Evidence for hypomotility in non-ulcer dyspepsia: a prospective multifactorial study

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Abstract
A prospective multifactorial study of symptoms and disturbance of gastrointestinal function has been undertaken in 50 patients with non-ulcer dyspepsia. Objective tests including solid meal gastric emptying studies, gastric acid secretion, E-HIDA scintiscan for enterogastric bile reflux, and hydrogen breath studies were carried out in all patients and validated against control data. Gastroscopy and biopsy were carried out in non-ulcer dyspepsia patients only. Non-ulcer dyspepsia patients were categorised on the basis of predominant symptoms as: dysmotility-like dyspepsia (n=22); essential dyspepsia (n=14), gastro-oesophageal reflux-like dyspepsia (n=11); and ulcer-like dyspepsia (n=3). In the total non-ulcer dyspepsia population, solid meal gastric emptying was delayed (T50 mean (SEM)=102 (6) minutes (patients) v 64 (6) minutes (controls), (p<0.01)) and high incidences of gastritis (n=26) and Helicobacter pyloridis infection (n=18) were found. An inverse correlation was observed between solid meal gastric emptying and fasting peak acid output (r=-0.4; p<0.01). Indeed gastric emptying was particularly prolonged in eight patients (T50 mean (SEM)=139 (15) minutes) with hypochlorhydria. In the non-ulcer dyspepsia population oral to caecal transit time of a solid meal was delayed (mean SEM=302 (14) minutes (patients) v 244 (12) minutes (controls) (p<0.01)). Seven patients had a dual peak of breath hydrogen suggestive of small bowel bacterial overgrowth. No association was observed between symptoms and any of the objective abnormalities. This multifactorial study has shown that hypomotility, including gastroparesis and delayed small bowel transit, is common in non-ulcer dyspepsia and may be related to other disorders of gastrointestinal function. No relation between symptoms and disorders of function, however, has been shown.

Although non-ulcer dyspepsia has been classified as dysmotility-like dyspepsia, gastro-oesophageal reflux-like dyspepsia, ulcer-like dyspepsia, aerophagia, and essential dyspepsia on the basis of suggestive symptoms, supportive evidence for a relation between symptoms and aetiology is lacking. Indeed, the pathogenesis of non-ulcer dyspepsia is obscure. Although previous studies have identified individual abnormalities of gastrointestinal function, including delayed gastric emptying, gastritis with or without Helicobacter infection, enterogastric bile reflux, and disorders of gastric acid secretion, a comprehensive approach has been lacking. Hence the relation between objective abnormalities within a single cohort of patients is unknown and no dominant aetiological factor has been identified.

This prospective study has evaluated and sought relations between symptoms and objective tests of gastric and small bowel function in a single cohort of patients with non-ulcer dyspepsia.

Patients and methods

DIAGNOSIS OF NON-ULCER DYSPEPSIA
Non-ulcer dyspepsia was diagnosed on the basis of persistent symptoms of abdominal pain, discomfort, bloating, or heartburn for a minimum of two months over at least two years, after exclusion of common organic disturbances (vide infra) on the basis of history, clinical examination, and a series of preliminary investigations.1

EXCLUSION CRITERIA
(1) Patients who gave a history of: recent abdominal surgery within one year of presentation; irritable bowel syndrome, which was defined as abdominal pain associated with predominant symptoms of diarrhoea or constipation;4 and angina pectoris were excluded from the study.
(2) On clinical examination, abdominal mass or hernia constituted exclusion criteria.
(3) On investigation, peptic ulceration, upper gastrointestinal malignancy, gall stones, and gastro-oesophageal reflux were sought in all patients by endoscopy, abdominal ultrasound, and 24 hour ambulatory pH monitoring respectively. Oesophageal pH monitoring was assessed using a pH sensitive radiotelemetry pill suspended 5 cm above the manometrically determined high pressure zone.

Recording of pH data was collected by a portable microprocessor receiving unit (Aspen Medical Ltd, Ross-shire, Scotland). Computer based analysis determined the mean time of oesophageal pH less than 4, the mean number and duration of reflux events in both the erect and supine positions, and also the cumulative acid exposure expressed as the percentage of data below each pH unit from 3 to 6 during the study. For each analysis method an individual record was considered abnormal (positive for reflux) if any one parameter was greater than 3 SD above the mean as determined from a control group consisting of 22 asymptomatic healthy volunteers.9,10

Patients who were free of the above conditions...
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but had persistent symptoms were diagnosed as having non-ulcer dyspepsia and entered the study.

