Faecal Lactoferrin, Capsule Endoscopy and Crohn’s Disease. Is there a Three Way Relationship? A Pilot Study

Reena Sidhu¹, David S Sanders¹, Perm Wilson², Laura Foye³, Stephen Morley², Mark E McAlindon¹

1) Gastroenterology & Liver Unit; 2) Department of Clinical Chemistry, Royal Hallamshire Hospital, Sheffield, United Kingdom.

Abstract

Background & Aims: Capsule endoscopy has been shown to be useful in diagnosing small bowel Crohn’s disease. Faecal lactoferrin has been shown to have a high sensitivity and specificity in discriminating between inflammatory bowel disease and irritable bowel syndrome. There have been no studies on the use of faecal lactoferrin in the setting of suspected Crohn’s disease using capsule endoscopy. Our aim was to investigate the clinical utility of lactoferrin in patients with suspected Crohn’s disease using capsule endoscopy. Methods: Data was collected prospectively on patient symptoms, family history and blood parameters. Patients were requested to return a stool sample and quantitative analysis using sandwich ELISA was performed for faecal lactoferrin. Results: Seventeen patients were recruited with all patients having more than one criterion for referral. The diagnostic yield for capsule endoscopy was 41%, of which 71% of patients had an elevated faecal lactoferrin (correlation coefficient 0.56, p=0.01). The sensitivity, specificity, positive predictive value and negative predictive value of faecal lactoferrin were 71%, 100%, 100% and 83%, respectively. Conclusion: Faecal lactoferrin has a high positive and negative predictive value for the diagnosis of small bowel Crohn’s disease, detected by capsule endoscopy. Faecal lactoferrin is a useful marker (in conjunction with clinical parameters) to determine which patients should be referred for capsule endoscopy.

Key words


Introduction

Patients with Crohn’s disease can present with a variety of symptoms including altered bowel habit or abdominal pain [1]. These symptoms can be similar to those of irritable bowel syndrome (IBS) and can even be confused with this entity. Thus, the reported mean delay of 1-7 years for the diagnosis of Crohn’s disease is unsurprising [2, 3].

Ileo-colonoscopy and biopsy is considered to be the gold standard for the investigation of colonic Crohn’s disease whilst small bowel radiology (small bowel barium meal/enema and more recently CT and MR enterography) is useful to detect the presence of strictures, dilatations and fistulae and provides the clinician with an estimated length of small bowel involvement [4].

Capsule endoscopy (CE), a novel and wireless method of investigating the small bowel [5] uses a remote instrument that is swallowed and propelled through the gastrointestinal tract by the action of peristalsis [5]. The capsule contains an imaging device, which transmits images of the intestine to sensors on the abdominal wall. It has the ability to detect diffuse mucosal disease but without the inadvertent radiation exposure. Numerous studies have compared the utility of small bowel radiology to CE for the investigation of Crohn’s disease [6, 7]. A recent meta-analysis showed that CE is superior to small bowel radiology, CT enterography and ileo-colonoscopy in the setting of suspected Crohn’s disease [8]. Capsule endoscopy has now developed an established role in the investigation pathway of small bowel Crohn’s disease [9].

Lactoferrin (LF) is an iron binding glycoprotein secreted by most mucosal membranes and a major component of secondary granules of polymorphonuclear neutrophils, a component of the inflammatory response [10, 11]. A number of studies have investigated the use of lactoferrin as a non invasive marker in the distinction of inflammatory bowel disease (IBD) and non inflammatory conditions. Whilst a high sensitivity of LF has been reported for active IBD in comparison to IBS, the distinction of inactive IBD and IBS is less clear [12-15].

Clinical indices for IBD (such as Harvey Bradshaw Index and Crohn’s Disease Activity Index) [16, 17] are widely
used but are hampered by the subjective nature of symptom reporting and recall bias. These indices have also been shown to be poorly correlated with mucosal activity [18,19]. Serological inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are helpful but have been shown to be not entirely reliable [20-22].

