Imperial College London

The effects of current treatments of obesity on food preferences, gut hormones, bile acids and hepatic glucose output in humans.

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Date: 12/06/2013

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Sponsor

Imperial College London is the main research Sponsor for this study.

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This protocol describes this study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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1. Introduction

1.1 Background

Obesity has reached epidemic proportions and is the biggest challenge our health care systems have to face both in terms of its personal and social deleterious consequences.

Lifestyle interventions including alterations in diet and increases in physical activity are effective in the short term only [1, 2]. Few pharmacological agents have been used for weight loss but unfortunately even fewer have survived the test of time.

The most effective treatment modality for obesity is obesity surgery which has sustainable weight loss effects over a 15 year period at least and also offers a mortality benefit [3]. The most popular surgical procedures used worldwide include the gastric bypass, gastric banding and the sleeve gastrectomy. These procedures cause weight loss primarily by reducing hunger and increasing satiety [4]. Bile has been implicated in the release of satiety gut hormones as well as a mediator of the metabolic effect of the operation [5].

In the last few years new pharmacological agents, also called Incretin therapies, have been introduced for the treatment of Type 2 Diabetes Mellitus. Exenatide, an Exendin 4 analogue and Liraglutide, a GLP-1 analogue, stimulate insulin secretion from the pancreas as part of their glucose reducing properties. They do however also have impressive weight reducing effects which is something unusual in the field of diabetes pharmacotherapy. They reduce food intake through their actions in the hypothalamus, by causing nausea -at least initially- and by reducing gastric emptying thus creating a sensation of fullness [6].

The EndoBarrier is fundamentally a gastrointestinal impermeable barrier or a gastric sleeve that prevents food from coming in contact with the intestinal wall. The device is implanted endoscopically through the mouth and is placed in such a way that it lines the first two feet of the small intestine. This helps to prevent easy absorption of food as long as it remains in the sleeve and has huge impact on the patients intake of nutrients and calories [7]. Research in animal models suggests that when the duodenum and proximal jejunum are surgically bypassed, the mid and distal jejunum is stimulated by undigested nutrients. The jejunum then signals to the brain to reduce hepatic glucose output [8]. In clinical studies, the Endobarrier improves fasting and post prandial glycaemia via a reduction in insulin resistance, as measured by HOMA-IR (Homeostatic model assessment-Insulin Resistance) [9]. This is thought to be mediated by bile acids [10]. The HOMA-IR is a surrogate and imprecise marker of hepatic insulin resistance and the hyperglycaemic euglycaemic clamping method is the gold standard. Bile acids are believed to be key mediators behind these metabolic improvements. By confirming that the bypass of the proximal bowel reduces hepatic insulin resistance and hepatic glucose output, we can then begin to understand the mechanisms through which this device (and eventually bariatric surgery) improves glycaemia and even food preferences through the signalling of the jejunum to the brain.

Anecdotal evidence from the Obesity and Diabetes clinics and also limited data from the literature, suggest that patients after obesity surgery [11-15] but also patients on incretin therapies not only reduce their total intake of calories but also change the macronutrient composition of their diets. The most consistent change patients describe includes a reduction in the proportion of fat and sugars in their diets and an increase in the consumption of fruit and vegetable. Potential mechanisms causing this impressive shift in

food preferences include alterations in sensory perception of these macronutrients (i.e. changes in taste) or post ingestive effects. Elucidation of these mechanisms can lead to safer and more effective targeted pharmacological and surgical treatments for obesity.

There is lack of prospective studies comparing the above obesity surgical procedures and their effects on food preferences, satiety, gut hormones, bile acids and hepatic glucose output. There is no data on incretin therapies and food preferences in humans [16].

2. Study Objectives

The objective of this study is to investigate the effects of obesity surgical procedures and incretin therapies on food preferences, satiety, gut hormones, bile acids and hepatic glucose output in overweight and obese patients.

