Gall bladder and gastric dysmotility shown by EPI in celiac disease is associated with abnormalities of 5-HT metabolism

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Introduction

Celiac disease (allergy to gluten), which may present with a range of gastrointestinal (GI) symptoms [1], is characterised by villous atrophy and hyperplasia of enterochromaffin cells [2]. Circulating levels of serotonin (5-HT) are also increased [3], which may have important effects on GI sensation and motility, acting on extrinsic afferent nerves via 5-HT_3 receptors. Untreated celiac disease is often accompanied by a marked disturbance of GI function in terms of gastric emptying, antral motility and gallbladder contraction [4]. MRI, and in particular EPI, showed great promise in monitoring gastric function and could encompass in one single multi-slice volume scan both the gastric lumen and the gallbladder.

Aims

The aim of this study was to examine gastric and gallbladder motility in patients with untreated celiac disease using EPI and to assess, in a separate study, circulating 5-HT levels together with mucosal 5-HT turnover.

Materials and methods

SUBJECTS: We recruited three groups: (**a**) 18 celiacs (with positive anti-endomysial antibodies and positive duodenal biopsy). They delayed starting a gluten free diet until study completion. (**b**) 18 age-sex matched controls. (**c**) 12 age-sex matched subjects attending the hospital for asymptomatic anaemia with no history of serious illness, normal endoscopy and no evidence of villous atrophy. The study was approved by the local Ethics Committees and subjects signed written informed consent. EPI: 15 patients from group (**a**) and 15 controls from group (**b**) attended fasted. A dedicated whole-body 0.5 T EPI scanner, equipped with actively shielded gradients and a 50 cm ∅ bird-cage coil (3.5×2.5×10 mm^3 resolution, 128×128 matrix) was used. Immediately after ingestion of a polysaccharide meal (323kcal; carbohydrate 63%, fat 37%) and every 15 min for 2 h, rapid multislice sets were acquired across the abdomen to measure gastric and gallbladder emptying. 47 rapid multislice sets of images (8 contiguous slices every 3 s) were acquired through the antrum at t=5 and 40 min after the test meal to assess antral motility [5]. Subjects sat outside the magnet between scans. PLASMA 5-HT: On a separate day 18 celiacs (**a**) and 18 controls (**b**) attended fasted. Blood samples were collected from a 19G intravenous cannula before, immediately after a carbohydrate-rich test meal (total energy 520kcal; carbohydrate 64%, fat 27%, protein 9%) and thereafter every 30 minutes for 3 hours. The abdominal symptoms were assessed using a standard questionnaire. DUODENAL BIOPSY: On a separate day 18 celiacs (**a**) and 12 controls (**c**) attended. A total of six biopsies were taken from the second part of the duodenum during endoscopy. We later measured the 5-HT and 5-HIAA content of duodenal mucosal biopsies from celiac patients and controls using HPLC and routine duodenal histology after staining with haematoxylin and eosin. The protein content of homogenized biopsy samples was determined using a commercially available assay. STATISTICS: Where values were normally distributed data was expressed as [mean (95% confidence intervals)] otherwise [median values (range)] are given. t-test for parametric or Mann-Whitney U-test for non-parametric data was used.

Results

The mean time to gastric half-emptying (T_{50}) was longer in celiacs [74 (50,99)] compared with controls [54 (39,69)] min, although this did not reach statistical significance due to marked variability (P<0.15). Pathologically delayed gastric emptying (T_{50} greater than 2 SD outside the mean control value) occurred in 3/15 celiacs. There was no significant difference in antral contraction speed or frequency between the two groups. However, contractions were absent in 36% of celiacs at t=5 min and in 2 of these at t=40 min. Mean fasting gallbladder volumes were significantly higher in the celiacs [34.7 (25.0,44.4)] than in the controls [20.6 (15.0,26.2)] ml, P <0.01 (**Fig. 1**). Celiac patients emptied a significantly larger volume of bile after the meal (P<0.05). The mean fasting 5-HT content per 10^9 platelets in platelet rich plasma was higher in celiacs [4.9 (4.0,5.7)] than in controls [3.8 (3.3, 4.4)] nmol/10^9 platelets, P<0.05. Mean peak postprandial plasma 5-HT level was higher for celiacs [99 (59,139)] than for controls [18 (12,24)] nmol/L, P<0.0005 (**Fig. 2**). Duodenal biopsies contained more mean mucosal 5-HT for celiacs [2.78 (1.67,3.89)] than for controls [0.93 (0.63,1.22)] nmol/mg protein, P<0.01 but significantly less mean 5-HIAA [0.30 (0.16,0.45)] versus [0.74 (0.30,1.19)] nmol/mg protein respectively, P<0.05. Hence the mean mucosal 5-HT turnover was lower for celiacs [0.17 (0.08,0.26)] than for controls [1.02 (0.22,1.81)], P<0.01.