STUDY PROTOCOL

Symptom assessment
All patients had objective evaluation of seven symptoms: (i) abdominal pain, (ii) early satiety, (iii) bloating, (iv) heartburn, (v) regurgitation, (vi) loss of appetite, and (vii) nausea. These symptoms were evaluated by a standard self administered questionnaire which sought the presence of symptoms and scored severity by visual analogue scale. On the basis of predominant symptoms, patients with non-ulcer dyspepsia were assigned to one of five categories as outlined by the Working Party on the Management of Dyspepsia:

- Dysmotility-like dyspepsia. Predominant symptoms of abdominal pain or discomfort, with typical onset after eating a meal and associated feeling of bloating, distension, early satiety, and nausea.
- Ulcer-like dyspepsia. Epigastric pain with a tendency to waken the patient at night, and relief after eating small meals or antacids.
- Gastro-oesophageal reflux-like dyspepsia. Predominant symptoms of epigastric or retrosternal heartburn, and regurgitation of acid or food.
- Aerophagia. Abdominal air swallowing with typical symptoms of repetitive belching, bloating, and frequent dry swallowing.
- Essential dyspepsia. Symptoms which do not fit into any of the categories described above and have no specific features on history or examination.

All patients then completed a series of gastrointestinal investigations as follows.

Gastroscopy and antral biopsies
Gastroscopy was carried out after midazolam sedation. Gastroscopic appearances were categorised as normal or hyperaemic and were noted on a standard form. Two endoscopic biopsy specimens were taken from cranial and caudal aspects of the gastric antrum distal to the incisura and were fixed in formalin, stained with haematoxylin and eosin and with giemsa, and were then examined by a histopathologist. The diagnosis of gastritis was established on the polymorphonuclear infiltrate into the submucosa and mucosal hyperaemia with or without epithelial dysplasia. The presence of Helicobacter pyloris organisms were sought histologically and their presence or absence was recorded.

Evaluation of peak acid output
Peak acid output was evaluated by the standard pentagastrin stimulation test. After an overnight fast gastric contents were aspirated continuously, first in the basal state and then after pentagastrin stimulation (6 μg/kg body weight by subcutaneous injection). Acid secretion after pentagastrin stimulation was expressed as peak acid output in mmol/hour. The normal range in our laboratory, which has been previously defined in volunteers, lies between 6 and 40 mmol/hour.

Solid phase gastric emptying
Solid phase gastric emptying was evaluated by scintigraphy using 111mTc labelled scrambled egg. The meal was prepared by injecting 10 MBq of 111mTc stannous colloid into two beaten raw eggs and 30 ml milk, which were then cooked until firm in consistency. This meal has a caloric value of 168 calories (13 g protein). After eating the meal, images were collected on a gamma camera (IGE 535 Maxicamera, International General Electric Medical Systems Ltd, Berks, England) which was interfaced to a mini computer (Nodec group V76, Byfleet, Surrey). Sequential anterior and posterior views were acquired at five minute intervals for the first hour and then at regular intervals until more than half the meal was perceived to have emptied from the stomach. The geometric mean of each image pair was generated to eliminate artifacts caused by movement of the meal through the stomach.

The resulting series of images were used to evaluate the lag period before onset of emptying and the time for 50% emptying (T50).

Enterogastric bile reflux
Enterogastric bile reflux was investigated in the fasting phase by 99mTc-E-HIDA biliary scintigraphy. After injection the isotope is cleared quickly from the blood pool by hepatobiliary function and secreted into the biliary system. Normally, the main hepatic ducts, common bile duct, cystic duct, gall bladder, duodenum, and small bowel are soon visualised. Enterogastric reflux of bile was defined as the demonstration of radioactivity visualised travelling in a retrograde fashion from the duodenum into the stomach.

