The effects of galactooligosaccharide (GOS) on peripheral insulin sensitivity and body weight control in obese adults with impaired glucose homeostasis

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Based on our hypothesis that orally administered GOS will be fermented into a SCFA pattern high in acetate and that this will lead to beneficial effects on human substrate and energy metabolism, we aim to address the following primary objective: To...

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

Summary

ID

NL-OMON40698

Source
ToetsingOnline

Brief title
GOS and human substrate and energy metabolism

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: Top Institute Food and Nutrition (TIFN)

Intervention

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

Outcome measures

Primary outcome

Primary endpoint: whole-body insulin sensitivity as assessed by a one-step

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)

- volatile organic compounds (VOCs) in exhaled air

Study description

Background summary

Gut microbiota is being increasingly recognized as an important factor in fat distribution, insulin sensitivity, and glucose and lipid metabolism.
Accordingly, the intestinal microbiota could play an important role in the development and treatment of obesity and type 2 diabetes mellitus.
One of the important activities of the intestinal microbiota is to break down dietary components such as dietary fiber, which are not or not completely hydrolyzed by host enzymes in the small intestine. In this study we will

supplement our human volunteers with the soluble dietary fiber galactooligosaccharide (GOS) produced from lactose. Soluble fibers are fermented in the colon to yield short chain fatty acids (SCFAs), primarily acetate, butyrate and propionate. Data derived from the TIM-2 model (TNO, Delft, the Netherlands) showed that fermentation of GOS resulted in a shift in the colonic SCFA ratio (normally ca. 60 % acetate, 20 % butyrate, 20 % propionate) towards an increase in acetate (ca. 75 %) (confidential data TNO Delft).

There is little known about the metabolic effects of a long-term human intervention with GOS. A study by Vulevic et al (2013) found that a 12-week supplementation of a GOS mixture in 45 overweight subjects altered fecal microbiota, plasma inflammatory markers, insulin, cholesterol and triglyceride concentrations, thereby improving the metabolic status of these patients. Next to this, the same group assessed this mixture in healthy elderly volunteers and showed positive effects on both the microflora composition and the immune response. However, mechanisms explaining these improved metabolic status are not elucidated in these studies, we hypothesize that the supplemented GOS will be fermented into a SCFAs, mainly acetate, which may have beneficial metabolic effects.

In one of our previous studies (METC 11-3-079) we have shown that acute colonic acetate infusions have beneficial effects on human substrate and energy metabolism. We found that colonic acetate administration increased fat oxidation, increased circulating concentrations of the incretin and satiety stimulating hormone PYY and reduced the pro-inflammatory marker TNF-* within 2 hours after administration in overweight males. In addition, in another study (METC 13-3-022), we rectally administered three different SCFA combinations in overweight men. In this study, we confirmed these effects of SCFAs on fat oxidation and metabolic plasma markers. Therefore, we hypothesize that a long-term manipulation of the colonic SCFA ratio towards an increase in acetate, reached by the oral intake of GOS, will have beneficial effects on human metabolism.
This hypothesis is supported by a study showing that acetate supplementation in mice protects against diet-related obesity and this was related to production of anorexic hormones and enhanced energy expenditure. In addition, in vitro studies showed that acetate affects adipose tissue lipolysis, decreases the production of pro-inflammatory markers and stimulates adipogenesis.

However, at the present time, our understanding of the effects of SCFA and GOS specifically on human metabolism (in gut or systemically) is still limited.
Yet, in light of the health claims of certain dietary fibers, a detailed picture of the physiology of human SCFA metabolism and its interaction with the microbiome is of pivotal importance. Therefore, we will investigate the effects of a 12-week supplementation of GOS on peripheral insulin sensitivity and body weight control in obese adults with impaired glucose homeostasis.
This study is an important part of a Gastrointestinal Health TIFN project

(GH003 WP 1.2), which will provide important insight in how increased availability of soluble dietary fiber-derived SCFA might serve as a strategy in the prevention and treatment of obesity and type 2 diabetes mellitus.

Study objective

Based on our hypothesis that orally administered GOS will be fermented into a SCFA pattern high in acetate and that this will lead to beneficial effects on human substrate and energy metabolism, we aim to address the following primary objective:
To investigate the effects of a 12-week supplementation of GOS on peripheral insulin sensitivity and body weight control in obese adults with impaired glucose homeostasis.

Study design

Placebo controlled, double-blind, randomized parallel design.

Intervention

The subjects will be divided in 2 intervention groups:
1. 1. GOS: Domo® Vivinal® galacto-oligosaccharide rich whey product 5g 3x per day (269.6kjoule/day)
2. Placebo: Maltodextrin 5.65g 3xper day (269.6kjoule/day), isocaloric

Intervention period will be 12 weeks (minimal 84 days, maximal 89 days intervention period). The products will be consumed with a low-fat milk drink during the breakfast, lunch and dinner.
The type of treatment will be blinded for both the volunteers and the researchers.

Study burden and risks

All subjects 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. Subjects 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 fibers will influence human substrate and energy metabolism.
Burdens that volunteers can experience, such as the time spent with the study (subjects will have to invest approximately 16 hours in the study, divided among 3 test days and a screening visit (see for an overview table 1

and figure 1)) 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 subjects.
During the test days, 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 visit 2, 15 ml blood will be taken. During visit 1 and 3 the total amount of blood sampled is 170ml per test day, totalling 315ml (screening 20ml) during the whole test period. During visit 1 and 3, 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 (OGTT (screening), and indirect calorimetry (visit 1 and visit 3)), 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.
GOS has been used before in metabolic studies in overweight to obese subjects and in elderly persons. In both groups, no side-effects were reported. Together with SCFA, H2 and CO2 are produced after fermentation of GOS, therefore it is possible that bloating and flatulence can occur in high dosages. Most of the studies with GOS to date have used a recommended dosage of 8 to 20 g day.

Contacts

Public
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

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) insulin impaired men and post-menopausal women with impaired glucose tolerance (IGT: 2h plasma glucose during 75g OGTT 7.8-11.1 mmol/l) and/or impaired fasting glucose (plasma glucose * 5.6 mmol/l) aged 45-70 years will be included in the study.
In addition, subjects have to be weight-stable for at least 3 months prior to participation (no change in bodyweight, i.e. < 3kg).

Exclusion criteria

Subjects will be excluded from participation when one or more of the following aspects are present:
- 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. *-blockers, lipid lowering-drugs (e.g. PPAR * or PPAR* (fibrates) agonists), glucose-lowering agents (including all sulfonylureas, biguanides, *-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;- use of antibiotics 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:	Recruitment stopped
Start date (anticipated):	24-11-2014
Enrollment:	46
Type:	Actual

Ethics review

Approved WMO Date:	08-09-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-12-2014
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	NL49422.068.14