3. Study Design

This is a prospective observational controlled trial. 400 overweight and/or obese patients (Body Mass Index ≥ 30 Kg/m^2) will be recruited from the Imperial College NHS Trust, Royal Surrey County Hospital, Musgrove Park Hospital, King's College Hospital and private obesity and/or Diabetes clinics and studied prospectively for 1 year. The study groups will be as follows (n=50 per group):

Group A: Patients due to undergo gastric bypass
Group B: Patients due to undergo gastric banding
Group C: Patients due to undergo sleeve gastrectomy
Group D: Patients due to undergo endoscopic Endobarrier insertion
Group E: Patients due to be commenced on Exenatide
Group F: Patients due to be commenced on Liraglutide
Group G (control): Patients due to be commenced on a lifestyle intervention programme
Group H (control): Patients due to have non bariatric surgery (i.e. cholecystectomy) or an elective diagnostic endoscopy

As part of routine care these patients will be seen by a qualified doctor or dietician/nutritionist/diabetes specialist nurse (DSN) before and after intervention. Patients in control group G and H will be asked to use a low calorie diet either as part of their routine care or for research purposes only. Patients will be asked to prospectively complete food diaries on three consecutive days which are representative of their usual dietary intake and have a dietary assessment. This assessment will take 30-45 minutes and will take the form of a short discussion of dietary habits and will include completion of eating behaviour questionnaires (assessing dietary/personality traits including restraint, disinhibition, external eating and emotional eating). The first dietary assessment will be completed before the intervention and at 1 month, 3 months, 6 months and 12 months after intervention. Total energy intake and macronutrient composition comparisons pre and post intervention will form the basis of our analysis.

20 patients in each group will undergo more detailed measurements of food intake, hunger, satiety, gut hormones and bile acids. The research protocol will be the similar to that previously published by the Department of Metabolic Medicine, Imperial College, London. Participants will be fasted for 12 hours overnight and will attend for the study on 5 occasions. On each occasion venous blood samples will be taken and visual analogue scores will be measured over a 3 hour period using previously published methodology (Appendix Table 1: Test Periods). Samples or sample containers will be anonymised before collection but will be traceable back to the individual patients. Urine will be collected once. A qualified medical doctor will insert a venepuncture cannula into the arm of the patient and 5ml blood will be withdrawn at baseline, 15, 30, 60, 90, 120, 150 and 180 minutes following ingestion of a

standard 400kcal meal as below (Appendix Table 2: Protocol of each Test). After each sample the cannula will be flushed with saline to keep it patent. The protocol will be carried out 5 times per patient, pre intervention, 2, 7-30 days, 3 and 6-12 months post intervention. Plasma samples will be analysed for gut hormones as well as for primary bile acids and lipids. An extra blood and urine test will be obtained 1 month after treatment but not followed by a meal test.

Ten to twenty patients in each group (different from those taking part in the meal studies) will undergo measurements of hepatic glucose output/insulin resistance through euglycaemic hyperinsulinaemic clamps (Metabolic Study). Patients will be studied up to 4 times: at baseline, within 1-2 weeks of a low calorie diet and within 1-2 weeks after their weight loss treatment, whilst on the same liquid diet. The low calorie liquid diet is nutritious and contains all appropriate macronutrients. Such diets are frequently used as part of obesity interventions to reduce weight and risk. Patients will provide the investigators with a detailed food diary of their food consumption for this period. The final study will take place 6-12 months after the weight loss treatment whilst patients are on their normal diet. Throughout this period, the investigators will be in close contact with those patients who have diabetes to optimise their glucose control through adjustments of their glucose-lowering medications. Our unit has a track record in safe and effective glycaemic management before and after weight loss interventions [17].

Patient will attend the investigation unit after an overnight fast. They will be weighed and an intravenous cannula will be inserted in the antecubital of each arm. The first cannula will be used for infusions and the other for blood sampling. Participants will be asked to provide a urine sample that will be tested for albumin creatinine ratio and metabolic/inflammatory markers. If blood glucose levels are high on arrival an insulin infusion will be started to attain a stable glucose level (4.0 -6.0 mmol/l) prior to commencement of the hyperinsulinaemic euglycaemia clamp (Time -120). A priming dose of a stable isotope tracer will be given directly into the cannula and stable isotope of glucose will be infused at -120 to +120 minutes to measure the rate of hepatic glucose production. At 0 minutes a low dose insulin infusion (0.3-0.5 mU/kg/min) will be commenced and a variable rate infusion of 20% dextrose “spiked” glucose tracer will be given to maintain the glucose level to 4.0-6.0 mmol/l. Blood samples of 4-13 mls each will be taken to measure glucose, insulin, c-peptide, glucagon, lipids and gut hormones at -120, -20, -15, -10, -5, 0, +30, +60, +90, +100, +110, +120, +150. At +120 minutes the insulin infusion and glucose tracer infusion will be stopped. At the same time points participants will be asked to complete appetite visual analogue scales. Participants will be fed and glucose infusion continued for a further 20 minutes to prevent hypoglycaemia. Depending on the patient’s blood glucose control on arrival, the maximum duration of the whole visit will be up to 7 hours.

