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Postprandial effects of genetic variation on carbohydrate digestion

Submission date
19/08/2013

Recruitment status
No longer recruiting

Registration date
06/11/2013

Overall study status
Completed

Last Edited
12/05/2017

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Dietary carbohydrates consist mainly of glucose molecules arranged together in different structures. Due to the wide variety of carbohydrates in the diet, humans have evolved a set of enzymes to digest carbohydrates efficiently to produce glucose, the bodys energy source. The level of glucose in the bloodstream after eating a digestible carbohydrate such as starch is related to the food's glycaemic index (GI). It is not currently understood how genetic variation affects digestion, or blood glucose levels, but it may be clinically relevant to identify people at risk of developing type 2 diabetes. This study investigates whether variations in DNA (genetic make-up) affect how carbohydrates are digested by measuring levels of glucose and insulin in the blood after eating carbohydrates. A study that investigates the body's response to food is called a postprandial study, which literally means after eating.

Who can participate?
Healthy, non-smoking, men and women aged between 18-40 years old who were born in the UK and who have four grandparents that were also born in the UK.

What does the study involve?
This research is being conducted in two stages. Stage 1 involves saliva sample donation for DNA extraction and genetic analysis. DNA is used for screening for participation in Stage 2, for investigating the frequency of genetic variation in carbohydrate enzymes in the UK population. Therefore, DNA collected during Stage 1 is used in this study even if participants do not participate in the postprandial study. Stage 2 is the postprandial study, where participants are selected based on inclusion/exclusion criteria and the outcome of genetic screening from Stage 1. Stage 2 involves a health check visit and two study days. If participants do not wish to participate in the postprandial study (Stage 2), but would like to donate their DNA to this study (Stage 1), they may be able to do this. However, it is not possible to participate in the postprandial study (Stage 2) if a saliva sample is not provided in Stage 1.

During the first visit, participants are asked to sign an informed consent form and complete a registration questionnaire. They are assigned a unique ID number, which is recorded along with contact details and held securely, to ensure they cannot be identified. Saliva samples are collected from which DNA is extracted and genetic testing is carried out. Genetic screening is

used only as a research logistic, and has no potential clinical significance or implications for health. The researchers are looking for a range of genetic variations, known as genotypes. The genotypes that they are interested in for the purpose of this study are present in 60% of the population. Therefore, only about 60 participants from Stage 1 are contacted to take part in Stage 2, health screening. After the health screening about 48 volunteers are enrolled into the postprandial study. Volunteers are asked to complete a 3-day diet diary to assess their diet before taking part in Stage 2.

Volunteers with the genotypes of interest are invited to attend a health screening appointment (lasting about 45 minutes) in the Metabolic Unit, 4th Floor, Corridor A, Franklin-Wilkins Building, KCL. Volunteers need to attend this visit after an overnight fast (no food or drink except water after 10 pm the night before). Volunteers are asked to complete a 3-day diet diary to assess their diet. At the health screening appointment a small blood sample (25 ml, or 5 teaspoons) is taken which is used to determine whether liver function, blood count, blood glucose, blood insulin and blood fats such as cholesterol are within normal ranges. Height, weight, waist and hip circumference, body fat percentage, blood pressure and heart rate are also measured. Volunteers are provided with a copy of the results. If any health concerns arise from these tests a copy of the results can be sent to their GP, using the details provided on the registration form, so that they can be followed up if wished.

During the postprandial study blood samples are taken over a period of 4 hours by inserting a single fixed needle (cannula) into a vein on the forearm, from which all blood samples are taken. Three small blood samples (9 ml, two teaspoons) are taken at the start of the study. Participants are then asked to consume the test meal, which contains 75 g of carbohydrate; they have 5 minutes to consume this. Further blood samples are then taken at 15-minute intervals for the first hour and then at 30-minute intervals between 1 and 4 hours. 13 blood samples are taken on the study day, a total of 216 ml blood. A grand total of 457 ml of blood is collected over the whole study period (25 ml at screening and 216 ml on each study day); this is less than the amount taken in a standard blood donation session. At the end of the 4 hours, the cannula is removed and participants are provided with a choice of snacks to consume before they leave. Each participant must attend two study days, they receive a different test meal on each visit.

What are the possible benefits and risks of participating?
The benefits are a comprehensive health check, and participants will be helping to improve our understanding of the causes of type 2 diabetes. Participants that complete the entire study receive compensation of £80 plus up to £10 reimbursement for their travel costs per visit. There is very little risk to the participants; all blood samples are taken by highly trained professionals and the methods used have been used and reproduced safely many times.

Where is the study run from?
The study is being run from the University College London (UK). Participants will also be required to attend the Metabolic Unit in the Franklin-Wilkins building of King's College London (UK).

When is the study starting and how long is it expected to run for?
March 2014 to December 2014

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

Who is the main contact?
Miss Katherine Brown
katherine.brown.11@ucl.ac.uk or genCHOstudy@kcl.ac.uk
+44 (0)20 7679 4397

Contact information

Type(s)
Scientific

Contact name
Prof Mark G. Thomas

Contact details
Department of Genetics, Evolution & Environment
University College London
Darwin Building
Gower Street
London
United Kingdom
WC1E 6BT

Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
An acute investigation into the relationship between genetic variation, digestion and blood glucose response upon consumption of carbohydrates

Acronym
GenCHO

Study objectives
Current hypothesis as of 10/03/2014:
The purpose of this research is to investigate whether genetic variation in the genes of carbohydrate digestive enzymes (CDEs) affects postprandial glycaemic and or insulinaemic response after consumption of carbohydrates.

The principal objective is to collect blood samples for 4 hours after consumption of the test CHO; these blood samples will be analysed for blood glucose and insulin levels. This study is designed to have two groups per gene, and will compare the glycaemic and insulinaemic responses between the two groups testing the same gene. This will enable us to identify differences in glycemic response that are due to enzyme activity caused by underlying genetic variation.

This study will help to unravel the involvement of carbohydrate digestion in the development and management of type 2 diabetes. We hope to identify genetic variants that affect the activity of digestive enzymes that cause elevated glycemic response after ingestion of carbohydrates. This study will also be able to investigate whether genetic variation in carbohydrate digestion enzymes explains the variability of glycemic response within the normal observed range.

In summary the question is: does genetic variation in genes coding for carbohydrate digestive enzymes affect digestion and impact the rate, peak or total glucose and/or insulin response when an individual consumes carbohydrate?

Secondary Objectives
The secondary objective is to use blood samples collected from this study to investigate whether different CHOs produce different responses in the gut hormones responsible for satiety. Measuring and comparing levels of c-peptide, glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY) and cholecystokinin (CCK), between groups ingesting different CHOs and also between sub-groups, will achieve this. This will contribute towards our understanding of how the food we eat makes us feel full and satisfied; much work has been done on this in regards to protein and fat ingestion but there remains a lot which is unknown in relation to consumption of CHO.

All DNA samples collected in this study will be used to estimate the frequency of genetic variations in carbohydrate digestive enzymes within the UK population. The frequency of these variations in the UK will then be compared to frequencies in global populations and used to interpret the cause for any population-specific distribution. This will contribute towards understanding human evolution and adaptation to dietary changes.

Previous hypothesis:
The purpose of this research is to investigate whether genetic variants in the genes of carbohydrate digestive enzymes (CDEs) affects postprandial glycemic and or insulinemic response after consumption of carbohydrates.

The principal objective is to collect blood samples for 4-hours after consumption of the test CHO solution. These blood samples will be analysed for blood glucose and insulin levels. This study is designed to have a case and a control group per CDE, as different CHOs elicit different glycemic response due to their composition. The glycemic and insulinemic responses will be compared between case and control groups for the same CDE, this will enable us to identify differences in glycemic response that are due to enzyme activity and not due to CHO composition.

This study will help to unravel the involvement of carbohydrate digestion in the development and management of type-2 diabetes. We hope to identify genetic variants that affect the activity of digestive enzymes that cause elevated glycemic response after ingestion of carbohydrates. This study will also be able to investigate whether genetic variation in carbohydrate digestion enzymes explains the variability of glycemic response within the normal observed range.

In summary the question is: does genetic variation in genes coding for carbohydrate digestive enzymes affect digestion and impact the rate, peak or total glucose and/or insulin response when an individual consumes carbohydrate?

Secondary Objectives
The secondary objective is to use additional blood samples collected from this study to investigate whether different CHOs produce different responses in the gut hormones responsible for satiety. Measuring and comparing levels of c-peptide, glucose-dependent

insulinotropic polypeptide (GIP), peptide YY (PYY) and cholecystokinin (CCK), between groups ingesting different CHOs and also between case and control groups, will achieve this. This will contribute towards our understanding of how the food we eat makes us feel full and satisfied, much work has been done on this in regards to protein and fat ingestion but there remains a lot which is unknown in relation to consumption of CHO.

All DNA samples collected in this study will be used to estimate the frequency of genetic variations in CDEs within a healthy sample of the UK population. The frequency of these variations in the UK will then be compared to frequencies in global populations and used to interpret the cause for any population specific distribution. This will contribute towards understanding human evolution and adaptation to dietary changes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NHS Research Ethics Committee London - Harrow, ref: LO/14/0063

Study design
Single-center double-blind single-dose intervention study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Nutritional health relating to carbohydrate digestion and metabolism, scope includes but the study is not designed to test association to type 2 diabetes

Interventions
Current interventions as of 22/09/2014:
As part of the screening procedures, participants will make a saliva sample by spitting into a collection pot. This is pain free and will be demonstrated to them. A small fasting blood sample will also be taken as part of the health screening processes; this will be done following standard venepuncture procedures and performed by highly trained professionals.

Participants will attend two study days where they will be asked to consume the test meals. The test meals each contain 75 g of carbohydrate. On one visit, a test meal will be given in the form of a drink, and on the other visit this will be given as cooked white rice, which is six tablespoons of rice (uncooked). Treatment allocation is randomized, so each participant will receive both test meals, but in a random order.

During each of the study days a fixed needle (cannula) will be inserted into the forearm of the participants following standard procedures and performed by a study clinician or nurse. This may cause temporary discomfort but has no long-lasting effects. The study day procedures follow that of a 4-hour oral glucose tolerance test (OGGT). Baseline samples will be collected using this cannula, as will all other blood samples collected during the study period.

Interventions from 10/03/2014 to 22/09/2014:
As part of the screening procedures, participants will make a saliva sample by spitting into a collection pot. This is pain free and will be demonstrated to them. A small fasting blood sample will also be taken as part of the health screening processes; this will be done following standard venepuncture procedures and performed by highly trained professionals.

During the study day a fixed needle (cannula) will be inserted into the forearm of the participants following standard procedures and performed by a study clinician or nurse. This may cause temporary discomfort but has no long-lasting effects. The study day procedures follow that of a 4-hour oral glucose tolerance test (OGGT). Baseline samples will be collected using this cannula, as will all other blood samples collected during the study period.

Participants will attend a single study day where they will be asked to consume a single test suspension. Test suspensions will contain 75 g of either trehalose, maltose, sucrose or corn starch, suspended in 500 ml of drinking water. The test suspension that a participant will receive shall be based on the group that they are in, which is allocated on the outcome of the genetic screening at the start of this study. There are four study arms, represented by the four different test suspensions; this study is not designed as a cross-over so each participant will only consume one test suspension and attend only one study day.

Interventions at time of registration:
As part of the screening procedures, participants will make a mouth swab by lightly wiping a cotton swab on the inside of their cheek for approximately 30 seconds. This is pain free and will be demonstrated to them. A small fasting blood sample will also be taken as part of the health screening processes; this will be done following standard venepuncture procedures and performed by highly trained professionals.

During the study day a fixed needle (cannula) will be inserted into the forearm of the participants following standard procedures and performed by a study clinician or nurse. This may cause temporary discomfort but has no long-lasting effects. The study day procedures follow that of a 4-hour oral glucose tolerance test (OGGT). Baseline samples will be collected using this cannula, as will all other blood samples collected during the study period.

Participants will attend a single study day where they will be asked to consume a single test suspension. Test suspensions will contain 75 g of either trehalose, maltose, sucrose or corn starch, suspended in 500 ml of drinking water. The test suspension that a participant will receive shall be based on the group that they are in, which is allocated on the outcome of the genetic screening at the start of this study. There are four study arms, represented by the four different test suspensions; this study is not designed as a cross-over so each participant will only consume one test suspension and attend only one study day.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)

Current primary outcome measures as of 10/03/2014:
The primary outcome measures will be the postprandial changes in indices of glucose metabolism and insulin secretion. Blood samples will be collected for the analysis of plasma glucose and plasma insulin.

Previous primary outcome measures:
Primary outcome measures are plasma glucose and plasma insulin concentrations, which are to be measured at t = baseline (blood samples taken before the participant consumes the test carbohydrate.-15, -5), 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 mins. Plasma glucose is used to determine postprandial glycaemic responses and plasma insulin is used to determine postprandial insulinaemic responses.