In the absence of a diagnostic colonoscopy or small bowel radiology, this group of patients with overlapping symptoms often pose a diagnostic challenge to clinicians. Hence for some time there has been a search for non invasive tests to diagnose small bowel Crohn’s disease. There remains a gap in the literature on the combined use of LF and CE for the investigation of small bowel Crohn’s disease.

The aim of this study was to investigate the utility of both faecal lactoferrin and CE for the diagnosis of small bowel Crohn’s disease compared to inflammatory markers such as C reactive protein.

Methods

Patients

Consecutive patients referred for CE on an outpatient basis for suspected Crohn’s disease were recruited. Data was collected on patient symptoms including the presence of abdominal pain, weight loss, diarrhoea, abdominal mass, extra-intestinal manifestations or family history of IBD. All patients had had a non diagnostic colonoscopy prior to CE referral. In addition, all patients had investigation of blood parameters: full blood count, albumin and C reactive protein (normal CRP <7). Patients were also asked about non-steroidal antiinflammatory drugs (NSAIDs) ingestion in the three months proceeding recruitment into the study.

Stool analysis

Patients were requested to return a stool sample in a container provided. Analysis was performed blind to the clinical details of the patient. Stool samples were frozen at -20°C immediately on receipt. Quantitative ELISA (IBD SCAN) faecal lactoferrin test was performed on each thawed sample. A cut off level of >7.25 µg/g was deemed positive, based on the manufacturers guide.

Capsule endoscopy

The description of CE is well reported in the literature (Pillcam SB, Given Imaging, Yoqneum,Ltd) [5]. Patients were fasted overnight for 12 hours after ingestion of two sachets of polyethylene glycol solution (Kleen-Prep, Norgine). Written informed consent was obtained in all patients and the study was approved by the Sheffield Ethics Committee. Patients were allowed to drink 2 hours after and eat a light snack 4 hours after ingestion of the capsule. The sensor array and recorder pack were disconnected after 8 hours and images were downloaded to a workstation. All videos were analysed by an experienced Consultant Gastroenterologist (MEM) who was blinded to the indication for CE and the result of the stool analysis. There are currently no validated criteria for the diagnosis of Crohn’s disease on CE. Hence we adopted the most commonly used diagnostic criterion of more than 3 ulcers with erythema or oedema on CE [23].

Statistical analysis

The data was analysed using SPSS. Kendall–Tau correlation calculations were performed between LF concentrations and CE findings.

Results

Seventeen patients were recruited with 59% female, average age 45.6 years (range 19-73). All patients had more than one criterion for referral (symptoms/ family history or elevated blood parameters) as detailed in Table I. No patients were on NSAIDs. The diagnostic yield of CE for small bowel ulceration was 41.2%. In the group of patients with evidence of small bowel ulceration on CE, 71% percent of patients had an elevated LF level. The correlation co-efficient between the positive capsule findings and faecal LF levels was 0.6 (p=0.03). Fig. 1 shows a comparison of LF levels in patients with a normal CE versus those with ulceration seen on CE. In the group with a positive capsule endoscopy, a significantly greater number of patients had elevated LF levels compared to an elevated CRP (71% versus 43%, p=0.04) as tabulated in Table II. The median LF levels in patients with a positive CE was 11.9 µg/g. (+ IQ 23) whilst the median LF levels in patients with a normal CE was 0 µg/g (+IQ 2.2).

Table I. Patient symptoms and parameters

<table>
<thead>
<tr>
<th>Patient symptoms and parameters</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (65%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Extra-intestinal manifestations</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>Family history of inflammatory</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>bowel disease</td>
<td></td>
</tr>
<tr>
<td>Elevated platelet count</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Elevated C reactive protein</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Elevated erythrocyte</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>sedimentation rate</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (24%)</td>
</tr>
</tbody>
</table>

Table II. Capsule endoscopy with corresponding faecal lactoferrin and C reactive protein levels

<table>
<thead>
<tr>
<th>Capsule endoscopy with findings of ulceration (n=number of patients)</th>
<th>Normal capsule endoscopy (n=number of patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Faecal Lactoferrin</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Normal Faecal Lactoferrin</td>
<td>2</td>
<td>0.003</td>
</tr>
<tr>
<td>Elevated C reactive protein</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Normal C reactive protein</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of LF using the quantitative analysis was 71%, 100%, 100% and 83%, respectively.

