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Effect of high- and low-fructose diets on intestinal fat production

Submission date
06/05/2020

Recruitment status
No longer recruiting

Registration date
06/05/2020

Overall study status
Completed

Last Edited
16/07/2020

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
This study aims to establish the effects of consuming fructose on the fat-producing capabilities of the cells in the intestine, known as 'enterocytes'. Fructose is one of the main natural sugars in the diet (50% of table sugar), and is also found in fruit. Research has shown that a high-fructose diet can lead to higher circulating fat (triglyceride) levels in the blood. Although most studies have focussed on the role of the liver in this process, the intestine is also thought to contribute to this effect, although this has been less well-studied. The current research will test whether fructose increases the production and absorption of fat particles in the intestine, and therefore blood triglyceride, which is known to increase the risk of cardiovascular disease (e.g. heart attack and stroke).

Who can participate?
Healthy, male adults aged 18 – 50 years, BMI 25 – 32 kg/m².

What does the study involve?
The study will involve five visits - a screening visit, where a blood sample will be taken, as well as four visits to the Centre for Diabetes and Endocrinology Research (Cedar) at the Royal Surrey County Hospital (RSCH). Two visits will be for a 'baseline' blood sample only and the other two visits to attend 'study days' (12 hrs). For the study days, participants will be given two special types of molecule ('D5-glycerol' and '2H2O water'), which are naturally-occurring at low levels in the body, and will allow us to calculate the body's fat production.

What are the possible benefits and risks of participating?
Results could help improve our knowledge of the effects of dietary fructose, especially in the intestine, in relation to the risk of cardiovascular disease (e.g. heart attack and stroke) and lead to further research that may inform government dietary recommendations for the UK public.
The risks of having a plastic tube in a vein are those associated with any blood sample. These are minor discomfort, possible bruising and, in principle, a local infection. In rare cases, participants may experience a slight and transient dizziness due to consuming the 2H2O water.

Where is the study run from?
Royal Surrey Country Hospital (UK)

When is the study starting and how long is it expected to run for?
March 2016 to June 2020

Who is funding the study?
Biotechnology and Biological Sciences Research Council (UK)

Who is the main contact?
Prof. Margot Umpleby, m.umpleby@surrey.ac.uk

Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
167084

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 19064, IRAS 167084

Study information

Scientific Title

The effect of fructose on intestinal triglyceride production and de novo fatty acid synthesis in humans.

Study objectives
1. Fructose meals significantly increase plasma triacylglycerol (TAG) concentration, in comparison to control meals, due to raised TAG-rich lipoprotein-TAG, chylomicron (CM) TAG and /or very low-density lipoprotein (VLDL) TAG concentration
2. Fructose meals significantly increase the CM-TAG production rate, or reduce CM-TAG fractional clearance rate, in comparison to control meals
3. Fructose meals stimulate significantly higher intestinal de novo lipogensis (DNL), in comparison to control meals

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/06/2015, NRES Committee South East Coast - Surrey (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8265; londonsoutheast.rec@hra.nhs.uk), ref: 15/LO/0891

Study design
Single-centre randomized acute single-blinded cross-over intervention study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
De novo lipogenesis (DNL) and post-prandial TAG levels, which are an established independent risk factor for cardiovascular disease.

Interventions
This is an acute dietary intervention study with a randomised crossover design, involving two post-prandial metabolic study days.
Participants are randomised following recruitment using an online randomisation programme.

On each study day, participants consume high-fat drinks every hour for 11 h, which are either high (30%) or low (0%) in fructose, in order to elicit a steady post-prandial TAG response. Drinks

contain deuterated water (2H20) to measure the rate of de novo lipogenesis. An intravenous bolus of 2H5-glycerol (75 µmol/kg) will be administered after 4 h to measure CM-TAG and VLDL-TAG kinetics (production and clearance rates). Following the first metabolic study day, participants underwent a 4-week washout period before completing the second study day.

The study will involve five visits - a screening visit, where a blood sample will be taken, as well as four visits to the Centre for Diabetes and Endocrinology Research (Cedar) at the Royal Surrey County Hospital (RSCH). Two visits will be for a 'baseline' blood sample only and the other two visits to attend 'study days' (12 hrs). For the study days, participants will be given two special types of molecule ('D5-glycerol' and '2H2O water'), which are naturally-occurring at low levels in the body, and will allow us to calculate the their body's fat production.

VISIT 1: Screening visit (approximately 1 hour)
If interested in taking part in this study, participants would come to the Cedar Centre at the Royal Surrey County Hospital in the morning, without having had breakfast (fasted). Someone from the research team will ask participants some questions about their health. A researcher or research doctor will measure their height, weight, take their blood pressure and take a small blood sample (3 teaspoons) to measure their blood glucose and triglycerides (fat) and check participants do not meet any of the exclusion criteria. After this participants will be provided with a snack and a drink. This is a screening visit to make sure participants have no disorder that would prevent participants from taking part in the study.

DAY 1: Start Diet 1
If participants are selected to take part in the study participants will be provided with all of the food and drinks for either the low- or high-fructose diet, which will be matched to their estimated daily energy requirements. The drinks will contain either fructose (high-fructose diet) or a calorie-free sweetener (low-fructose diet). Participants should consume only these foods and drinks during days 1-4 of the study, although water and certain non-caffeinated sugar-free beverages, such as decaffeinated coffee, are also permitted.

DAY 4: VISIT 2 - Baseline blood sample (30 minutes)
Participants will be asked to attend the Cedar centre on the afternoon of the final day of diet 1 (day 4) to give a blood sample. Participants will not need to have fasted. This will allow us to measure the background level of naturally-occurring 2H2O water in their blood. Following this visit, participants will consume a standardised meal at 7 pm that evening and drink two small bottles of special 2H2O-enriched water. One should be drunk with the meal and the other at 10 pm. Participants will also be given additional water containing a lower level of 2H2O water, to drink exclusively until the end of visit 3 the next day (day 5). This process will allow us to tag, and therefore calculate, their body's production of new fat.

DAY 5: VISIT 3 - Study Day 1 (12 hours)
The purpose of this visit is to measure the effect of fructose on fat production and absorption in the body, especially in the intestine, including the production of 'new fat' from other nutrients. Participants should attend the Cedar centre in the morning at approx. 7.30 am, having fasted overnight and having only drunk the 2H2O water provided. A researcher will measure their height, weight, blood pressure, fat-free mass, waist-to-hip ratio, and take a fasted blood sample. Participants will be given small meals to consume every hour during the study. The total energy content of these meals will be similar to their usual energy intake.

A plastic tube will be inserted into a vein in one of their arms at the start of the study for blood sampling. A second tube will be inserted into a vein of the opposite arm four hours after the start of the study, to allow for administration of the D5-glycerol. This is a component of fat that

is naturally-occurring at low levels in the body and will allow us to calculate their production of fat in the liver and intestine. The amount used here has been shown to be safe in previous studies. Blood samples will then be taken at approximately hourly intervals until the end of the day (7 hours later).

Participants will only be given 2H2O water to drink, in addition to the hourly meals, and may not consume any solid food until the end of the study day. Participants will be able to read, use a laptop, tablet, mobile phone etc. although participants will be asked to remain in a sitting position. Participants may use the toilet whenever participants wish. At the end of the study day, the blood sampling tube will be removed and participants will be given a meal and a drink (e.g. sandwich, crisps and drink) and will be free to go home.

DAYS 6-33 - 'Washout' Period
During this period participants will return to their usual diet with no restrictions. This washout period acts as a rest for their body between the two diets.

DAY 34: Start Diet 2
As for days 1-4, participants should consume only the food and drinks provided during this period (Days 34-37), with the exception of water and certain non-caffeinated sugar-free beverages.

DAY 37: VISIT 4 - Baseline blood sample (30 minutes)
Participants will be asked to attend the Cedar centre for a second baseline blood sample, which will be identical to visit 2. Again, participants will be given 2H2O water to drink in the evening and throughout the following day (study day 2).

DAY 38: VISIT 5 - Study Day 2 (12 hours)
Participants will be asked to attend a second study day at the Cedar centre, having fasted overnight, which will be identical visit 3. Following this visit participants will have completed the study.

Intervention Type
Supplement

Primary outcome measure
CM-TAG production rate and clearance rate, measured at using intravenous stable isotope labelled glycerol (2H5-glycerol) administered during the post-prandial steady-state during each study visit

Secondary outcome measures
Measured during by hourly blood sampling at each post-prandial study visit:
1. VLDL-TAG production rate and clearance rate (measure using stable isotope 2H5-glycerol infusion)
2. Rate of intestinal (CM) and hepatic (VLDL) de novo lipogenesis (measured using oral 2H2O)
3. Post-prandial TAG concentration (measured via enzymatic assay)

Overall study start date
15/06/2015

Completion date
15/06/2020

Eligibility

Key inclusion criteria
1. Gender: Male
2. Ethnicity: Caucasian
3. Age: 18 – 50 years
4. BMI: 25 – 32 kg/m²
5. < 3 sessions of aerobic exercise per week
6. Weight stable for the previous 3 months (± 2.5 kg)
7. Normal blood haemoglobin content (13.5-17.5 g/dL)
8. Blood pressure below 160/100 mmHg (systolic/diastolic)

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
10

Total final enrolment
6

Key exclusion criteria
1. Fasting plasma glucose > 7 mmol/L
2. Fasting plasma TAG > 4 mmol/L
3. Smoker
4. Type 1 or type 2 diabetes
5. Prescribed lipid-lowering medications
6. Endocrinological, cardiovascular, gastrointestinal and liver diseases or renal impairment
7. History of eating disorders, nausea or vomiting
8. Alcohol intake > 32 g/day or history of drug abuse
9. Relevant food allergies or intolerances e.g. fructose

Date of first enrolment
08/03/2016

Date of final enrolment
19/01/2018

Locations

Countries of recruitment

England

United Kingdom

Study participating centre
Royal Surrey Country Hospital
Cedar Centre
Egerton Rd
Guildford
United Kingdom
GU2 7XX

Sponsor information

Organisation
University of Surrey

Sponsor details
Research Integrity & Governance Office (RIGO)
Senate House
Guildford, Surrey GU2 7XH
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Sponsor type
University/education

Website
http://www.surrey.ac.uk/

ROR
https://ror.org/00ks66431

Funder(s)

Funder type
Government

Funder Name

Biotechnology and Biological Sciences Research Council

Alternative Name(s)
UKRI - Biotechnology And Biological Sciences Research Council, BBSRC UK, BBSRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results from the trial will be published in a peer-reviewed journal within approximately two years of completion. This project was undertaken in partial fulfilment of requirements for a PhD and are available as part of an e-thesis that can be accessed via the University of Surrey online repository (http://epubs.surrey.ac.uk/view/type/thesis/2019.html)

Intention to publish date
15/06/2020

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		13/03/2015	15/05/2020	No	No
Results article	results	15/06/2020	16/07/2020	Yes	No
HRA research summary			26/07/2023	No	No