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Effect of propionate on mesenteric adipose tissue and insulin sensitivity

Submission date
17/07/2023

Recruitment status
No longer recruiting

Registration date
27/07/2023

Overall study status
Completed

Last Edited
20/01/2026

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Metabolic diseases, including obesity, hypertension, and cardiovascular disease, significantly increase the risk of type 2 diabetes. About 25% of adults worldwide suffer from metabolic diseases, leading to 2.8 million deaths each year. The composition of fat in the body is closely linked to metabolic diseases. Recent research has highlighted the role of abdominal adipose tissue, specifically mesenteric adipose tissue (MAT), in causing insulin resistance and type 2 diabetes. MAT surrounds the portal vein, which carries blood from the gastrointestinal tract to the liver, and has the potential to impact insulin responses in both local and systemic ways. However, the exact mechanism by which MAT influences insulin resistance is not well understood. Propionate, a short-chain fatty acid produced during carbohydrate fermentation in the colon, is thought to play a role in reducing the release of free fatty acids (FFA) from adipocytes (fat cells) through receptors FFA2 and FFA3. This, in turn, may decrease hepatic glucose generation and increase insulin utilization. While several studies have demonstrated the effects of propionate on obesity and type 2 diabetes, few have explored its mechanism of action and the specific involvement of MAT during metabolic processes. The goal of this project is to investigate the role of propionate in maintaining a healthy MAT phenotype and to gain a deeper understanding of how mesenteric adipocyte biology influences insulin sensitivity in humans. These findings will be crucial for developing strategies to prevent metabolic syndrome and its associated complications.

Who can participate?
Adult participants aged between 18 and 75 years old chosen because they are scheduled to have an operation that will make it possible to take samples of fat from their waist area

What does the study involve?
The study will investigate the effect of propionate on fat tissue and the cell isolated from the fat tissue. We will culture the tissue and isolate the cells in vitro to detect the metabolite release and histological changes with the propionate treatments.

The study will randomly allocate participants into either of the following two groups to receive:
1. 10 g/day cellulose (poorly fermentable carbohydrate) as a control
2. 10 g/day inulin propionate ester (IPE)

This is the lowest dose that the study team has repeatedly shown has a wide metabolic impact with little adverse event profile. The IPE and control will be given to the participants as 10 g of white powder in a sachet which participants can easily mix into their habitual diet. Participants will receive telephone visits every four weeks to assess progress and compliance. They will receive face-to-face review visits every 4 weeks. At the end of the 12th week, they will undergo their planned surgery and at the time of the operation, tissue samples will be taken for analysis.

What are the possible benefits and risks of participating?
Taking part in the study will provide no direct personal benefit for participants and surgery participants over what they currently have. The information that we gain from this study will help us to better understand metabolic disease. If any of the screening questionnaires or blood tests reveal any medical problems (e.g. diabetes, kidney or liver problems), the participant's GP will be informed so that they can coordinate participants' care, arrange any further tests, and refer participants to Hospital Doctors if necessary.
The procedure of taking fat samples will cause an extended operation time of up to 5-10 minutes. There is a small risk of complications. These complications include infection, bleeding, blood clots, and injury to nearby structures, such as the liver and small gut.

Where is the study run from?
Hammersmith Hospital Campus, Imperial College London (UK)

When is the study starting and how long is it expected to run for?
November 2019 to November 2024

Who is funding the study?
BBSRC Strategic Programme in Food Innovation and Health (UK)

Who is the main contact:
Prof Gary Frost, g.frost@imperial.ac.uk (UK)

Contact information

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Additional identifiers

Integrated Research Application System (IRAS)
288071

Central Portfolio Management System (CPMS)
47793

Protocol serial number
20HH6218

Study information

Scientific Title

Impact of the short chain fatty acid propionate on mesenteric adipose tissue, liver metabolism and insulin sensitivity: The PROMIS study

Acronym
PROMIS

Study objectives
The mesenteric adipose tissue will be exposed to high propionate flux following the colonic delivery of propionate to the colon. This will result in multifactorial impacts on mesenteric adipose tissue:
1. Stimulate a change in adipocyte phenotype with an increase in beige and brown adipocyte and a decrease in adipocyte size.
2. Hepatic insulin sensitivity will increase and hepatic glucose output will be suppressed leading to improved metabolic sensitivity.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 25/01/2021, London - Riverside Research Ethics Committee (Ground Floor Temple Quay House 2 The Square, Bristol, BS1 6PN, United Kingdom; +44 (0)2071048193; riverside.rec@hra.nhs.uk), ref: 20/LO/1297

Study design
Double-blind randomized controlled trial

Primary study design
Interventional

Study type(s)
Prevention, Quality of life

Health condition(s) or problem(s) studied
Metabolic disease

Interventions
Metabolic disease is defined as a range of diseases that increase the risk of type 2 diabetes, such as obesity, hypertension and cardiovascular disease. Worldwide, approximately 25% of the adult population has metabolic diseases and there are 2.8 million deaths annually due to these diseases. There is a strong correlation between fat composition and metabolic diseases. Recent research has demonstrated that abdominal adipose tissue has a causal role in the development of insulin resistance leading to type 2 diabetes.