Blood samples will be centrifuged and the separated plasma kept in a - 20°C freezer. The isotopic enrichment of plasma glucose will be determined by gas chromatography mass spectrometry (GCMS) at the Wolfson Centre for Translational Research, Postgraduate Medical School, University of Surrey.

The stable labelled isotope tracers [6,6 $^{2}H_{2}$] is not a drug, but a naturally occurring metabolite which has been labelled with a stable, i.e. non-radioactive label. Stable isotope tracers are widely used in metabolic research by groups throughout the UK and worldwide. All labelled isotope tracers are ordered from Cambridge Isotopes Ltd through their UK suppliers CK gases Ltd. They are prepared as sterile solutions suitable for intravenous use by the Pharmacy Production Unit at Guys & St. Thomas’ NHS Trust to ensure they are safe for the participants. The products are supplied with the appropriate

certificate of analysis and MSDS. We have used the same manufacturer to be sure of the quality of the products and the supporting documentation.

3.1 Study outcome measures

Primary Endpoint
The primary outcome measure will be total energy intake and dietary composition in terms macronutrient proportions (fat, saturated fat, carbohydrates, sugars, fibre, protein and salt).

Secondary outcomes
The secondary outcome measures will be the ratings of hunger and satiety, gut hormones, bile acid and lipid levels before and after a standardised meal. In the clamp studies, the outcome will also be hepatic glucose output and insulin resistance.

4. Participant Entry

4.1 Inclusion criteria
Adult patients with overweight or obesity (BMI ≥30 Kg/m^2) who are having a weight loss intervention.

4.2 Exclusion criteria
None.

5. Adverse events

5.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 Reporting procedures
All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs
All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to non-obesity or diabetes related causes, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. All SAEs should be reported to the Charing Cross Hospital REC where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs

Fax: 02083830673, attention Dr Carel le Roux

Please send SAE forms to: Dr Carel le Roux, Imperial Weight Centre, 9E Room 8, Charing Cross Hospital, Fulham Palace Road, London W6 8RF.

Tel: 07970719453 (Mon to Fri 09.00 – 17.00)

6. Assessment and Follow Up

Assessment will take place through the use of dietary assessments, standardized meal tests and metabolic clamp tests. The dietary assessments will be completed once before and 1, 3, 6 and 12 months post all interventions. The meal tests will take place once before and 2 days, 7-30 days, 3 and 12 months after intervention. The metabolic study will be performed 4 times: at baseline, within 1-2 weeks of a low calorie diet and within 1-2 weeks after their weight loss treatment, whilst on the same liquid diet. The final study visit will take place 6-12 months after the weight loss treatment whilst patients are on their normal diet.

7. Statistics and Data Analysis

The groups will be allocated at random and thus the distribution of the data should be similar. A student's t-test will be used to compare the two groups for the primary and secondary end points. Descriptive statistics (proportions, mean, medians, standard errors and ranges) will be computed for all baseline variables with 95% CI using either exact binomial confidence intervals or t-confidence intervals for continuous outcomes (after appropriate transformation of the outcome to symmetry). All tests will be conducted at alpha=0.05. Previous studies investigating the effects of obesity surgery on macronutrient intake have recruited 50 patients per group and had power to detect significant differences. This type of study has never been performed with incretin pharmacotherapies and therefore will serve as a pilot for the investigation of the effects of this treatment intervention. The standardised meal study will have 80% statistical power to detect a difference of 5 pmol/L from the expected mean PYY level of 30 pmol/L when the usual standard deviation is 8 pmol/L, the sample size 20 subjects and the alpha error level 5%. This power calculation has been based on previous published results by the same group. Therefore 20 patients in each group are needed.

For the metabolic study, the endpoint is the minimum endogenous glucose production rate. Based on the HOMA-IR results from the only published study on patients having undergone the Endobarrier procedure, we will have a power of 81% at a p level of <0.05 if 6 patients complete the study. To allow for patients dropping out, a maximum of 10 patients will be enrolled to ensure 6 patients complete the study.

8. Regulatory Issues

8.1 Ethics approval
The Chief Investigator has obtained approval from the West London 2 Research Ethics Committee. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 Consent
Consent to enter the study will be sought from each obese patients and healthy volunteers only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 Confidentiality
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 Indemnity
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 Sponsor
Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 Funding
The Moulton Charitable Foundation.

