ISRCTN17563146 https://doi.org/10.1186/ISRCTN17563146

The influence of whey protein on free-living glycaemic control in type 2 diabetes

Submission date
13/05/2019

Recruitment status
No longer recruiting

Registration date
21/05/2019

Overall study status
Completed

Last Edited
15/08/2024

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
Type 2 diabetes mellitus (T2D) is a metabolic disease characterised by an inability to secrete insulin in response to carbohydrates. However, where carbohydrate-induced insulin secretion is lost, protein-stimulated insulin secretion remains normalised in T2D. As such, dietary interventions have shown that consuming large amounts of whey protein (WP) before meals reduces high-blood sugars within patients with T2D. However, research to date has included unrealistically large whey doses (250kcal) consumed often 30 minutes before test meals, which does not represent patient real-world situations nor normal eating habits. It is therefore not known if the reported benefits are retained in smaller amounts of WP consumed at more realistic times before conventional meals. Similarly, it is yet to be determined if WP consumption influences blood glucose control in patients' home settings, limiting the practicality of WP as a nutritional treatment for T2D.

We aim to assess if consuming a small WP drink before meals improves patients' blood glucose control within their home settings and to examine potential mechanisms.

Who can participate?
Adults (30 - 68 years old) with T2D (HbA1c below 9.5% [80 mmol/mol]), treated with either lifestyle modifications or oral medications who have no known dietary intolerances.

What does the study involve?
Patients will be randomised to consume one of two 100ml WP beverages 10mins before each of their main meals (breakfast, lunch and dinner) at home for 7 days (termed: “free-living” period). Fourteen days later, patients will consume a different WP drink (i.e. crossover) before each of their main meals for a further 7 days. Prior to and immediately following each free-living period, patients will consume their assigned beverage prior to a mixed-meal tolerance test consisting of a standardised breakfast meal and an “all you can eat” lunch. A short interview will be conducted to assess patient experiences upon completion, highlighting potential barriers surrounding the use of WP for diabetes care.

Patients will attend the NIHR Clinical Research Facility (CRF), Royal Victoria Infirmary, Newcastle upon Tyne a total of 6 times over a 5-week period. On patients first and fourth visit, a continuous

glucose monitoring system will be fitted to capture free-living glucose control and a standardised diet will be provided to be consumed 24h before subsequent visits (visit's 2, 3, 5 and 6). During trial days (visits 2, 3, 5 and 6), patients will report to the NIHR CRF in a fasted state via a pre-arranged taxi to perform the mixed-meal tolerance tests. Once settled in the CRF, a small cannula will be introduced for repeated-blood sampling and a fasting sample will be collected. Patients will consume a small WP beverage 10mins before a breakfast meal, where blood samples and subjective appetite measurements will be collected periodically for a 4h period. Immediately following, a further WP beverage will be consumed before an "all you can eat" lunch meal. Upon completion of the mixed-meal tolerance test (visit's 2 and 5), patients will be provided with their assigned beverages to be consumed during the free-living period. Throughout the intervention, physical activity and dietary intake will be monitored.

What are the possible benefits and risks of participating?
Participants will have access to the latest top of the range continuous glucose monitoring systems, allowing for greater insight into their 24h blood glucose control, where they will be given personalised feedback on their glucose control. Participation in this study may help us develop larger trials within T2D which may help influence future treatments and nutritional advice for diabetic control.

Blood samples will be collected from a small cannula where it is possible there might be some slight discomfort when it is being inserted and/or bruising when it is being taken out. However, all blood sampling will be performed by trained phlebotomists reducing the risk of this occurring.

Where is the study run from?
Newcastle upon Tyne NHS Foundation Trust

When is the study starting and how long is it expected to run for?
February 2019 to September 2021

Who is funding the study?
This study is funded by Arla Foods Ingredients Group P/S (Viby J, Denmark) from a grant awarded to Newcastle University.

Who is the main contact?
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Contact information

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Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
246180

Protocol serial number
IRAS ID: 246180

Study information

Scientific Title
The influence of pre-meal whey protein supplementation on appetite and energy intake and free-living glycaemic control in adults with type 2 diabetes: a randomised-control trial.

