Carolyn Costigan

College of Radiographers Doctoral Fellowship 004

£24,206.13 awarded

Title: MRI assessment in newly diagnosed coeliac disease and following gluten-free diet treatment.

Principle Aim

Based on our pilot data and on the literature available, this study aims to test the main hypotheses that in adults newly diagnosed with coeliac disease treatment with gluten-free diet (GFD) will:

1. reduce the water content of the fasting small bowel
2. reduce the volume of the fasting colon
3. increase whole gut transit time

Objectives

The specific objectives of the study are to quantify any change following treatment with a GFD in:

1. the water content of the fasting small bowel
2. fasting colon volume
3. whole gut transit time
4. in adults newly diagnosed with coeliac disease using non-invasive MRI

This study will also include a parallel pilot study involving healthy volunteers (HVs) frequency matched for age (in 20 years bands) and gender, to provide descriptive statistics on a likely reference range for the healthy population to inform the design of future studies.

Outcomes

We expect this study to answer important questions about the relationship between some aspects of bowel function and the symptoms that coeliac patients experience. Understanding how these factors interact and the effects of gluten-free diet will improve our understanding of the disease.

It could also offer novel and significant insights into the complex mechanisms surrounding the persistence of symptoms in patients with treated coeliac disease, and could pave the way for future treatment studies.

Review of literature and identification of current gap in knowledge

Coeliac disease affects 1 in 100 people, i.e. over 600,000 in the UK. It is an autoimmune disease induced in genetically susceptible individuals after ingestion of gluten. Histological features include total villous loss (initially blunting, progressing to flattened mucosa). Additionally, serum endomysial antibodies may be raised.

The small bowel mucosa is primarily affected (submucosa, muscularis and serosa remain normal), resulting in progressive degrees of villous inflammation and destruction (which starts in the duodenum and extends into the ileum) with resulting induction of crypt hyperplasia. There is no cure and no medication and the only treatment is a strict gluten-free diet for life. Previously, when the diagnosis of coeliac disease was based exclusively on clinical observations, almost all patients were reported to present with clinically overt malabsorption.

Classic accounts emphasised severe disease with major constitutional upset including anaemia, steatorrhoea, profound weight loss, hypoproteinaemia, osteomalacia and or tetany [1, 2]. This generalised small bowel hypomotility with abnormal jejunum dilatation [3] was thought to be functional due to impaired motor response to jejunal distension [4, 5].

Contemporary observational studies involving manometric, breath test and camera pill measurements have independently observed an underlying gastrointestinal motility disorder in coeliac disease. Oesophageal transit, gastric, gallbladder emptying, and oro-coecal transit time are delayed [6-10] and some of the abnormalities can reverse after treatment with gluten-free diet (GFD) [7].

GFD results in recovery of the small bowel mucosa and reversal of the enteropathy [11-16]. Despite a long-term and strict adherence to a GFD, some patients have been reported to have persistent gastrointestinal symptoms [17-20]. Assessing fluid volumes in the small bowel and whole gut transit, their relationship with symptoms and changes induced by GFD would provide novel understanding of mechanism of disease and effects of treatment. However this has proven difficult so far due to limitations and use of ionising radiation of previous methods. Magnetic resonance imaging could provide these assessments, noninvasively in a single scanning session.

Preliminary data:

Our team at the University of Nottingham has recently developed a unique magnetic resonance imaging (MRI) method and semi-automated analysis protocols to non-invasively measure the luminal water content of the small bowel water or "small bowel water content (SBWC)", which has been validated against naso-duodenal infusions [24]. We used this method to assess fluid volumes in the fasting small bowel of healthy volunteers and patients with irritable bowel syndrome with diarrhoea [22], and changes with feeding and drug intervention [23].

Pilot data from our laboratory indicates that the water content of the fasting small bowel is increased in adults newly diagnosed with coeliac disease compared to a group of healthy volunteers [24]. Figure 1 shows one coronal 'small bowel water content' MRI image of the abdomen of a healthy volunteer and of a coeliac patient. These MRI images are strongly 'T2 weighted' which means they show very little signal from tissue and very bright signal from freely mobile fluid.

