Gastroparesis symptoms and its treatment using low-viscosity soluble dietary fibres

**1. TITLE AND LIST OF INVESTIGATORS**

**Title of Study**: Gastroparesis symptoms and its treatment using low-viscosity soluble dietary fibres

**Abbreviated Title**: Treating gastroparesis using soluble dietary fibres

**Coordinating principal investigator:**

Dr Jerry Zhou –Western Sydney University– Postdoctorate Research Fellow

**Co Investigators:**

Mr Harsha Suresh –Western Sydney University– PhD candidate

Dr Vincent Ho – Western Sydney University– Clinical Academic Gastroenterologist

**2. SYNOPSIS**

**Background:**

Gastroparesis is a chronic gastric motility disorder characterised by delayed gastric emptying. There are an estimated 125,000 people diagnosed with gastroparesis in Australia as of 2016. The majority of gastroparesis that is diagnosed in patients is idiopathic and 30% to 50% of gastroparesis patients also experience either type 1 or type 2 diabetes. It is usually characterised by symptoms such as early satiety, nausea, vomiting, upper abdominal pain and postprandial fullness. There is no known cure for gastroparesis and the objective of this project is to relieve its symptoms**[1]**.

The treatment of patients is focused on dietary modification using low-viscosity test fibres and controlling the blood glucose levels in patients with diabetes through the use of prokinetic and antiemetic agents alone or in combination. The viscosometric properties of the test fibres will be measured using rheometry. The chemical properties of the fibres will be studied using mass spectrometry and 2-dimentional nuclear magnetic resonance spectroscopy (2D NMR). Unsuitable high-viscosity fibres will be phased out as candidates for the clinical trial and the most promising low-viscosity fibres will be selected for the clinical trial.

**Objective:**

To discover whether the consumption of low-viscosity dietary fibres by gastroparesis patients can lead to symptom relief and which among those selected dietary fibres are the most promising for recommendation for symptom treatment.

**Study plan:**

The project design utilises routine blood glucose measurements collected from the gastroparesis patients using three different test fibres one control sample consisting of water. The mouth-to-caecum transit time will also be measured using a H2 measurement probe. The intent of the clinical trial is to determine which low-viscosity dietary fibre provides the best symptom relief and why it does so. The rheological properties of each test fibre will be studied and characterised in detail. Further, the percentage composition and size of sugar units in each fibre such as mannose, dextrose and other fibre-specific sugars will be calculated using refractive-index chromatography and Q-ToF mass spectrometry. The structure of the fibres and its repeating sugar units will be characterised using 2D NMR if possible. Using statistical analysis and collating data from all these approaches we hope to provide as much information as possible for clinical practitioners who wish to alleviate gastroparesis symptoms using dietary fibres in the future.

**3. RATIONALE/BACKGROUND**

The most common sufferers are young adults, with the majority of them being women. People are known to suffer postviral gastroparesis, but there is a low level of evidence for this being the cause **[1, 2]**. Gastroparesis is also known to aggravate gastroesophageal reflux disease (GERD) **[1]**. Gastroparesis is known to cause delayed gastric emptying, nausea, vomiting, stomach fullness, bloating and loss of appetite. Due to these chronic symptoms, the day-to-day well-being and productivity of the sufferers is significantly affected.

Currently there is no known cure for gastroparesis and the best relief that any sufferer can look forward to is using gastric electric simulation (GES) and metoclopramide, which does not adequately address any day-today clinical needs. Antiemetics are also used by practitioners in order to alleviate symptoms such as nausea and vomiting. Unapproved medications include erythromycin and domperidone for short-term relief **[1]**.

There are many medications used to treat gastroparesis symptoms and delayed gastric emptying but they often come with harmful side effects. There is moderate level of evidence that uncontrolled glucose levels (>200 mg/dl) can lead to aggravation of gastroparesis symptoms **[3]**. Glycemic control for the treatment of gastroparesis symptoms through dietary modification using low-viscosity soluble fibres has not been attempted before. This approach is less harmful on the body than prescriptions and symptoms can be managed in a day-today basis.

The test fibres included in the study are guar gum, partially hydrolysed guar gum (PHGG), psyllium husk, oat bran and Arabica gum. These fibres have been commonly used in the treatment of delayed gastric emptying, constipation and irritable bowel syndrome (IBS) **[3, 4, 5]**. Fibres such as oat bran and psyllium husk have been used in the treatment of hypercholesterolaemia through glycemic control **[6, 7]**. Guar gum and partially hydrolysed guar gum have been studied in involving IBS and blood glucose levels in young men **[8, 9]**. Arabica gum has been used in combination with psyllium husk in constipation and incontinence clinical trials with significant effect **[10]**.

While the physiological effects of these dietary fibres are well understood, the chemical and physical properties of the fibres are not well known. The fibres are usually processed plant material and not well standardised. It is important that percentage composition of the sugar units in each fibre is listed in the commercial packaging if they are to be prescribed for gastroparesis patients. To this end, mass spectrometry using refractive index chromatography and Q-ToF mass spectrometry will be used for the standardisation of the fibre unit length in daltons and each method will be properly validated for future use. 2D NMR will be used to elucidate and confirm the structure of each fibre.

