

# Effect of propionate on mesenteric adipose tissue and insulin sensitivity

<b>Submission date</b> 17/07/2023	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered
		<input type="checkbox"/> Protocol
<b>Registration date</b> 27/07/2023	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
<b>Last Edited</b> 08/08/2023	<b>Condition category</b> Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Individual participant data
		<input type="checkbox"/> Record updated in last year

## 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

### Type(s)

Principal Investigator

### Contact name

Prof Gary Frost

### Contact details

Imperial College London  
Hammersmith Hospital Campus  
6th Floor  
Commonwealth Building  
Du Cane Road  
London  
United Kingdom  
W12 0NN  
+44 (0)1273 833 480  
g.frost@imperial.ac.uk

### Type(s)

Public

**Contact name**

Miss Baichen Lu

**Contact details**

Imperial College London  
Hammersmith Hospital Campus  
6th Floor  
Commonwealth Building  
Du Cane Road  
London  
United Kingdom  
W12 0NN  
+44 (0)7925703916  
b.lu18@imperial.ac.uk

**Type(s)**

Scientific

**Contact name**

Miss Baichen Lu

**Contact details**

Imperial College London  
Hammersmith Hospital Campus  
6th Floor  
Commonwealth Building  
Du Cane Road  
London  
United Kingdom  
W12 0NN  
+44 (0)7925703916  
b.lu18@imperial.ac.uk

## **Additional identifiers**

**EudraCT/CTIS number**

Nil known

**IRAS number**

288071

**ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

20HH6218, IRAS 288071, CPMS 47793

## **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

**Secondary study design**

Randomised parallel trial

**Study setting(s)**

Home, Hospital, Telephone, University/medical school/dental school

**Study type(s)**

Prevention, Quality of life

**Participant information sheet**

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

**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:  $\text{HOMA-IR} = (\text{fasting glucose} \times \text{fasting insulin}) / 22.5$  (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 measure**

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).

## **Secondary outcome measures**

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.

## **Overall study start date**

11/11/2019

## **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/m<sup>2</sup>
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/m<sup>2</sup>
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

## **Age group**

Mixed

## **Lower age limit**

18 Years

## **Upper age limit**

75 Years

## **Sex**

Both

**Target number of participants**

56

**Key exclusion criteria**

In vivo study:

1. Abnormal ECG
2. Screening blood results outside of normal reference values
3. Weight change of  $\geq 3$  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  $\geq 3$  kg 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**

England

United Kingdom

**Study participating centre**

**Imperial College Healthcare NHS Trust**

The Bays

St Marys Hospital

South Wharf Road

London  
United Kingdom  
W2 1NY

## Sponsor information

### Organisation

Imperial College London

### Sponsor details

C/o: Ms Cheuk Fung Wong  
Joint Research Compliance Office  
Imperial College London and Imperial College Healthcare NHS Trust  
Room 221, Level 2,  
Medical School Building  
Norfolk Place  
London  
England  
United Kingdom  
W2 1PG  
+44 (0)2075949832  
cheuk-fung.wong@imperial.ac.uk

### Sponsor type

University/education

### Website

<http://www.imperial.ac.uk/>

### 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, BBSRC UK, BBSRC

### Funding Body Type



Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

## **Results and Publications**

**Publication and dissemination plan**

Planned publication in a high-impact peer-reviewed journal

**Intention to publish date**

20/02/2025

**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