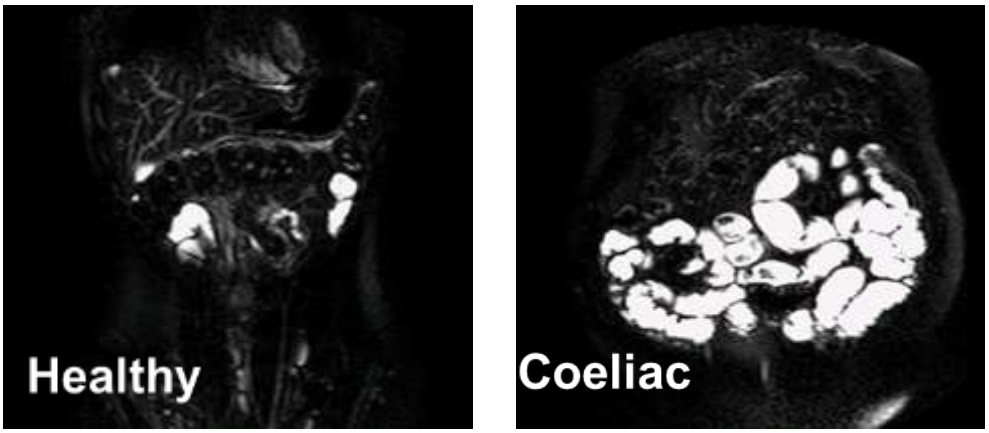


Figure 1: image from the coeliac patient shows a substantial volume of fluid resting in the fasted small bowel

MRI imaging is also widely used to measure organ volumes. Within research conducted during a study of IBS patients (06GM006) and on the mode of action of Moviprep (10/H0906/50), the University of Nottingham has recently developed protocols to measure regional colonic volumes from coronal dual-Fast Field Echo imaging [25] as briefly illustrated in Figure 2.

Pilot data from our laboratory also indicates that the volume of the fasting colon in adults newly diagnosed with coeliac disease correlates with disease severity [24].

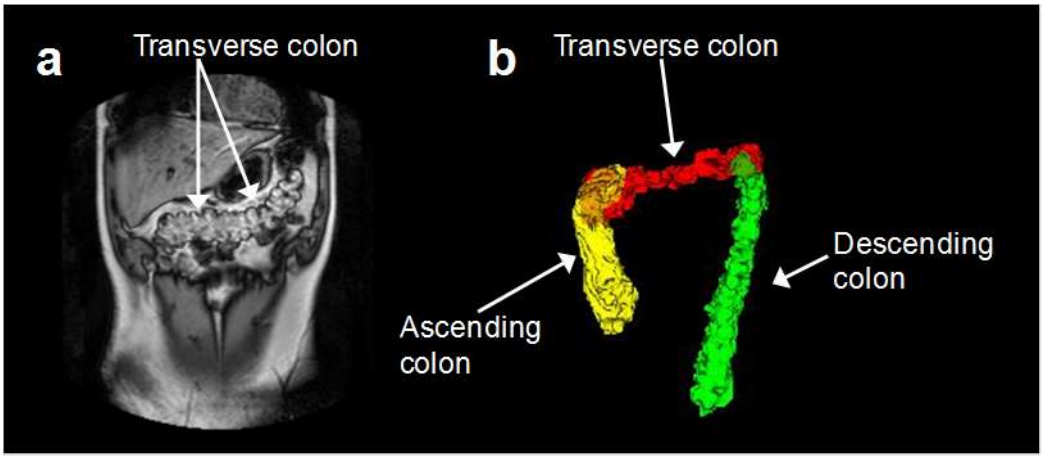


Figure 2: (a) Coronal 'dual FFE' MRI image of the transverse colon of a healthy volunteer taken at fasted baseline. (b) Three-dimensional reconstruction of the different regions (ascending, transverse and descending) of the colon of another healthy volunteer.