The rheological properties of the dietary fibres will be characterised under both normal and simulated gastric conditions using a rheometer. The rheological properties of these fibres have been studied before, but have not been extensively characterised **[11]**. The objective of this study is to bring together information about the fibres using physical, chemical and clinical techniques in order to provide the optimal amount of information for the clinical practitioner before they are prescribed for gastroparesis relief.

**4. AIMS/OBJECTIVE/HYPOTHESIS**

**Aim:**

To relieve gastroparesis symptoms using dietary modification

**Hypothesis:**

Consumption of low-viscosity soluble dietary fibres before a test meal can reduce gastroparesis symptoms such as delayed gastric emptying and lead to symptom relief.

**Objectives:**

1. Select appropriate test low-viscosity soluble test fibres as candidates for the gastroparesis symptom relief clinical trial using rheometry.
2. Monitoring the blood glucose level and mouth-to-caecum transit time the patients participating in the trial after they have been fed 10g of dietary fibre along with a test meal of 50g sugar.
3. Discover which test fibre is the most effective in relieving gastroparesis symptoms and whether this is due to physical and chemical properties that have been studied using the rheometry and mass spectrometry.
4. **PARTICIPATING SITES**

Macarthur Clinical School - Western Sydney University

**6. RESEARCH PLAN/STUDY DESIGN**

**6.1 Type of study:**

Research involving the collection and/or use of human blood for testing

**6.2 Rheometry of samples**

The rheological (visco-elastic) properties for each test fibre will be determined using a Dynamic Stress Rheometer (NO.SR-200, Rheometric ScientificTM). Fibres will be tested, at varying concentrations, under normal conditions (25oC, soluble in de-ionized water, pH 7) and simulated gastric conditions (37oC, soluble in gastric fluid, pH 2). A dynamic stress sweep protocol will be implemented, applying linear rotational force (torque) over a set range. The visco-elastic yield and cross-over points, at which the fibre structure transitions from solid-like properties into liquid-like properties, will be determined. The amount of force required to reach the cross-over point will provide information about the viscosity and consistency of our test fibres, and how they may react in the stomach once ingested. Quantitative properties of our test fibres will allow us to predict and correlate fibres with physiological changes in participants. Future work will aim to tailor soluble fibre diets with severity of gastroparesis symptoms by combining test fibres to achieve desirable visco-elastic consistency.

**6.3 Low viscosity fibre diet for gastroparesis patient**

The study will be a prospective, randomised study. A randomised sequence list of fibres will be provided to the tester on the day of the test, the participants will not know which fibre they are ingesting. Participants will need to fast overnight before conducting the test. During their first visit, a detailed history will be taken (GI disorders, diabetic history, food allergies), general characteristics (gender, height, weight) and general health (diet and exercise history). A base-line symptom (gastroparesis cardinal symptom index) and blood-glucose level (blood glucose meter) is established.

Participants are required to ingest 75g of glucose and test fibre with water **(Figure 1)**. Blood glucose concentration and symptom index are taken at 30min intervals over a 3 hour period. Traditionally, glucose concentration will peak around 30min and will subside in 2 hours, however, given the reduced gastric transit speed of gastroparesis patients we have increased the monitoring time to 3 hours. We have chosen to avoid measuring insulin concentration as the participants will consist of insulin sensitive, type I and II diabetics, therefore insulin concentration changes cannot be compared between participants as they produce and react differently to insulin. This also avoids the need for more invasive blood sample collection in favour of portable glucometers.



**Figure 1:** Participants will ingest a negative control (water), positive control (psyllium husk) and two low viscosity fibres (PHGG and acacia gum).

Following the test the participants will have a wash-out period of at least 3 days to remove all traces of test fibre from their system. Participants will be recommended to perform each test in consecutive weeks over a 4 week period. The data obtained from the four treatments (negative/positive controls and two test fibres) will be compared for statistical significance by Friedman’s test (treatment and subject), at P<0.05 when the results are significant and Wilcoxon pairwise comparison (control vs PHGG and control vs gum arabica) with Bonferroni correction applied if necessary.

**6.3 Mass spectrometry and NMR**

Little is known about the chemical structures of these soluble fibres. Currently, there are only estimates on the polysaccharide length of some fibres. We plan to investigate the percentage composition and size of the sugar units in each test fibre such as mannose, dextrose and other fibre-specific sugars by using refractive-index chromatography and Q-ToF mass spectrometry. The structures of each individual fibre unit and its constituent sugar units will be characterised using 2D NMR if possible. Using statistical analysis and data collation from all these approaches we hope to provide as much information as possible for clinical practitioners who wish to alleviate gastroparesis symptoms using dietary fibres. In addition, these techniques may whether reveal the structural characteristics contribute to a fibre’s beneficial effects. We will not go into specific detail of the protocol as it is not relevant to this ethics application.