Key secondary outcome(s))

Current secondary outcome measures as of 10/03/2014:
Secondary outcome measures will be to use blood samples collected in the postprandial study to analyse the effect of gut hormone response to the ingestion and digestion of different CHOs. This will be done by analysing concentrations of gut hormones including incretin, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like polypeptide-1 (GLP-1) peptide YY (PYY) and cholecystokinin (CCK). Blood fractions for C-peptide analysis will also be collected, as a marker of the rate of insulin synthesis, to be used in addition to insulin concentrations to understand the postprandial insulinaemic response. Finally, the DNA samples collected in this study will be used to further investigate genetic variation in the genes of CDEs and to estimate the frequency of the polymorphic genetic loci in CDEs within the healthy UK population. This data will then be used in population-based genetic analysis to draw conclusions about human evolution and adaptation to dietary changes.

Previous secondary outcome measures:
Further genetic analysis of the DNA samples collected in this study will take place after the conclusion of the trial so that participants do not lose interest. The informed consent form signed prior to swab collection ensures that the volunteers know that their DNA will be analysed using population genetic techniques. Data generated from genetic analysis of DNA samples collected as part of this trial will be analysed to make estimates of the frequency of variant alleles in CDEs within the healthy UK population. Doing this in conjunction with the latter stages of this trail may identify new genetic variants that affect the digestive health of the UK population. These data will also be incorporated into genotype data collected bioinformatically to inform on the global distribution of the studied genetic variants.

Secondary outcome measures of blood-borne molecules include:
1. C-peptide concentrations measured at t = -15, -5, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 mins, which is used to assess insulin secretion and provide an additional measurement of insulin metabolism.
2. Concentration of various gut hormones will also be measured as differences in the rates of absorption and digestion of the test carbohydrates may have subsequent effects on rates of gastric emptying and may affect the rates of glycaemic responses via gut hormone mediated effects which have subsequent implications for metabolism and satiety. Concentrations are measured at t = -15, -5, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240 mins. The specific hormones are:
2.1. Glucose inhibitory peptide (GIP), which is released in response to a mixed meal and plays an important role in determining postprandial insulin concentrations, and acts as a good indicator of glucose absorption.
2.2. Peptide YY (PYY), which is associated with the postprandial handling of lipids, whereby ingested fat stimulates the release of PYY by an early, probably hormonal mechanism, and later by the entry of fat into the distal small intestine.

2.3. Glucagon-like peptide 1 (GLP-1), the secretion of which is influenced by the presence of carbohydrate, protein and lipid in the small intestine, and is involved in insulin regulation, gastric emptying and satiety.

Completion date
31/12/2014

Eligibility

Key inclusion criteria
Current inclusion criteria as of 10/03/2014:
1. Healthy, non-smoking, men and women aged between 18-40 years old
2. British participants who were born in the UK and who have four grandparents that were also born in the UK

Previous inclusion criteria:
Healthy, non-smoking, men and women, aged 18-40 years, of British ethnicity

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
40 years

Sex
All

Key exclusion criteria
Exclusion criteria identified during visit 1 using questionnaire:
1. The subject is an employee of Unilever
2. Medical history of myocardial infarction, angina, thrombosis, stroke, cancer or diabetes
3. Medical history of eating disorders such as anorexia nervosa, bulimia, binge eating disorder
4. Medical history of digestive dysfunction, or intestinal disease such as IBS and Crohns disease
5. Medical history of pancreatitis (Acute, Chronic or Hereditary) and exocrine pancreatic insufficiency
6. Alcohol intake exceeding a moderate intake (>28 units per week)
7. Needle phobic, fear of blood and blood clotting disorders such as haemophilia
8. Pregnant, breast-feeding and post-menopausal women

Exclusion criteria identified after visit 2, using genetic and health screening methods:
1. Fasting plasma glucose > 6.0 mmol /L

2. Fasting plasma insulin > 60 pmol/L
3. Fasting plasma cholesterol > 7.8 mmol /L
4. Body fat percentage < 8% or >25% for men and < 20% or >35% for women
5. Body mass index (BMI) <18.5 or >25.5
6. Blood pressure < 90/60 or >120/80
7. Abnormal liver function

The following will be recorded but are not considered grounds for exclusion, as there is no evidence that this will cause adverse response or distress to the subjects, but it may be of interest.
1. Diagnosed lactose intolerance
2. Confirmed gluten sensitivity, including coeliac disease

Date of first enrolment
10/03/2014

Date of final enrolment
31/12/2014

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London
London
United Kingdom
WC1E 6BT

Sponsor information

Organisation
University College London (UCL) (UK)

ROR
https://ror.org/02jx3x895

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

IPD sharing plan summary