In Vivo Study: 12-week Randomised Controlled Study
Participants will be randomized into two groups. In the control arm, participants will be given 10 g/day cellulose (a control fibre supplement that is poorly fermentable) for 12 weeks. In the intervention arm (IA), participants will be given 10 g/day of inulin propionate ester (IPE) (at the dose found in the dose-finding study) for 12 weeks.

During 12 weeks, participants will be asked to undergo several assessments including:
1. Two Assessment visits at the beginning of Week 1 and the end of Week 12
• Weight, Height, Body Fat Composition
• Mixed meal tolerance test (MMTT)
• Blood, BH2, Urine and stool samples
2. Two Review visits in Weeks 4 and 8
• Fasting blood
• Receive the intervention compounds
3. Three telephone call visits in Weeks 3,7 and 11
• To guarantee compliance

In Vitro Study: Adipose Tissue Study
Participants will undergo their planned surgery. At surgery volunteers will undergo three biopsies, these will include subcutaneous, omental and mesenteric close to the colon, mesenteric at the tip furthest away from the colon. Adipose tissue samples will be taken for analysis in vitro. Participants will not be treated with any intervention.

The in vivo study will investigate whether long-term raised colonic propionate could cause beneficial changes in adipocyte and insulin sensitivity in humans. Changes in insulin sensitivity were assessed using the Homeostatic model assessment (HOMA-IR) by the following formula: HOMA-IR = (fasting glucose x fasting insulin) / 22.5 (Fasting insulin is in mU/L and fasting glucose in mmol/L).

The in vitro study will investigate whether the high concentration of propionate could have a positive effect on the adipose.

Intervention Type
Supplement

Primary outcome(s)
1. Adipose tissue morphology measured using adipose tissue samples fixed for microscopic examination imaging and Haematoxylin and Eosin staining to determine adipocyte cell size, number and histological characteristics at the end of Week 12 after the tissue is collected
2. Insulin sensitivity and liver glucose metabolism measured using the Homeostatic model assessment (HOMA-IR). The blood insulin and glucose levels measured using the corresponding testing reagent kits at 0, 15, 30, 60, 90, 120, 180, 240, and 300 min during each assessment visit.

In vitro Study:
1. Adipose tissue gene expression measured using Quantitative polymerase chain reaction (qPCR) after tissue is cultured for 24 h
2. After the preadipocyte is isolated from the tissue, the differentiation function will be measured via lipid accumulation on D14 (The last day of the differentiation period).

Key secondary outcome(s))
In vivo study:
Circulating levels of glucose, insulin, free fatty acids, gut hormones and SCFA levels measured using the corresponding testing reagent kits. Venous blood samples will be collected at the fasting state during each review visit.

In Vitro Study:
Metabolite levels in adipose tissue and preadipocytes after treatment such as triglyceride and

free fatty acid levels measured using the corresponding testing reagent kits after 24 h and on Day 14, respectively.

Completion date
11/05/2025

Eligibility

Key inclusion criteria
In vivo study:
1. The participants on the waiting list for cholecystectomy
2. Male or female
3. Age between 18-75 years (inclusive)
4. Body mass index (BMI) of 18-35 kg/m2
5. Willingness and ability to give written informed consent and willingness and ability to understand, participate and comply with the study requirements

In vitro study:
1. The participants on the surgery waiting list of the team with Dr Madhava Pai
2. Male or female
3. Age between 18-75 years (inclusive)
4. Body mass index (BMI) of 18-35 kg/m2
5. Willingness and ability to give written informed consent and willingness and ability to understand, participate and comply with the study requirements

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
33

Key exclusion criteria
In vivo study:
1. Abnormal ECG
2. Screening blood results outside of normal reference values

3. Weight change of ≥3 kg in the preceding 2 months
4. Current smokers
5. History of substance abuse and/or excess alcohol intake
6. Pregnancy
7. Formal medical diagnosis of Type 2 Diabetes, Cardiovascular disease, Cancer, Gastrointestinal disease (e.g. inflammatory bowel disease or irritable bowel), Kidney disease, Liver disease and Pancreatitis
8. Participation in a research study in the 12-week period prior to entering this study
9. Any blood donation within the 12-week period prior to entering this study
10. Use of antibiotics in the past 3 months
11. New medication in the past 3 months
12. Any other reason in the opinion of the investigator

In vitro study
1. Screening blood results outside of normal reference values
2. Weight change of ≥ 3kg in the preceding 2 months
3. History of substance abuse and/or excess alcohol intake
4. Pregnancy
5. Any other reason in the opinion of the investigator

Date of first enrolment
20/02/2021

Date of final enrolment
11/11/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College Healthcare NHS Trust
The Bays
St Marys Hospital
South Wharf Road
London
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Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Research council

Funder Name
Biotechnology and Biological Sciences Research Council

Alternative Name(s)
UKRI - Biotechnology And Biological Sciences Research Council, Agricultural and Food Research Council, Biotechnology & Biological Sciences Research Council, BBSRC, BBSRC UK, AFRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		18/12/2025	20/01/2026	Yes	No