Study objectives
Compared to a protein-depleted beverage, consuming a small whey protein drink before meals will improve free-living glycaemic control in adults with type 2 diabetes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/01/2019, North East – Newcastle & North Tyneside 1 Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ; 0207 104 8084; nrescommittee.northeast-newcastleandnorthtyneside1@nhs.net), ref: 18/NE/0372.

Study design
A single-centred, randomised-control, counterbalanced, cross-over design.

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Type 2 diabetes mellitus

Interventions
Participants will randomly consume either a small dose (15g) of whey protein (Arla Foods Ingredients Group P/S., [AFI], Denmark) or a protein-depleted placebo supplement (AFI, Denmark) 10 minutes before each of their main meals (breakfast, lunch, dinner) for a period of 7 days. Prior to and immediately following each 7 day period, participants will perform a "mixed meal tolerance test" where they will consume their assigned supplement 10 minutes before a breakfast and lunch meal. Trial order will be determined by an online randomiser (www.randomization.com), randomly assigning participants, in a balanced permutation, into two treatment groups.

Twenty-two adults with type 2 diabetes mellitus treated with diet and lifestyle modifications and /or oral medications will be recruited into a nutritional intervention examining the influence of a novel small whey protein beverage on free-living blood glucose control and energy intake. Patients will attend the NIHR Clinical Research Facility (CRF), Royal Victoria Infirmary, Newcastle upon Tyne a total of 6 times over a 5-week period. On patients first and fourth visit, a continuous glucose monitoring system (G6, Dexcom, USA) will be fitted to capture pre-trial and free-living glucose control. On subsequent visits [visits 2, 3, 5 and 6] patients will enter the CRF to perform a mixed meal tolerance test. A standardised evening meal (~900 kcal) will be provided to be consumed before each mixed meal tolerance test to ensure standardisation between appetite and gut hormone parameters.

Following an overnight fast, patients will enter the CRF to perform a mixed meal tolerance test to assess acute and intermediate effects of whey protein pre-meal consumption on plasma glucose, insulin, lipid and gut peptide responses [visits 2, 3, 5 and 6]. In a single-blinded, randomised, counterbalanced manner, patients will consume a protein-rich whey [WP; 15g protein] or a protein-depleted shot [PLA; 0g protein] immediately prior to a mixed-nutrient breakfast meal. Trial sequences will be determined prior to participant enrolment using a computerised online random generator randomly assigning patients in a balanced permutation into two trial groups: WP and PLA. The WP and PLA shots will be similar in appearance and presented in identical bottles and volume (Arla Foods Ingredients Group P/S, Denmark), where patients will be blinded to the origin of the test and placebo supplement. Blood samples and subjective appetite sensations will be periodically measured over a 4 hour postprandial period before patients consume a further beverage before an all you can eat lunch meal.

Following visits 2 and 5, patients will be instructed to consume one of their assigned beverages before each of their main meals at home for a 7-day free-living period before returning to perform the mixed meal tolerance test. A 14-day washout period will separate each trial arm, where patients will repeat the mixed meal tolerance tests and free-living intervention whilst

consuming the second beverage (i.e. crossover). Physical activity, glycaemic control and dietary intake will be monitored throughout the free-living periods via a wrist worn activity monitor (GENEActiv, Activinsights LTd., USA), a continuous glucose monitoring system (G6, Dexcom, USA) and an online dietary recall questionnaire (Intake24, UK), respectively. Other than the ingestion of their assigned supplements, patients are asked not to make any changes to their habitual lifestyle or diet for the duration of the intervention. A short interview will be conducted to assess patient experiences and attitudes upon completion of the trial [visit 6], highlighting potential barriers surrounding the use of WP for diabetes care.