Alteration of bowel habit particularly diarrhoea is a common symptom amongst patients with IBD and IBS. In this study, 88% (n=15) of patients had symptoms of diarrhoea. However CE was normal in 10 of these patients. The combination of diarrhoea and elevated CRP provided a sensitivity of 29% for the detection of small bowel ulceration on CE in this study.

The subsequent management was altered in 6 patients who were treated as Crohn’s disease with either 5 ASA drugs (n=3), a combination of 5 ASA and budesonide (n=1), budesonide and 6 mercaptopurine (n=1) and azathioprine alone (n=1). A watch and wait policy was adopted in the remaining patient. In 4 patients, subsequent enteroscopy and biopsies supported the diagnosis of Crohn’s whilst despite the presence of ulcers on enteroscopy, biopsies were normal in 2 patients.

Discussion

The identification of small bowel lesions/ulcers in patients with suspected Crohn’s disease is crucial to prevent a delay in diagnosis and aid clinical decisions and strategies. Capsule endoscopy offers a non invasive technique with a high diagnostic yield (40-70%) [24, 25] for the detection of small bowel Crohn’s disease whilst avoiding radiation exposure to a cohort of patients who are often young and of child bearing age. Lactoferrin has been a useful marker to detect the presence of gastrointestinal inflammation [13, 14, 25, 26]. This study evaluated the relationship between LF and findings of small bowel ulceration on CE. The results of this study support that LF is a useful non invasive marker to predict patients who may have evidence of small bowel ulceration consistent with Crohn’s disease on CE. The yield of 40% for the detection of small bowel ulceration using CE is comparable to that in the published literature [24, 27].

This is the first study in adults to use the combination of these two non invasive tests for the investigation of suspected small bowel Crohn’s disease. As with other imaging modalities, a diagnosis of Crohn’s disease should not be made on CE appearances alone [23]. In our study, we used a diagnostic criterion of a minimum of three ulcers (in the absence of NSAIDs) with the presence of oedema and erythema on CE in combination with positive patient symptoms and family history/ blood parameters to make a diagnosis compatible with Crohn’s disease. We also assessed the impact of CE findings on subsequent management of patients and enteroscopy and histology were performed in the majority of patients.

In this study, all patients recruited did not have a history of NSAID ingestion. Ulceration seen on CE in patients that are on regular NSAIDS should be interpreted with caution. Goldstein et al investigated the incidence of small bowel injury in healthy subjects receiving celecoxib or ibuprofen plus omeprazole by using CE, with correlation to faecal calprotectin levels [28]. The authors found, apart from significantly higher levels of mucosal breaks in the ibuprofen group (compared to the placebo and celecoxib group), the mean faecal calprotectin levels were also higher in the ibuprofen group. However, there was no correlation between faecal calprotectin levels and degree of small bowel lesions [28]. The relationship between CE, LF and NSAIDs has yet to be investigated.

C-reactive protein is an acute phase protein produced by the liver in response to inflammation, infection and tissue injury [29]. In this study, LF had a higher sensitivity than CRP for the detection of small bowel ulceration. Previous studies have demonstrated that the correlation between CRP and disease activity can be inconsistent [30].

A limitation of this study is the small number of patients recruited. We believe that despite the small number, our preliminary results are encouraging in this group of suspected Crohn’s disease which is often a diagnostic challenge to the clinician.

In our study, LF has demonstrated to have a high PPV and NPV for the diagnosis of small bowel Crohn’s disease, detected by CE. Arguably despite the small numbers, LF is a useful marker (in conjunction with clinical parameters) to determine which patients should be referred for CE. Larger studies are required to validate these results.

Conflicts of interest

No conflict of interest.

Acknowledgment

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Contribution

RS designed the study. All authors were involved in the
References