With MRC funding our research group has also recently completed validation of a measure of whole gut transit time using MRI localisation of MRI transit marker capsules made of polyoxymethylene, a biologically inert substance [26].
The patients swallow a few inert plastic MRI transit markers filled with water and traces of common MRI contrast agent. The capsules are inert, the size of an adult super-vitamin pill and do not interact with the body. 24 hours later they attend for a 10 minute MRI scan to locate the pills in the gut (Figure 3B). We can calculate the whole gut transit time by scoring the position of the markers in the gut according to a simple position scoring card (Figure 3A) and calculating a weighted average position, as validated against conventional X-ray methods [26].
We do not have pilot data on gastrointestinal transit in coeliac disease. However, data available in the literature suggests that gastrointestinal transit is delayed in coeliac disease.

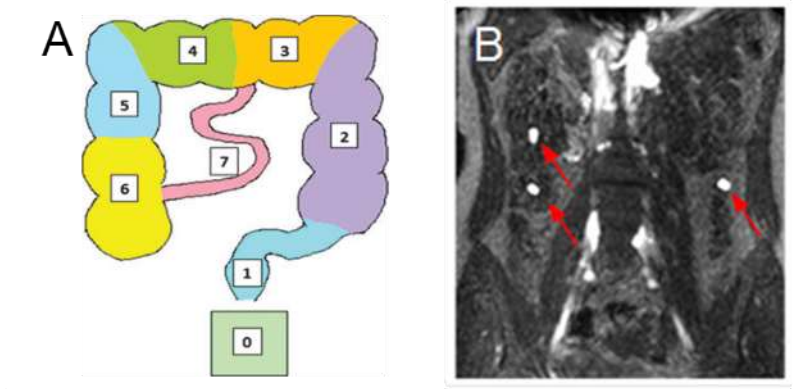


Figure 3: (A) Diagram used to score the location of the MRI transit markers in the bowel and (B) Image of 3 MRI transit markers in the colon of a volunteer, indicated by the red arrows

Methodology

Patient participants will be recruited through specialist clinics at Nottingham University Hospitals NHS Trust. The initial approach will be from a member of the patient's usual care team (which may include the investigator).

General advertisement for participants in the healthy volunteer group will take place in parallel, on the campuses of the University, including the Cripps Health Centre (primary care), and Nottingham University Hospitals, by poster. We will also recruit using social media such as the Nottingham Digestive Diseases Unit Facebook and Twitter accounts. The advertising copy has been approved by the Research Ethics Committee and the NUH Research and Development department.

Eligibility criteria

- 36 participants newly diagnosed with Coeliac disease before starting treatment with a gluten free diet
- 36 participants who do not meet criteria for a clinical diagnosis of Coeliac disease (healthy volunteers) as determined by screening blood sample.

Criteria for diagnosis

Patient on a gluten-containing diet, IgA-TG2 or IgA-DGP, or IgG-DGP, EMA positive and duodenal biopsy showing villous atrophy

Pilot study in patients

Inclusion criteria:

- Patients newly diagnosed with coeliac disease
- Aged 18-65
- Male or female
- Able to give informed consent
- Able to schedule the first MRI scan (Visit 2 of the study) within a month of having had a duodenal biopsy.

Pilot study in healthy volunteers

Inclusion criteria:

- Healthy volunteers (without any co-morbidities)
- Aged 18-65
- Able to give informed consent