Hydrogen breath test
This test was used to evaluate orocecal transit time and also as a screening measure for small bowel bacterial overgrowth. Subjects were instructed to avoid non-absorbable dietary saccharides for 48 hours before the test. After an overnight fast, each subject was given a chlorhexidine mouth wash to eliminate oral bacteria, then breath samples (20 ml) were taken using a modified Haldane Priestly tube, before and at 20 minute intervals after eating a meal. Baked beans contain indigestible oligosaccharides, which are not absorbed in the small bowel, but are rapidly fermented by anaerobic bacteria, generating hydrogen gas which diffuses rapidly into capillaries and is excreted in the breath. Hydrogen concentration in parts per million (ppm) was evaluated using a GMI exhaled hydrogen monitor (GMI Instruments Ltd, Renfrew, Scotland). The standard meal comprised 200 g mashed potato, 100 g baked beans, and 25 ml of water with 6-25 g glucose, which had a caloric value of 273 Kcal.

A dual peak of breath hydrogen was regarded as suggestive of small bowel bacterial overgrowth. In these circumstances, the first peak
Reproducibility tests of isotope based methods were avoided on the grounds of the requirement for repeated radiation exposure.

**ETHICAL APPROVAL**

The study protocol was approved by the Faculty of Medicine and Dentistry Ethics Committee, Ninewells Hospital. Each patient gave written, informed consent before participation.

**DATA ANALYSIS**

Because of the unequal number of patients and volunteers, analysis of gastric emptying and small bowel transit data was performed by the Mann-Whitney U test. The Pearson product-moment test of correlation was used to seek any relation between symptoms and objective tests, or any relation between objective tests themselves. Reproducibility was evaluated by one way analysis of variance and results expressed as a coefficient of variance.

**Results**

Twenty eight patients were ineligible for the study on the grounds of the exclusion criteria (Table I). Fifty patients then entered (36 women, 14 men) aged 18 to 75 years (mean (SEM)=44 (2) years).

**SYMPTOMS**

Individual symptoms and severity scores are shown in Table II. On the basis of predominant symptoms, patients were assigned to the following categories viz: dysmotility-like dyspepsia (n=22); essential dyspepsia (n=14); gastro-oesophageal reflux-like dyspepsia (n=11); ulcer-like dyspepsia (n=3); and aerophagia (n=0).

**OBJECTIVE TESTS**

**Volunteer studies**

Solid meal gastric emptying in volunteers (T<sub>50</sub>) was mean (SEM) 64 (6) minutes, with a range (mean (2 SD)) between 22 and 106 minutes. Enterogastric bile reflux of 5% and 6% respectively of the administered isotope were seen in two of 10 volunteers. Hence, in this study, reflux of more than 5% was considered abnormal.

Hydrogen breath studies showed that the mean (SEM) oro-caecal transit time in volunteers was 244 (12) minutes with a range (mean (2 SD)) between 125 and 355 minutes. The coefficient of variance for oro-caecal transit times in volunteers was 0-15 (Fig 1). One volunteer had a dual peak of breath hydrogen during the study, suggestive of bacterial overgrowth.

**Patient studies**

Solid meal gastric emptying was slower in the non-ulcer dyspepsia population than in volunteers (T<sub>50</sub> mean (SEM)=102 (6) minutes (patients) vs 64 (6) minutes (controls) (p<0.01)). Gastric emptying delay, as previously defined, was identified in 21 patients (Fig 2). Histology of

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**TABLE I** Conditions in excluded patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-oesophageal reflux</td>
<td>12</td>
</tr>
<tr>
<td>Gall stones</td>
<td>3</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1</td>
</tr>
<tr>
<td>Oesophageal carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Symptom regression</td>
<td>2</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
</tr>
</tbody>
</table>

**TABLE II** Individual symptoms and mean (SEM) severity scores in 50 non-ulcer dyspepsia patients

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients (no)</th>
<th>Severity score (scale 0-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>50</td>
<td>4.8 (0.3)</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>40</td>
<td>4.5 (0.4)</td>
</tr>
<tr>
<td>Early satiety</td>
<td>34</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>3.2 (0.4)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>24</td>
<td>2.6 (0.4)</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>27</td>
<td>2.0 (0.4)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>15</td>
<td>2.1 (0.5)</td>
</tr>
<tr>
<td>Total symptom score/patient</td>
<td>22 (1-4)</td>
<td></td>
</tr>
<tr>
<td>No of symptoms/patient</td>
<td>22 (1-4)</td>
<td></td>
</tr>
<tr>
<td>Length of history (months)</td>
<td>65 (12)</td>
<td></td>
</tr>
</tbody>
</table>
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antral biopsy specimens showed inflammatory gastritis in 26 patients, of whom 18 had *Helicobacter pyloridis* infection. Eight patients had a peak acid output of less than 6 mmol/hour after fasting pentagastrin stimulation, indicative of hypochlorhydria.