Discussion

This study provides an insight into the complex abnormalities of upper GI function in celiac disease. EPI allowed non-invasive measurement of gastric emptying, antral motility and gallbladder volumes in a single study. Gastric emptying is delayed in celiacs [4] and in man gastric emptying is delayed by 5-HT_3 receptor agonists [6]. The small delay we observed probably reflects differences in disease severity since in our study almost half of the celiacs had only mild villous atrophy and many were asymptomatic. Increased fasting gallbladder volumes were observed in previous studies [7]. Previous studies have also shown a reduced overall percentage of gallbladder emptying following a meal [7], which has been attributed to impaired synthesis of cholecystokinin [8]. However our data suggest that following a meal both the volume of bile and the ejection fraction are increased in celiacs. The reasons for this disparity are unclear since our patient and control groups were closely matched and our test meal was similar to those previously described. We observed no association between gallbladder volumes and 5-HT levels.

The large postprandial rise in plasma 5-HT levels of celiacs is likely to be due to increased 5-HT release from the small intestine as a result of enterochromaffin cell hyperplasia [9]. This study also shows that celiacs release more 5-HT following a meal than healthy controls. The early postprandial rise in 5-HT suggests increased release from the upper small intestine where the mucosal abnormalities are greatest but the persistent elevation of plasma 5-HT even after 3 hours suggests that excessive release extends into the distal intestine and possibly colon.

Conclusion

This study shows the potential of the use of EPI to monitor simultaneously and non-invasively gastric emptying, antral motility and the emptying of the gallbladder. No enhancing agents are needed. An EPI multi-slice scan across the abdomen takes only a few seconds to perform, the motility scan only a few minutes. Hence, several subjects could be interleaved within the same experimental session saving machine time costs. Semi-automation of the volume measurements could be aided by increasing the T_2 weighting of the EPI module.

References: [1] Sanders et al, Lancet 2001;358:1504. [2] Challacombe et al, Gut 1977;18:373. [3]. Sjolund et al, Scand J Gastroenterol 1985;20:304. [4] Benini et al, Scand J Gastroenterol 2001;36:1044. [5] Marciani et al, Neurogastroenterol Mot 13;511:2001. [6] Coleman et al, Aliment Pharmacol Ther 2003 (in press). [7] Fraquelli et al, Am J Gastroenterol 1999;94:1866. [8] Deprez et al, Clin Sci 2002;103:171. [9] Sjolund et al, Gut 1982;23:42.

Figure 1. The effect of a test meal on gallbladder volumes in patients with celiac disease (n=14) and healthy controls (n=15). Data are represented as mean with standard errors.

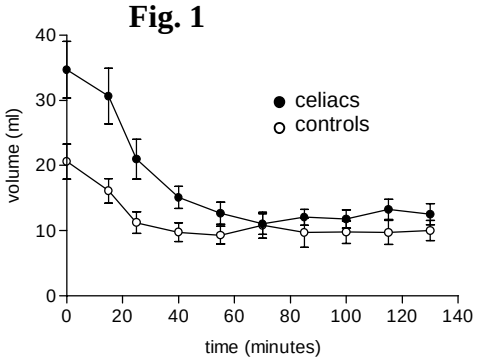

Figure 2. Individual peak postprandial plasma 5-HT levels in celiacs (n=18) and healthy controls (n=18) following a 500 kcal carbohydrate-rich test meal.