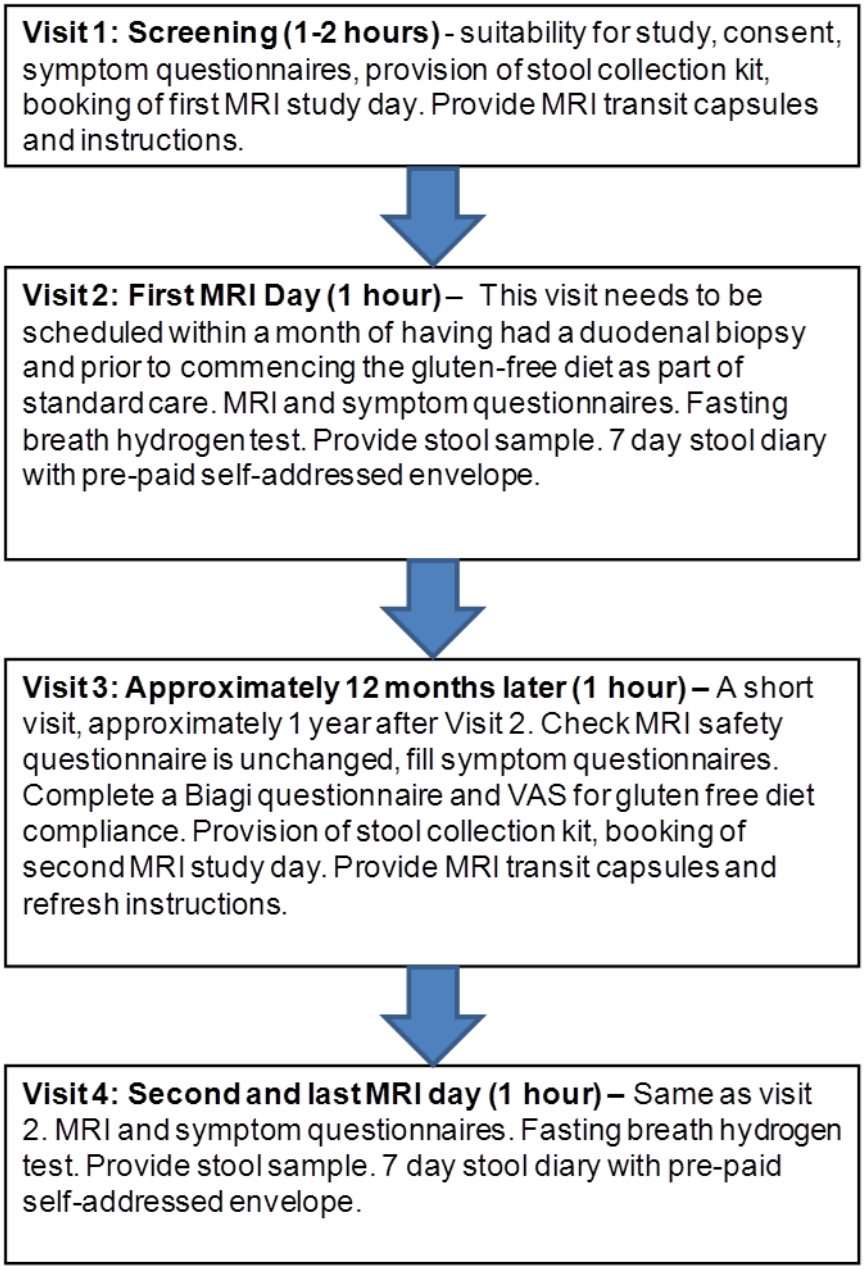
From enrolment, participants will be invited for their first MRI study day within a month, and their second approximately 12 months later. This will give a maximum duration of involvement of approximately 13 months.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study.

Details of study involvement for coeliac patients

This study consists of 4 visits to the Hospital or the MRI site, Sir Peter Mansfield Imaging Centre, University of Nottingham.

