of SCFA and microbiota.

At CID1, the baseline measurements are taken. After CID1, the participants receive the intervention products and are instructed to take the dietary supplement on the following day for 24 weeks (six months).
1. Oil containing butyrate/hexanoate-enriched triglycerides (dosage approximately 2g of butyrate) twice a day
2. Placebo oil without the butyrate/hexanoate-enriched triglycerides twice a day

The intervention period will be 24 weeks (168 days) with a minimum of 159 days and a maxi-mum of 178 days intervention due to practical reasons. The oil will be incorporated in the participant*s breakfast and dinner. The type of treatment will be blinded for both the volunteers and researchers. After the 24-week intervention, CID2 is performed in week 24 in which the same measurements occur as CID1. This way, we can detect long-term effects of the butyrate/hexanoate-enriched triglyceride oil on peripheral insulin sensitivity and other important health markers. This study is designed to examine the butyrate effect independent of any diet or exercise intervention. For this reason, participants will be encouraged to maintain their regular lifestyle, to eat till they feel satiated, and not to consciously try to gain or lose weight throughout the study. Finally, after completion of the trial, all data will be gathered and analyzed. The participants will receive a financial compensation for their participation as well as reimbursements for their travel expenses.

Intervention

This study has two different groups receiving either the investigational product or placebo:
- Investigational product: butyrate/hexanoate-enriched triglyceride oil (approximately 12.5 mL per day for 24 weeks)
- Placebo: similar oil in volume and amount but without butyrate/hexanoate-enriched triglyceride (approximately 12.5 mL per day for 24 weeks)

The type of intervention will be blinded for both the volunteers and the researchers and provided in randomized order.

Study burden and risks

In general, obesity and its related diseases bring a high burden to a patient*s 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 and gut 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 participating in the study, the participants will receive information about their health and may profit from general health benefits if they are randomized in the intervention group.

By testing the pre-established, possibly beneficial dietary component, it will help us understand particular metabolic pathways, examine the relationship between food and the gut, and determine how this affects the regulation of metabolic health. 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, carbohydrate and fat metabolism and emotional wellbeing.

The butyrate-hexanoate enriched oil will not pose any risk to general health in participants, since the components are natural and present in foods such as milk, cheese and yoghurt. However, they might cause mild gastro-intestinal discomfort. In an acute setting, we showed that the butyrate-hexanoate enriched oil was well-tolerated and did not increase gastrointestinal complaints or discomforts which was determined by GSRS (METC NL75253.068.20). Furthermore, adhering to a diet for 24 consecutive weeks requires motivation, compliance, time and 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 participant*s health, but come with possible side-effects or complications. All questionnaires, collecting and providing of faecal and urine sample, DEXA scan, indirect calorimetry and gut permeability test will not harm the participant, nor pose a threat to their health. For all the 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 (~31 hours in total, see table 1). These tests will not pose a health risk for participants. However, the mental burden posed by these may be relevant. The filling in of the questionnaires and the intake record of the supplements can be viewed as time consuming. Moreover, the collection of faecal samples can be experienced as a burden as they have to handle them themselves and have to store them at home. Also, the 24-week intake of the oil might be seen as a burden for the subjects. Individual results will only be shared with

the participant at their own request.
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 invasive tests (i.e., blood samples, tissue biopsies, hyperinsulinemic-euglycemic clamp) can pose a burden to participants. This is particularly true for the hyperinsulinemic-euglycemic clamp, as it involves drawing blood samples and inserting intravenous cannulas on multiple occasions, for which a sharp needle will need to penetrate skin tissue. This procedure may hurt a participant or cause bleeding and hematoma, although the risk can be minimized with good clinical practice. Furthermore, the clamp is a long test day (approximately 9 hours) during which 205 mL of blood per CID will be sampled. The remaining will be 25 mL for screening and 10 mL during the week 12 visit resulting in a total of 445 mL blood withdrawn over the course of the entire study. Additionally, the clamp brings a small risk of hypo- or hyperglycemia. However, from our own extensive expertise, these conditions do not occur very often and can be reserved immediately. A medical doctor is always available during the clamp. To summarize, while the measurements of the study, particularly the clamp procedure, imposes a burden for the participants, the method is well-performed in our department mitigating the associated risks. Finally, the tissue biopsy is also an invasive test and might cause pain, hematoma, bruising or bleeding to a participant. Pressure will be applied to the insertion site after the adipose tissue biopsy to reduce risk of hematoma. The insertion site will leave a small scar (~ 3 mm).

Standard operating procedures (SOPs) for each measurement are available on the UM Human Biology Department*s server.

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 20-70 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 postprandial glucose (2h) 7.8-11.1 mmol/l OR HOMA-IR>2.2

Exclusion criteria

Cardiovascular, pulmonary, metabolic (including diabetes mellitus), gastro-intestinal, liver, kidney or auto-immune disease
Malignancy or disease with life expectancy <5 years
Substance abuse (drugs, alcohol)
Weight change >3kg in past 3 months
Pre/pro/antibiotic use past 3 months or during trial
Use of medication interfering with study outcomes
Streneous physical activity (>3h per week)
Diet-restrictions (hypocaloric, vegan, vegetarian)
Pregnancy
Use of laxatives
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:	Recruiting
Start date (anticipated):	18-09-2024
Enrollment:	48
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	15-07-2024
Application type:	First submission
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	NL86266.068.24