Intervention Type
Supplement

Primary outcome(s)
Postprandial glycaemic responses (incremental area under the curve) to patient's free-living main meals (breakfast, lunch and dinner) following prior consumption of the protein-rich and protein-depleted supplement (i.e. "pre-load"). Glycaemic responses will be measured from interstitial glucose concentrations collected from patient's continuous glucose monitoring system (CGM) over a 7-day free-living period, where a postprandial period will be defined as an uninterrupted 2-hour phase following commencement of a reported meal. Postprandial glycaemic responses will be calculated using the trapezoidal rule.

Key secondary outcome(s))
1. Energy intake (kcal) measured by an ad libitum lunch meal served during the mixed meal tolerance tests [visits 2, 3, 5 and 6]. Energy intake will be calculated from weighing both served and unserved amounts of the test meal, and before and after meal consumption.
2. Time-course changes in subjective appetite sensations measured using a linear visual analogue scale during the mixed meal tolerance tests [visits 2, 3, 5 and 6].
3. Time-course responses in blood glucose, insulin, lipids and gut hormones following a standardised mixed-nutrient breakfast meal prior to and immediately following the 7 day period. All markers will be analysed by routinely available assays [mixed meal tolerance tests: visits 2, 3, 5 and 6].
4. Changes in pro-inflammatory cytokine concentrations (interleukin-6, tumour necrosis factor alpha and high-sensitivity C-reactive protein) following 7-days of supplementation. Pro-inflammatory cytokine concentrations will be measured from a fasting blood sample collected during the mixed-meal tolerance tests measured by routinely available assays [mixed meal tolerance tests: visits 2, 3, 5 and 6].
5. Patient experiences and attitudes towards consuming a nutrient pre-load as a mode to treating their diabetes as analysed by a patient interview conducted at the end of the trial [visit 6]. Interviews will be transcribed into a written format and analysed for themes.
6. Markers of free-living glycaemic variability (MAGE, M-Value, SD and CONGA) will be calculated from interstitial glucose concentrations measured from a CGM over a 7-day free-living period using EasyGV V9.0.R2 (Oxford University, UK). Circulating concentrations of 1, 5-anhydroglucitol collected from fasting blood samples during the mixed-meal tolerance tests will be measured by routinely available assays [visits 2, 3, 5 and 6].
7. Time spent in hypoglycaemia (< 3.9 mmol/L), euglycaemia (3.9 - 10 mmol/L), hyperglycaemia (10 – 13.9 mmol/L) and severe hyperglycaemia (> 13.9 mmol/L) during a 7-day free-living period as measured from interstitial glucose concentrations reported from the CGM. Time spent in subsequent thresholds will be expressed as a % of time: number of readings within a specific threshold divided by total CGM readings provided.
8. Free-living energy intake (kcal) will be measured using an online dietary recall (Intake 24, UK), completed daily throughout the 7-day free-living period.

Completion date
01/09/2021

Eligibility

Key inclusion criteria
1. Diagnosed with type 2 diabetes mellitus for at least 1 year prior to participation in this trial.
2. Treated with either lifestyle modifications and/or oral medications, which have been stable for 3 months or more.
3. Weight stable for 1 month or more (i.e. weight has not fluctuated by more than 1kg prior to study enrolment).
4. HbA1c of below 9.5% (80mmol/mol)
5. Aged between 30-68 years of age
6. Regularly consume breakfast
7. Adhere to a normal sleep/wake cycle

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
26

Key exclusion criteria
1. Treated with insulin or incretin mimetic therapies.
2. History of severe cardiovascular events, renal failure or liver disease within the last 12 months.
3. Gastrointestinal issues.
4. Known food intolerance's or allergies.
5. Substance abuse.

Date of first enrolment
01/03/2019

Date of final enrolment
01/08/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Newcastle upon Tyne NHS Foundation Trust
Level 1, Regent Point, Gosforth
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NE3 3HD

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
University/education

Funder Name
Newcastle University

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/05/2022	27/05/2022	Yes	No
HRA research summary			28/06/2023	No	No
Other publications	Qualitative interview study	27/01/2022	14/06/2023	Yes	No
Other publications	Secondary analysis	13/08/2024	15/08/2024	Yes	No