Schematic diagram of study involvement for coeliac patients

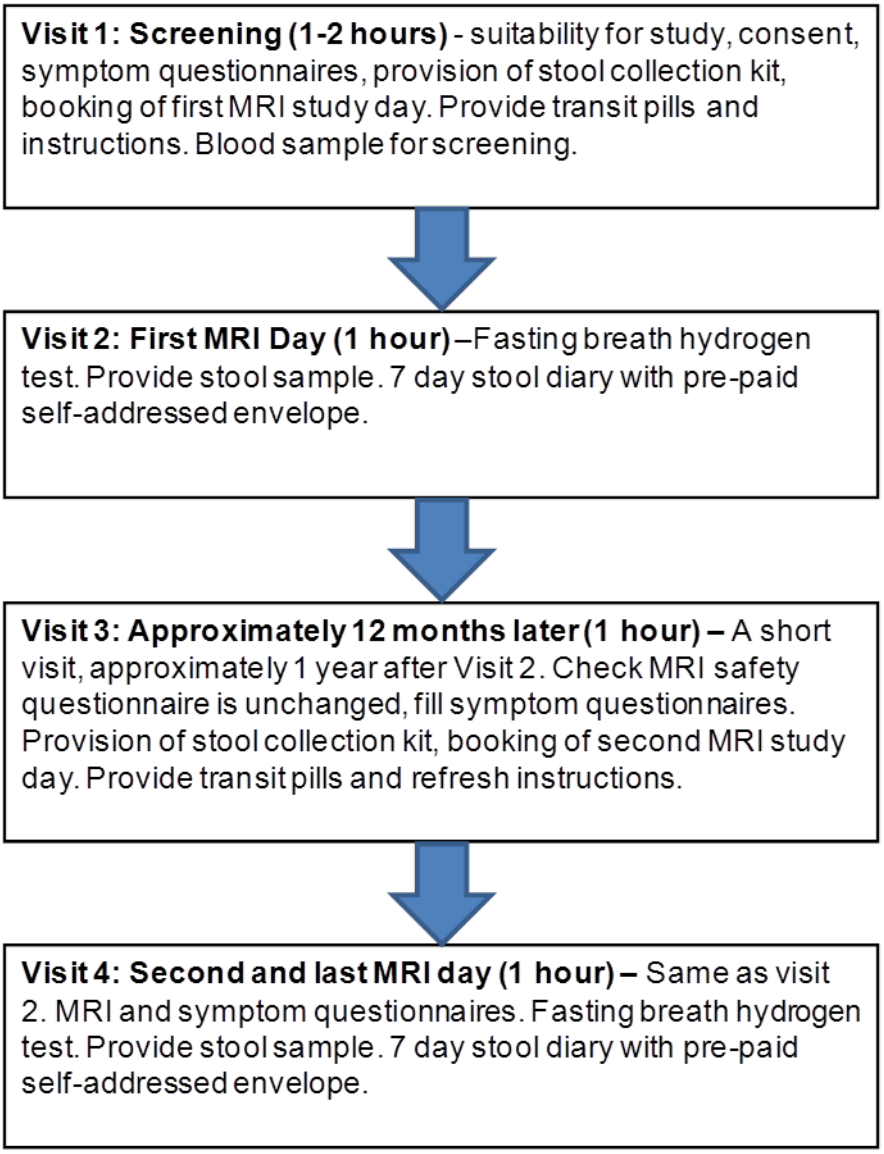


<u>Details of study involvement for healthy volunteers</u>

The healthy volunteer study consists of 4 visits to the Hospital or the MRI site, Sir Peter Mansfield Imaging Centre, University of Nottingham.

Healthy volunteers will not be asked to follow a gluten-free diet (GFD).

Schematic diagram of study involvement for healthy volunteers



Compliance

Compliance with GFD will be assessed using the Biagi score [27].

Analysis

Data will be recorded on paper Case Report Forms/ Study Forms and then transcribed to an SPSS database.

All data management and statistical analysis will be carried out using SPSS 22 (IBM) with assistance from the study statistician. The basic characteristics of the study population would be calculated using frequencies and proportions.

Potential impact

Assessment of changes in small bowel water volume and colon organ volumes with gluten free diet may help explain the mechanisms driving gastrointestinal symptoms and their persistence.

Such observations would also allow clinicians a more informed discussion with patients on likely cause and course of their symptoms with treatment. In the future, this may impact on guidelines for how CD is managed.

MRI could also allow evaluation of the effectiveness of new treatments without costly and invasive repeat biopsies and ultimately lead to more efficient use of resources in a budget constrained system.

Dissemination Strategy

The results of this trial will be presented at national and international scientific meetings including Digestive Disease Week® (DDW), the largest and most prestigious meeting in the world for GI professionals and the International Society of Magnetic Resonance in Medicine annual meeting. They will also be submitted for publication in peer-reviewed journals including Radiography, the official professional journal of the College of Radiographers.

The research will also be shared at the Coeliac UK's bi-annual research conference which is attended by healthcare professionals and patients and families affected by coeliac disease. We will also use existing social media groups on Facebook and twitter to allow us to disseminate to traditionally hard to reach groups such as teenagers.

The study also comprises one part of the work for Ms Carolyn Costigan's PhD thesis and will be reported in part or in whole within that submission.

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