8.7 Audits and inspections
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. Study Management
The day-to-day management of the study will be co-ordinated through Dr Carel le Roux.

10. Publication policy
Publication to be aimed for medical conferences and peer-reviewed journals.

11. References

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Appendix

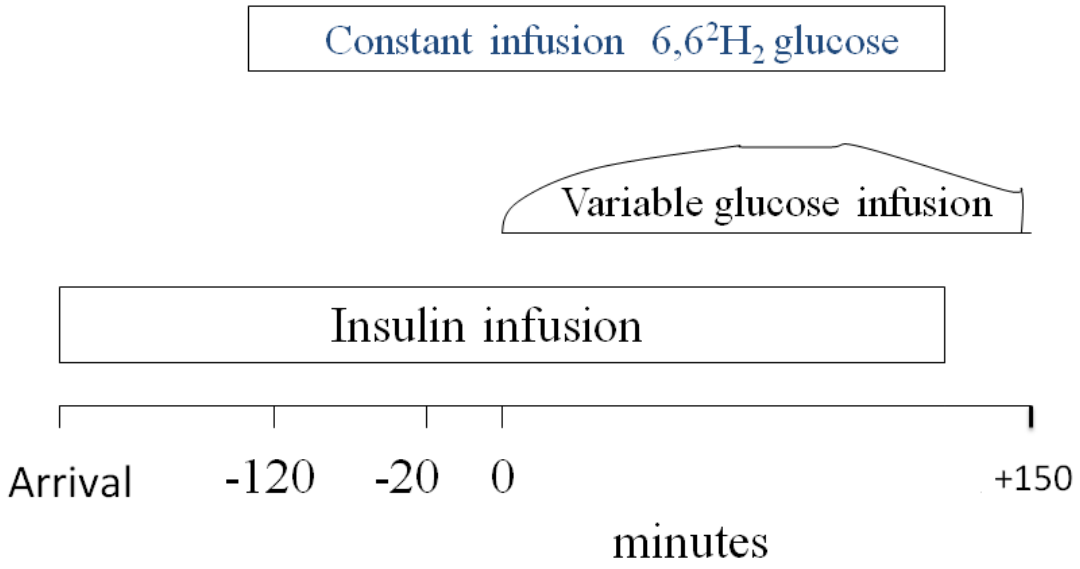
Table 1: Testing time points

Frequency test performed	Test
Preoperatively	400kcal standard meal plus venous blood sampling and visual analogue scores
Day 2	400kcal standard meal plus venous blood sampling and visual analogue scores
Day 7-30)	400kcal standard meal plus venous blood sampling and visual analogue scores
3 months	400kcal standard meal plus venous blood sampling and visual analogue scores
6-12 months	400kcal standard meal plus venous blood sampling and visual analogue scores

Table 2: Meal study protocol

Time	Intervention	Outcome measured	Outcome measured
0’	400kcal standard meal	Venous blood sampling 5ml	Visual analogue score
15’		Venous blood sampling 5ml	
30’		Venous blood sampling 5ml	
60’		Venous blood sampling 5ml	Visual analogue score
90’		Venous blood sampling 5ml	
120’		Venous blood sampling 5ml	Visual analogue score
150’		Venous blood sampling 5ml	
180’		Venous blood sampling 5ml	Visual analogue score

Diagrammatic representation of the metabolic study protocol



Metabolic study protocol

Time (min)	Action	Blood sampling (volume)				
		Glucose Conc and Enrichment (1ml)	Insulin (Serum) (3ml)	Glucagon (Serum) (2ml)	c-peptide/lipids/Gut hormones (Serum) (7ml)	
– 120 to 0	Sliding scale insulin infusion 1 U/ml (0.1 - 6 ml/h) 15 minute interval blood glucose monitoring; maintenance of glucose at 4.0 – 6.0 mmol/l;					
-120		X	x			
-120 to +120	Start 6,6 $^{2}H_{2}$ glucose infusion					
-20		X	x			
-15		X	x			
-10		X	x			
-5		X	x			
0		X	x	x	x	
0-240	Low dose insulin infusion 0.3-0.5 mU/kg/min Initiation of variable infusion of 20% glucose spiked with 2H2 glucose; maintenance of clamp glucose at 4.0 – 6.0 mmol/ l					
+30		X	x	x	x	
+60		X	x			
+90		X	x	x	x	
+100		X	x			
+110		X	x			
+120	Stop isotope and insulin Food will be given to the patient	X	x	x	x	
+150		X	x	x	x	
.						