Reflux oesophagitis in adult coeliac disease: beneficial effect of a gluten free diet

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Background: Coeliac disease patients show a number of gastrointestinal motor abnormalities, including a decrease in lower oesophageal sphincter pressure. The prevalence of endoscopic oesophagitis in these subjects however is unknown.

Aim: To evaluate whether untreated adult coeliac patients had an increased prevalence of reflux oesophagitis and, if so, to assess whether a gluten free diet exerted any beneficial effect on gastro-oesophageal reflux disease (GORD) symptoms.

Patients and methods: We retrospectively studied 205 coeliac patients (females/males 153/52, median age 32 years) who underwent endoscopy for duodenal biopsy and 400 non-coeliac subjects (females/males 244/156, median age 37 years) referred for endoscopy for upper gastrointestinal symptoms. Each patient was given a questionnaire for evaluation of GORD symptoms prior to and 4–12 months after endoscopy. Coeliac patients were given a gluten free diet. Oesophagitis patients of both groups, following an eight week course of omeprazole, were re-evaluated for GORD symptoms at four month intervals up to one year. Significance of differences was assessed by Fisher’s exact test.

Results: Oesophagitis was present in 39/205 (19%, 95% confidence interval (CI) 13.8–25.0%) coeliac patients and in 32/400 (8%, 95% CI 5.5–11.1%) dyspeptic subjects. At the one year follow up, GORD symptoms relapsed in 10/39 (25.6%, 95% CI 13–42.1%) coeliacs with oesophagitis and in 23/32 (71.8%, 95% CI 53.2–86.2%) non-coeliac subjects with oesophagitis.

Conclusion: Coeliac patients have a high prevalence of reflux oesophagitis. That a gluten free diet significantly decreased the relapse rate of GORD symptoms suggests that coeliac disease may represent a risk factor for development of reflux oesophagitis.

Abbreviations: GORD, gastro-oesophageal reflux disease; LOS, lower oesophageal sphincter; EMA, endomysium antibodies.
Endoscopy
Oesophagitis was defined as one (or more) mucosal break on the top of the folds of the distal oesophagus, identified during partial air inflation. Severity of oesophagitis was assessed according to the Los Angeles classification system. Each patient was also evaluated for *Helicobacter pylori* infection by rapid urease test and histology by a modified Giemsa staining. Diagnosis of *H pylori* infection was based on positivity on both histology and the rapid urease test.

24 hour oesophageal pH monitoring
In 15 coeliacs with oesophagitis who agreed to undergo the procedure, a 24 hour pH recording was performed to detect acid pathological reflux. Patients had not been taking proton pump inhibitors, H2 receptor blocking agents, or prokinetic drugs for at least eight weeks prior to the test. Data analysis showed that coeliac patients with oesophagitis had LOS pressures lower than those observed in our control population consisting of 10 healthy volunteers (18.1 (5.2) vs 21.5 (6.1) mm Hg, respectively). Such a difference reached statistical significance.

24 hour oesophageal pH monitoring
We performed dynamic pH recording in 15 of 39 coeliac patients with oesophagitis who agreed to undergo this procedure, before treating them with omeprazole. Data analysis showed the presence of GORD (percentage of total reflux time below pH 4 9.1 (2.3)% in 14/15 patients (table 4). In particular, supine reflux time was 2.2 (0.7)% and upright reflux time was 12.1 (3.5)%.

Statistical analysis
Significance of differences was assessed by Fisher’s exact test and ANOVA or Student’s t test for unpaired observations, as appropriate. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Endoscopy
Oesophagitis was found in 39/205 (19%), 95% confidence interval (CI) 13.8–25.0% on coeliac subjects and in 32/400 (8%, 95% CI 5.5–11.1%) dyspeptic patients (p<0.0001) (fig 1). Hiatal hernia was endoscopically detected in 43/205 (20.9%) coeliac subjects and in 32/400 (8%, 95% CI 5.5–11.1%) dyspeptic patients (p<0.0001) (fig 1). Moreover, 15/39 (38.5%) coeliac patients with oesophagitis and 13/32 (40.6%) non-coeliac oesophagitis patients were infected with *H pylori*, as determined by positivity on both histology and the rapid urease test.