In the small bowel studies, orocecal transit time was slower in patients than in controls (mean (SEM) 302 (14) minutes (patients) vs 244 (12) minutes (controls) (p<0.01)) (Fig 3). A dual peak of breath hydrogen suggestive of small bowel bacterial overgrowth was identified in seven patients. Enterogastric bile reflux of >5%, was observed in only one patient.

Multivariate analysis showed an inverse correlation between solid meal gastric emptying time (T₅₀) and fasting peak acid output (r = -0.4; p<0.01) (Fig 4) and a direct correlation between gastritis and *Helicobacter pyloridis* infection (r = 0.62; p<0.01). Age was directly related to gastritis only (r = 0.35; p<0.05). Gastric emptying delay was commonly present in association with other abnormalities although statistical significance was not observed (Table III).

No relation was found between individual symptoms, severe symptoms, or symptom categories and any of the objective abnormalities (Table IV).

**Discussion**

Non-ulcer dyspepsia is six to 10 times as
TABLE III  Relation of gastroparesis to other abnormalities in non-ulcer dyspepsia patients

<table>
<thead>
<tr>
<th>No of patients</th>
<th>No with delayed gastric emptying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis</td>
<td>26</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>18</td>
</tr>
<tr>
<td>Delayed OCTT</td>
<td>11</td>
</tr>
<tr>
<td>Hypochlorhydria</td>
<td>8</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>7</td>
</tr>
<tr>
<td>Enterogastric reflux</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
</tr>
</tbody>
</table>

OCTT = orocaecal transit time.

TABLE IV  Symptom categories and objective abnormalities in non-ulcer dyspepsia patients*

<table>
<thead>
<tr>
<th>Dyspepsia category</th>
<th>Gastric emptying</th>
<th>PAO</th>
<th>Gastritis</th>
<th>Helicobacter</th>
<th>OCTT</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmotility-like (n=22)</td>
<td>0.83</td>
<td>0.49</td>
<td>0.76</td>
<td>0.85</td>
<td>0.97</td>
<td>0.09</td>
</tr>
<tr>
<td>GOR-like (n=11)</td>
<td>0.55</td>
<td>0.59</td>
<td>0.32</td>
<td>0.91</td>
<td>0.61</td>
<td>0.11</td>
</tr>
<tr>
<td>Ulcer-like (n=3)</td>
<td>0.49</td>
<td>0.38</td>
<td>-</td>
<td>-</td>
<td>0.75</td>
<td>0.98</td>
</tr>
<tr>
<td>Essential (n=14)</td>
<td>0.66</td>
<td>0.42</td>
<td>0.21</td>
<td>0.76</td>
<td>0.53</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*Results expressed as p values for each association by the Pearson product moment test for correlation. No significant association was observed.

PAO = peak acid output; OCTT = orocaecal transit time; GOR = gastro-oesophageal reflux.
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gestive rather than conclusive. Hyperacidity was uncommon in this study, which may go some way to explaining the poor results in trials of acid reducing agents. Similarly, enterogastric bile reflux was uncommon in this study.

In this study we found no correlation between any of the objective tests and any of the individual symptoms, severe symptoms, or symptom categories as defined according to the recommendations of the Dyspepsia Working Party. Hence, in this respect, our findings are in accord with those of Malegalada et al, who reported a lack of correlation between symptoms and gastrointestinal motility disorders in patients with functional abdominal pain, and also with Jian et al, who found no relation between symptoms and objective gastric stasis in non-ulcer dyspepsia.

In conclusion, this prospective multifactorial study has identified a heterogeneous spectrum of gastrointestinal dysfunction in non-ulcer dyspepsia. However, hypomotility in the form of delayed gastric emptying, or small bowel transit, or both, seems to dominate.

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