**6.5 Outcome measurements**

**Demographics and background history**

Age, gender, BMI, gastroparesis, delayed gastric emptying, GI disorders, type 1 diabetes, type 2 diabetes, general diet and exercise.

**Sample collection**

Blood glucose monitoring, Gastroparesis cardinal symptom index

**6.7 Population/Sample size**

We wish to study 30 participants who are referred to the Campbelltown Hospital, Gastrointestinal Motility Unit for blood glucose measurements. The typical patient population will be an individual suffering from gastroparesis alone or in conjunction with type 1 or type 2 diabetes. Other studies involving fibres normally include between 60 to 120 patients, but the trial involved only one sample and control **[1]**. In this study the participants will experience 4 tests, once for each fibre and one control spread once week apart.

**6.8 Expected duration of study and start times**

The start time is anticipated to be 09 August 2017 with completion of the project expected to be 09 August 2020. The length of the study is expected to last for 3 years.

**7. ETHICAL CONSIDERATIONS**

**7.1 Recruitment and selection of participants**

Thirty patients referred for gastroparesis ailments are selected for dietary fibre pre-loading with water after the consumption of 50g glucose dissolved in 125mL of water. Dr Ho will initiate contact with the potential participants through social media (The Inside Story: Gastroparesis support group) by presenting them the patient information sheet during their pre-admission clinic appointment. Patients will have approximately one week to consider whether they wish to take part in the study. If the patient consents to provide regular blood glucose measurements during the test, the investigators will elaborate on the project and the participant’s involvement as well as answer any questions in detail. At the end of this meeting investigators will obtain informed consent by signature of the patient consent form if the participant is willing to participate in the study.

**7.2 Inclusion and exclusion criteria**

Inclusion criteria:

* Males and females 18 and over
* Able to provide verbal and written consent

Exclusion Criteria:

* Pregnant women and the human foetus
* People under the age of 18
* People with a cognitive impairment, an intellectual disability or a mental illness
* Participants who suffer from celiac disease and allergies to wheat based dietary products
* Participants who suffer from any severe ailment other than gastroparesis, type 1 and type 2 diabetes

**7.3 Informed consent**

Initial contact will be made through gastroparesis support group and the investigators will give an overview of the project's aims and methods as outlined in the information sheet that will be provided to them on site. If the patient is interested in the clinical trial, the details of the participant's involvement will be explained in full detail as well as the potential risks to being involved in the study. It will be made clear that participation in the study is voluntary and that the participant may withdraw at any stage with no detriment to their health care. The investigators will discern the understanding of the potential participants by asking them what they believe they are being asked to participate in. The investigators will also address any questions that arise regarding to the study. If the participants have any concerns or questions that arise at any stage in the future, they may contact the investigators to discuss those issues further.

Formal consent will be obtained on the day of the first dietary fibre test. Suitable amount of time is given to each participant to ensure that the information sheet and consent form is read by/to the participant, who may then indicate their voluntary participation by signing the consent form. The participant may choose to have a health care worker or family member present during the consent process.

**7.3 Confidentiality and Privacy**

The information needs to be individually identifiable, so as to compare the results of each test fibre and assign population groups in statistical meta-analysis. Confidentiality and privacy of this information will be strictly maintained using the measures outlined in section 7.4 for data storage and retention.

**7.4 Data storage and Record retention**

The information collected on paper survey copies of participant information will be physically locked up in a physical cabinet located in the office of the Macarthur Clinical School, Western Sydney University. The electronic records will be secured under password protection and encryption on computers stored at and belonging to the School of Medicine, Western Sydney University. Only the investigators will be able to access to this information on site in order to ensure confidentiality and privacy for the participants.

The information will be closely monitored by the principal investigators/researchers. If the confidentiality of participants is violated it will be immediately reported to the central monitoring committee. The information collected will be retained for 15 years after the completion of the project. At the end of 15 years the paper copies will be shredded and disposed while electronic data will be deleted.

**8. OUTCOMES AND SIGNIFICANCE**

The results of this study will potentially characterise whether routine consumption of low-viscosity soluble dietary fibres provide patients suffering from gastroparesis symptom relief. The rheological properties of these dietary fibres will be measured and percentage composition of their sugar units will also be determined using mass spectrometry. The structures of the dietary fibres will also be determined using 2D NMR if possible.

**9. TIMELINES**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Month | 1-9 | 9-12 | 12-18 | 18-24 | 24-30 | 30-33 | 34-36 |
| Dietary fibre selection and initial rheometry |  |  |  |  |  |  |  |
| Rheometry under simulated gastric conditions |  |  |  |  |  |  |  |
| Patient recruitment and clinical data collection |  |  |  |  |  |  |  |
| Mass spectrometry and 2D NMR |  |  |  |  |  |  |  |
| Data analysis |  |  |  |  |  |  |  |
| Write up |  |  |  |  |  |  |  |

**10. PUBLICATION POLICY**

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participants cannot be identified. It is anticipated that the results of the research project will be presented at local and international conferences, published as a research article in a gastric research or food science journal. A copy of this will be made available to participants on request.

**11. REFERENCES**

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