24 hour oesophageal pH monitoring
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In particular, oesophageal motor abnormalities of the upper gastrointestinal tract. Untreated coeliac disease has been shown to be associated with a number of motor abnormalities of the upper gastrointestinal tract. In particular, oesophageal motor abnormalities and manometrical abnormalities were observed in 50% and 30% of 30 untreated coeliac patients, respectively. Moreover, untreated coeliac subjects show a significant decrease in LOS pressure. However, whether adult coeliac patients are more susceptible to reflux oesophagitis is still unknown. To address this issue, we retrospectively studied 205 adult coeliac disease patients and 400 non-coeliac adult subjects with upper gastrointestinal symptoms as a control group. We found a twofold increase in the prevalence of endoscopic oesophagitis in adult patients who had been diagnosed with coeliac disease compared with control non-coeliac subjects. The increased prevalence of oesophagitis was associated with an increased prevalence of GORD related symptoms even though this did not reach statistical significance. The prevalence of GORD related symptoms in our control population of dyspeptic subjects (that is, 30.2%) was similar to that reported in the literature. In fact, Locke et al and Valle et al described a prevalence of heartburn ranging from approximately 18% to 45%, depending on whether symptoms were experienced at least weekly or only occasionally, respectively. Moreover, the prevalence of oesophagitis found in our control group (that is, 8%) is comparable with that described in an Italian multicentre survey of a large patient population undergoing routine endoscopy (that is, 8.6%).

Interestingly, the prevalence of hiatal hernia was comparable in the two groups of patients, thus making it unlikely that the increased prevalence of oesophagitis in coeliacs might be due to alteration of the physical barrier to acidic reflux from the stomach. We also studied the 24 hour pH metry profile in 15 coeliac patients with oesophagitis without hiatal hernia and found pathological reflux in 14/15 subjects.

Based on these results, the question arose as to whether the increased prevalence of oesophagitis in coeliac patients might be related to the underlying disease. To this end we retrospectively evaluated the relapse rate of GORD related symptoms in oesophagitis patients both with and without coeliac disease, after they had been treated with omeprazole 20 mg twice daily for eight weeks. Oesophagitis patients with coeliac disease were also given a gluten free diet. Approximately 70% of oesophagitis patients without coeliac disease compared with 25% of oesophagitis patients with coeliac disease showed recurrence of GORD related symptoms (p<0.0001). The decreased recurrence of GORD related symptoms in oesophagitis patients with coeliac disease on a gluten free diet compared with oesophagitis non-coeliac patients suggests that coeliac disease may play a role in the pathogenesis of GORD.

The results of our study are apparently in contrast with those of Oderda et al who, in a paediatric population, found an increased prevalence of oesophagitis in coeliac children compared with control non-coeliac subjects. The apparent discrepancy with our study might be due, at least in part, to the fact that they included all coeliac children, irrespective of whether they were on a gluten containing diet or a gluten free diet. In fact, coeliac children on a gluten free diet had a very low prevalence of mucosal damage and the prevalence of peptic oesophagitis was significantly higher in coeliac children on a gluten containing diet compared with coeliac children on a gluten free diet (15% vs 4%, respectively). This supports our findings, including the beneficial effect exerted by a gluten free diet on GORD symptoms in coeliac subjects with oesophagitis.

The mechanism whereby coeliac disease may predispose to the development of oesophagitis is only hypothetical. An increase in plasma levels of enteroglucagon and neurotensin, which are known to decrease LOS pressure and delay gastric emptying, has been demonstrated in coeliac patients. One may therefore hypothesise that untreated coeliac disease patients are more susceptible to the development of oesophagitis due to a derangement of the gastrointestinal hormone profile which may eventually lead to a decrease in LOS pressure together with delayed gastric emptying. That LOS pressure values in coeliac patients with oesophagitis were lower than in healthy control subjects is in partial support of our hypothesis.
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Other factors might be involved in the increased prevalence of oesophagitis in coeliac patients. Recently, reflux oesophagitis has been shown to be associated with a Th1-type pro-inflammatory response as opposed to a Th2 predominant response observed in Barrett's oesophagus. Similarly, small bowel damage in the course of coeliac disease is believed to be caused by a Th1/Th2-type proinflammatory response developed by CD4+ gluten sensitive T cells. This suggests that specific gastrointestinal mucosa immune responses to a noxious agent may influence disease development and progression and may explain the increased prevalence of oesophagitis in coeliac patients.

In conclusion, coeliac patients have a high prevalence of endoscopic oesophagitis which does not seem to be accounted for by alteration of the physical barrier to acidic reflux. That a gluten free diet decreased the relapse rate of GORD related symptoms suggests that oesophagitis might be directly related to the underlying coeliac disease through a mechanism as yet not identified. A prospective study is underway in our unit to confirm our retrospective observation and to correlate small bowel lesions and relapse of GORD related symptoms in coeliac patients with oesophagitis. Based on our study, a thorough examination of the duodenum at endoscopy is warranted in subjects with reflux oesophagitis.

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