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Investigating the impact of glucagon timing and protein replacement on metabolism

Submission date	Recruitment status	[X] Prospectively registered
06/12/2023	Recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
01/02/2024	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
28/05/2025	Nutritional, Metabolic, Endocrine	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Obesity and fatty liver disease are very common problems in the UK affecting one in three people. These conditions are risk factors for type 2 diabetes. To treat diabetes, obesity and fatty liver disease, drug companies are developing drugs based on two hormones, glucagon-like peptide-1 and glucagon. Combined, these two hormones reduce weight, eliminate liver fat, and improve blood glucose control. Glucagon helps weight loss by increasing the amount of calories burnt, and also reduces fat (lipids) in the liver and the bloodstream.
However, treatment with the hormone glucagon may cause a reduction in circulating amino acids (the building blocks of protein and muscle). There is a possibility that a long-term reduction in circulating amino acids reduces muscle mass, which is extremely important for overall health. The aim of this study is to find out how to avoid low circulating amino acids by changing the timing of giving glucagon.

Who can participate?
Males or females aged 18-65 years with a body mass index (BMI) between 25 and 45 kg/m² and with normal glucose control.

What does the study involve?
Following an initial screening visit, participants will attend the Clinical Research Facility four times, and on each occasion will stay from Monday morning to Thursday afternoon (4 days, 3 nights). On each of the four visits to the Research Facility, participants will receive an infusion of either glucagon or placebo; This will occur through a cannula inserted into a vein in the arm . On one inpatient visit, the diet will also be supplemented with extra protein. The researchers will assess the effect of glucagon timing and dietary protein replacement on blood levels of amino acids and fat molecules. They will also monitor glucose control, appetite and energy expenditure.

What are the possible benefits and risks of participating?
Participants may not benefit directly from participating in the study. However, the information collected from this study will help us understand the best way of giving glucagon as a treatment for obesity and fatty liver disease. This may have a big impact in the future on the development

of drugs using glucagon. Expected side effects of a glucagon infusion include temporary nausea and vomiting, and possibly minor discomfort/bruising from insertion of the cannula into the arm for blood sampling and infusion.

Where is the study run from?
The study will be run from the NIHR/Wellcome Trust Imperial Clinical Research Facility (CRF) at the Hammersmith Hospital (UK). The study team is located at the Division of Metabolism, Digestion and Reproduction, Imperial College London at Hammersmith Hospital (UK).

When is the study starting and how long is it expected to run for?
September 2023 to July 2027

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Prof. Tricia Tan, t.tan@imperial.ac.uk.

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
336170

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 336170

Study information

Scientific Title
The impact of glucagon timing and protein replacement on metabolism

Acronym
GTPRO

Study objectives
1. Continuous 24-h exposure to glucagon leads to amino acid breakdown
2. Excess amino acid breakdown may be avoided by timing glucagon in shorter ‘bursts’ during the day, mimicking the physiological variation of this hormone
3. Dietary protein supplementation also mitigates the reduction in circulating amino acids during a glucagon infusion

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 01/03/2024, London - Fulham Research Ethics Committee (2 Redman Place, London, E20 1JQ, United Kingdom; -; fulham.rec@hra.nhs.uk), ref: 24/LO/0044

Study design
Single-blind randomized cross over study

Primary study design
Interventional

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Overweight/obesity

Interventions
Following an initial screening visit, participants will attend the NIHR Imperial Clinical Research Facility for a 4-day inpatient stay, where they will undergo a 72-hr intravenous infusion. Participants will be allocated to the following groups in a cross-over design and receive intravenous infusions for 72 hours with a washout period:
Group 1. Continuous infusion of glucagon
Group 2. Continuous infusion of placebo
Group 3. Daytime infusion of glucagon (0800h to 2000h) and night-time infusion of saline (2000h to 0800h)
Group 4. Continuous infusion of glucagon with dietary protein supplementation
Participants allocated to receive glucagon (continuous or daytime) will receive increasing doses on study days 2 and 3, prior to discontinuation of the infusion on the morning of study day 4. Doses of glucagon administered as an intravenous infusion will be as follows: Day 1 glucagon

dose: 6 ng/kg/min, Day 2 glucagon dose: 12.5 ng/kg/min, Day 3 glucagon dose: 25 ng/kg/min, Day 4: Infusion discontinued. Participants will be randomised to groups and a follow up visit will be arranged after completion of the four inpatient visits.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Glucagon

Primary outcome(s)
1. Circulating amino acids and lipids will be measured using mass spectrometry prior to infusion commencement, during the daytime and nighttime.
2. Energy expenditure will be measured using indirect calorimetry at baseline and at steady state during the infusion

Key secondary outcome(s))
1. Appetite will be measured using visual analogue scales before and after each meal.
2. Glucose will be monitored using continuous glucose monitoring, over the 72 hour infusion period.

Completion date
01/07/2027

Eligibility

Key inclusion criteria
1. Aged 18-65 years
2. Male or female
3. Glycated haemoglobin (HbA1C) <48 mmol/mol
4. BMI 25-45 kg/m², stable weight for >3 months

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Key exclusion criteria
1. Diabetes mellitus of any type
2. Previous bariatric surgery
3. Current pregnancy or breastfeeding
4. History of having donated blood in the preceding 3 months
5. Alcohol intake >14 units/week
6. History of autoimmune liver disease or viral hepatitis
7. Pancreatic diseases
8. Severe gastrointestinal diseases
9. Drugs that affect hepatic steatosis
10. Subjects who have used prescription drugs within 4 weeks of first dosing, except antihypertensive treatments provided that the doses have not been altered within 4 weeks prior to entering the study
11. Subjects using Hypolipidaemic treatments
12. Subjects who have a history of relevant and severe atopy e.g. asthma, angioedema requiring emergency treatment, severe hayfever requiring regular treatment (i.e. taking antihistamines and/or glucocorticoids more regularly than 3 times a week), severe eczema requiring regular treatment (i.e. taking antihistamines and/or glucocorticoids more regularly than 3 times a week)
13. Subjects who have a history of relevant drug hypersensitivity
14. Subjects who have a history of alcohol abuse or alcohol dependence according to DSM-IV criteria within the last 2 years
15. Subjects who have a history of drug or substance abuse according to DSM-IV criteria within the last 2 years
16. Subjects who have a history of clinically significant migraine as judged by the Investigator. Subjects can be included if they have not had a migraine for the last 3 years
17. Subjects who have a significant infection or known inflammatory process on screening
18. Subjects who have acute gastrointestinal symptoms at the time of screening or admission (e. g. nausea, vomiting, diarrhoea, heartburn)
19. Subjects who have an acute infection such as influenza at the time of screening or admission
20. Subjects who have donated blood within 3 months prior to screening
21. Subjects who have donated plasma within the 7 days prior to screening
22. Subjects who have donated platelets within the 6 weeks prior to screening
23. Subjects who have used any investigational drug in any clinical trial within 3 months of their first admission date
24. Subjects who have received the last dose of investigational drug greater than 3 months ago but who are on extended follow-up

Date of first enrolment
06/06/2024

Date of final enrolment
01/07/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
NIHR Imperial Clinical Research Facility
Hammersmith Hospital
Du Cane Rd
Shepherd's Bush
London
United Kingdom
W12 0HS

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

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
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes