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A substantial proportion of non-ulcer dyspepsia patients have the same abnormality of acid secretion as duodenal ulcer patients

E El-Omar, I Penman, J E S Ardill, K E L McColl

Abstract

Acid secretion in response to gastrin releasing peptide (GRP) is increased sixfold in *Helicobacter pylori* positive duodenal ulcer (DU) patients and threefold in *H pylori* positive healthy volunteers, and this fully resolves after eradication of the infection. This study was undertaken to determine whether a proportion of *H pylori* positive patients with non-ulcer dyspepsia (NUD) have an acid secretion disturbance similar to DU patients. Basal and GRP stimulated gastrin concentrations and acid output were examined in 25 *H pylori* positive NUD patients and the results compared with those of 25 *H pylori* positive healthy volunteers, 25 *H pylori* negative healthy volunteers, and 25 *H pylori* positive DU patients. Compared with the *H pylori* negative healthy volunteers, GRP stimulated gastrin was increased approximately three fold in each of the three infected groups. GRP stimulated acid secretion (median, range) was higher in the *H pylori* positive NUD patients (29·6 mmol/h (5·2–46·5)) ($p<0·005$) than in the *H pylori* positive healthy volunteers (19·0 (1·0–38·3)) ($p<0·001$) or *H pylori* negative healthy volunteers (6·3 (2·8–20·9)) ($p<0·0001$). The *H pylori* positive NUD patients, however, had lower acid output than the DU patients (39·1 (17·9–64)) ($p<0·005$). These findings are consistent with approximately 50% of the NUD patients having a similar disturbance of GRP stimulated acid secretion to DU patients.

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Keywords: gastrin releasing peptide, *Helicobacter pylori*, duodenal ulcer, non-ulcer dyspepsia.

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Dyspepsia occurs in 30–40% of the general population in the UK.[1 2] It accounts for 10–20% of GP consultations[3] and 30% of hospital gastroenterology referrals.[4] In over 50% of dyspeptic patients upper gastrointestinal investigations do not prove definitive and these patients are categorised as having non-ulcer dyspepsia (NUD).[5 6] Consequently, NUD is the commonest diagnosis in patients presenting with dyspepsia.

The recent recognition of the pathogenic role of *Helicobacter pylori* infection in duodenal ulcer (DU) disease is transforming the management of that condition and removing the need for long term treatment with expensive acid inhibitory therapy. The cause of NUD remains unknown but there is considerable interest in its relationship to DU disease and in the possible role that *H pylori* infection may have in the condition.

Recent studies in our unit have shown that *H pylori* positive DU patients have a sixfold increase in acid secretion both basally and in response to stimulation by gastrin releasing peptide (GRP), when compared with *H pylori* negative healthy volunteers.[7] GRP stimulated acid secretion is also increased in healthy volunteers with the infection but their median output is only three times that of *H pylori* negative healthy volunteers.[3] The very noticeable increase in acid secretion in DU patients is likely to represent a key pathophysiological defect underlying their disease. More recent studies indicate that the hypersecretion of acid in both *H pylori* positive DU patients and healthy volunteers is entirely due to the infection as it fully resolves after eradication of the organism.[8]

This recent recognition of disturbed gastric secretory function caused by *H pylori* and associated with DU disease may be helpful in investigating the pathogenesis of NUD. In particular, the assessment of GRP stimulated acid secretion may provide a means of identifying NUD subjects with a similar disturbance of gastric function as DU patients and which could be reversed by eradication of their *H pylori* infection.

The aim of the present study was to determine whether the underlying disturbance of acid secretion characteristic of DU disease is also present in a proportion of *H pylori* positive non-ulcer dyspepsia NUD patients.

Patients and methods

Twenty five *H pylori* positive NUD patients (16 men) were studied. Their median age was 35 years (range: 18–59). The patients were recruited consecutively from our gastrointestinal outpatient clinic and all fulfilled the following three criteria: (1) a six month or longer history of dyspepsia. This consisted of upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptom considered referable to the proximal alimentary tract, and unrelated to exercise. (2) No macroscopic abnormality of the upper gastrointestinal tract demonstrable despite at least two upper gastrointestinal investigations, including one endoscopy. (3) Evidence of *H pylori* infection as confirmed by microscopic examination of antral biopsy specimens, rapid

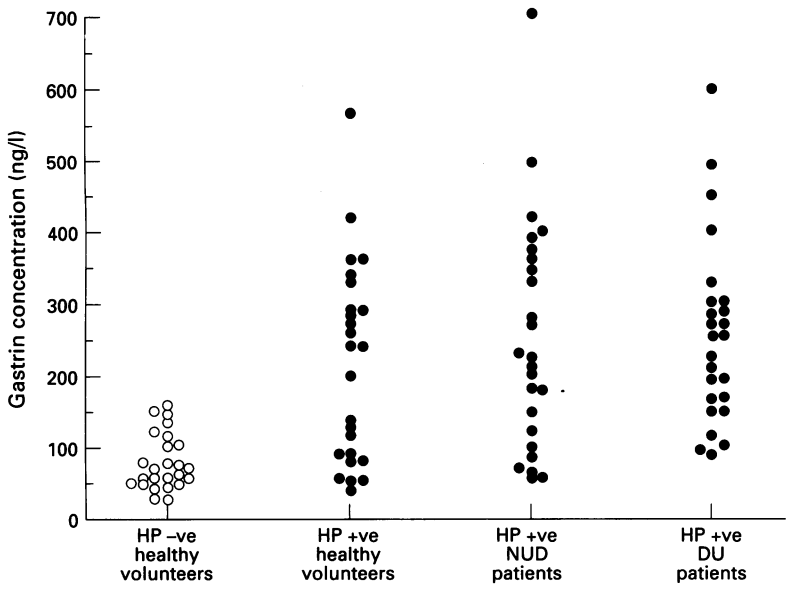

Figure 1: Basal gastrin concentrations in the four groups of subjects studied. The Helicobacter pylori *positive (HP+ve) non-ulcer dyspepsia (NUD) patients had higher values than the HP−ve healthy volunteers ($p<0.002$) and values similar to the HP+ve positive healthy volunteers and duodenal ulcer (DU) patients.*

urease test (CLO test) on antral biopsy tissue, and ^{14}C urea breath test.

The NUD patients were compared to three groups of subjects: 25 *H pylori* negative healthy volunteers (17 men), 25 *H pylori* positive healthy volunteers (17 men), and 25 *H pylori* positive DU patients (17 men). The DU patients all had an active ulcer confirmed by endoscopy within the previous 12 months. All groups were matched for age and body weight.

NUD and DU patients were asked to stop any antisecretory therapy at least four weeks before the secretory studies. None of the healthy volunteers was on any medication and none had consulted a doctor about dyspepsia. *H pylori* infection in the DU patients was confirmed as for the NUD patients. In the healthy volunteers, *H pylori* status was determined by the ^{14}C urea breath test.

SECRETORY STUDIES

All subjects reported at 09:00 h after a 12 hour fast. An orogastric tube (Anderson Inc, New York) was swallowed and its position in the dependent part of the stomach was checked by the water recovery test. After emptying the stomach, intermittent suction was applied by intermittent suction unit (Ohmeda, Columbia, USA) which applies suction for 20 seconds in each 32 second cycle. Three 15 minute collections were obtained basally and at each of the following rates of intravenous infusion of GRP: 10 and 40 pmol/kg/h. Blood samples were collected every 15 minutes for gastrin determination and the plasma was stored at −20°C.

GRP was purchased from Cambridge Research Biochemicals (Cheshire, England) in 1 mg aliquots of freeze-dried lyophilised powder. Subsequent preparation was performed under sterile conditions by the Western Infirmary Pharmacy department. Each aliquot was made up into a 10 ml stock solution by dissolving in sterile water and 0·1 ml of 50% acetic acid solution was added to stabilise into solution. Vials containing 100 μg of GRP in 1 ml of solution were prepared and stored at −80°C until the day of study. For each study, the content of each vial was further diluted in 0·9% NaCl solution. The peptide solution was filtered through a low protein binding bacterial filter (Gelman Sciences, Northampton, England) before the final concentrations of the peptide were made up.

The volume and pH of each gastric juice collection was recorded and its hydrogen ion concentration was measured by titration with 0·1 M NaOH to pH 7 using an autotitrator (Radiometer ETS 822).

Basal acid output was calculated by taking the mean of all three 15 minute samples before GRP infusion. Acid output for each GRP infusion rate were calculated by taking the mean of the second and third 15 minute collections.

Gastrin was measured by radioimmunoassay using antiserum R98 which has a sensitivity of 5 ng/l. The basal gastrin value for each subject was determined by taking the mean of the three samples obtained before GRP infusion. The gastrin value at each infusion rate of GRP was determined by taking the mean of the two values at 30 and 45 minutes of each infusion.

STATISTICS

Statistical analysis was performed using the Mann-Whitney U test. A p value of <0.05 was taken as significant.

In the NUD patients linear regression analysis was performed to look for any correlation between acid output and age and duration of dyspeptic symptoms.

The study was approved by the Western Infirmary ethical committee.

Results

BASAL GASTRIN

The basal gastrin concentration (ng/l) was similar in the *H pylori* positive healthy volunteers (median=45, range: 10–90), *H pylori* positive NUD patients (60, range: 25–270), and *H pylori* positive DU patients (60, range: 22–175) and all were higher than the *H pylori* negative healthy volunteers (32, range: 15–50) ($p<0.005$ for all three) (Fig 1).

GASTRIN RESPONSE TO GRP

At the GRP infusion rate of 40 pmol/kg/h, the median gastrin concentrations (ng/l) were increased to similar levels in the *H pylori* positive healthy volunteers (238, range: 38–563), *H pylori* positive NUD patients (225, range: 55–700), and *H pylori* positive DU patients (255, range: 90–600), which were higher than that of the *H pylori* negative healthy volunteers (70, range: 28–157) ($p<0.002$ for each) (Fig 2).

The gastrin response in the four groups of subjects at the GRP infusion rate of 10 pmol/kg/h showed the same pattern of response to that seen in response to GRP 40

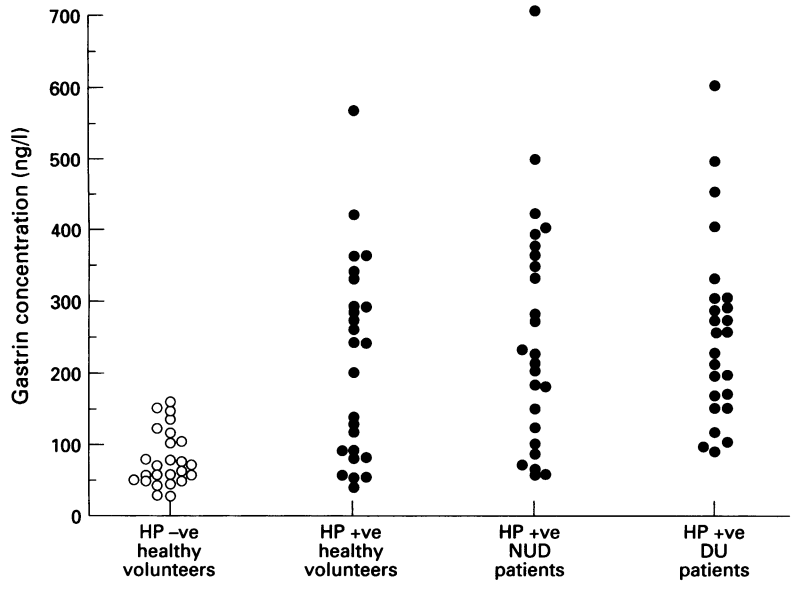

Figure 2: Serum gastrin concentrations in response to stimulation with gastrin releasing peptide (40 pmol/kg/h) in the four groups studied. The Helicobacter pylori *positive (HP+ve) non-ulcer dyspepsia (NUD) patients had higher values than the HP−ve healthy volunteers (p<0·002) and values similar to the HP+ve healthy volunteers and duodenal ulcer (DU) patients.*

pmol/kg/h. We chose to present the results of the individual data points for the 40 pmol/kg/h GRP rate as the gastrin levels stimulated by this are closer to those seen after a meal.

BASAL ACID SECRETION

The median basal acid output (mmol/h) was higher in the *H pylori* positive healthy volunteers (2·9, range: 0·5–13·3) (p<0·05) and *H pylori* positive NUD patients (4·8, range: 0·3–16·7) (p<0·01) than in the *H pylori* negative healthy volunteers (1·8, range: 0·5–7·9). However, there was no statistically significant difference between the basal acid output in the *H pylori* positive healthy volunteers and NUD patients (p=0·2). The median basal acid output in the *H pylori* positive DU patients was 6·6 mmol/h (range: 2·6–25·8) and was significantly higher than that of the *H pylori* positive NUD patients (p<0·03), *H pylori* positive healthy volunteers (p<0·001), and *H pylori* negative healthy volunteers (p<0·0001) (Fig 3).

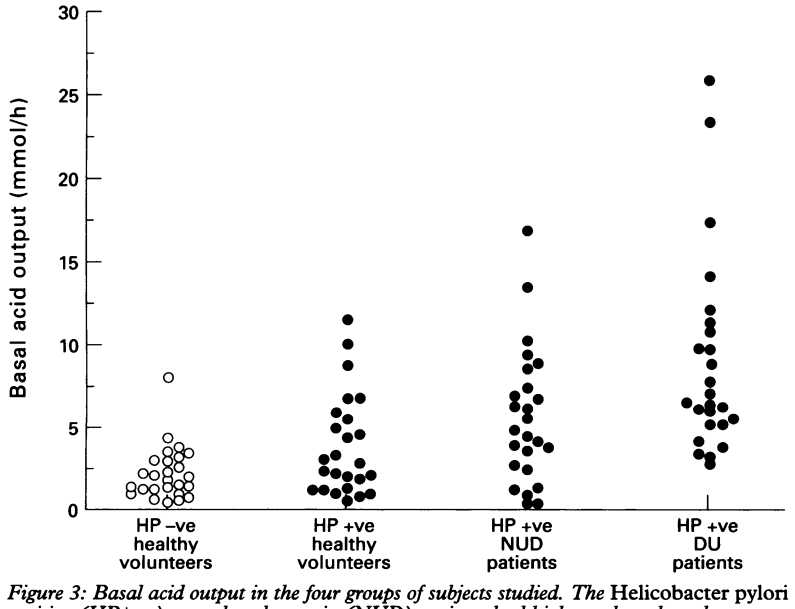

Figure 3: Basal acid output in the four groups of subjects studied. The Helicobacter pylori *positive (HP+ve) non-ulcer dyspepsia (NUD) patients had higher values than the HP−ve healthy volunteers (p<0·01) and lower values than the duodenal ulcer (DU) patients (p<0·03), but were not different from the HP+ve healthy volunteers.*

ACID RESPONSE TO GRP

At a GRP infusion rate of 40 pmol/kg/h, the median acid output (mmol/h) in the *H pylori* positive healthy volunteers (19·0, range: 1·0–38·3) was approximately three times that of the *H pylori* negative healthy volunteers (6·3, range: 2·8–20·9) (p<0·001). At this infusion rate the median acid output in the *H pylori* positive NUD patients was 29·6 (range: 5·2–46·5), which was approximately five times that of the *H pylori* negative healthy volunteers (p<0·0001) and 1·5 times that of the *H pylori* positive healthy volunteers (p<0·001). The median acid output in the *H pylori* positive DU patients was 39·1 (range: 17·9–64), which was approximately six times that of the *H pylori* negative healthy volunteers (p<0·0001) and twice that of the *H pylori* positive healthy volunteers (p<0·005). Acid output was significantly higher in the *H pylori* positive DU patients than in the *H pylori* positive NUD patients (p<0·001) (Fig 4).

Acid outputs in response to 10 pmol/kg/h of GRP followed the same pattern in the four groups as those obtained in response to 40 pmol/kg/h.

In the NUD patients, linear regression analysis showed that there was no correlation between acid output and either the age (r=0·2, p=0·87) or duration of dyspeptic symptoms (r=0·1, p=0·9).

Discussion

H pylori is now established as the major acquired factor in the pathogenesis of DU disease. The mechanism by which it predisposes to DU disease is probably related, at least partly, to its effects on gastric acid secretion. *H pylori* increases basal, meal stimulated, and GRP stimulated gastrin concentrations and the magnitude of the hypergastrinaemia is similar in DU patients and healthy volunteers with the infection (9–15). The hypergastrinaemia is accompanied by a threefold increase in basal and GRP stimulated acid output in infected healthy volunteers and a more noticeable sixfold increase in DU patients.[7] DU patients with *H pylori* thus resemble infected healthy volunteers in having a similarly exaggerated gastrin response, but differ from them in producing twice as much acid for equivalent gastrin levels basally and during GRP stimulation. In the present study we have studied gastric function in *H pylori* positive NUD patients to see whether a subgroup have a disturbance similar to that in DU patients.

Both basal and GRP stimulated gastrin concentrations were increased to a similar extent in the NUD patients and in the *H pylori* positive healthy volunteers and DU patients. This confirms previous findings that the magnitude of basal and stimulated hypergastrinaemia is similar in the presence of *H pylori* infection

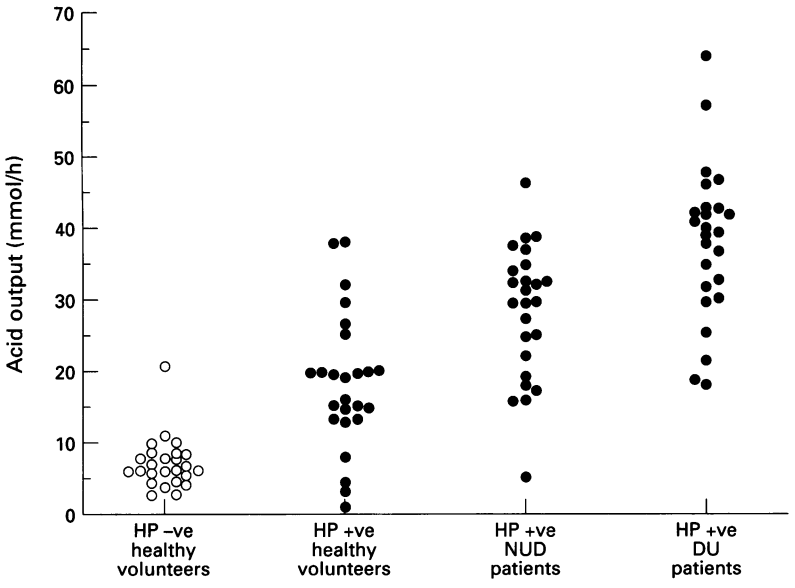

Figure 4: Acid output in response to stimulation with gastrin releasing peptide (40 pmol/kg/h). The acid output in the Helicobacter pylori *positive (HP+ve) non-ulcer dyspepsia (NUD) patients was higher than that in the HP−ve healthy volunteers ($p<0.0001$) and the HP+ve healthy volunteers ($p<0.001$), and lower than that in the duodenal ulcer (DU) patients ($p=0.001$).*

regardless of whether the subject is healthy or has dyspeptic disease.[10]

The basal acid output was significantly increased in the *H pylori* positive NUD patients compared with the *H pylori* negative healthy volunteers, but was also significantly less than in the DU patients. There was no statistically significant difference in basal acid output between the infected healthy volunteers and NUD patients, though there was a trend in favour of it being higher in the latter.

GRP stimulated acid output in the NUD patients was five times higher than in the *H pylori* negative healthy volunteers but was significantly lower than in the *H pylori* positive DU patients. The GRP stimulated acid output in the NUD patients was also 60% higher than that of the *H pylori* positive healthy volunteers. The median GRP stimulated acid output in the NUD patients thus fell half way between that of the *H pylori* positive healthy volunteers and the *H pylori* positive DU patients. This could be explained by approximately half the NUD patients having GRP stimulated acid secretion similar to the DU patients and half having acid secretion similar to the *H pylori* positive healthy volunteers. Alternatively, it could be due to NUD patients having GRP stimulated acid output which falls between that of DU patients and infected healthy volunteers. The former explanation is the more likely as previous studies indicate that NUD is a heterogeneous condition.[16]

The mechanism of the increased GRP stimulated acid secretion in the NUD patients was similar to that in the DU patients. The DU patients had a gastrin response similar to that of the infected healthy volunteers and thus their higher acid response was the result of an increased acid response to gastrin during GRP stimulation. Likewise, the NUD patients had the same gastrin response to GRP as the infected healthy volunteers and thus their higher acid output was again due to an increased acid response to gastrin during GRP stimulation.

The finding that a subgroup of *H pylori* positive NUD patients have a disturbance of gastric function similar to DU patients may be relevant to the underlying cause of their dyspeptic disease. It is well recognised that symptoms in DU patients correlate poorly with the presence of actual ulceration[17–21] and the pain is thus not simply due to the effect of excess acid on an active ulcer. The precise mechanism of pain in DU disease is unknown but is likely to be due to the interaction of excess acid secretion and inflammation of the gastroduodenal mucosa.[22] This mechanism could also explain the pain in the NUD patients who have an exaggerated GRP stimulated acid response similar to that in the DU patients.

If a subgroup of *H pylori* positive NUD patients has a similar reason for their dyspeptic symptoms as DU patients then eradication of the infection is likely to benefit them in a similar way to DU patients. Such treatment would both lower their GRP stimulated acid secretion and resolve the inflammation of their mucosa. Previous studies of the value of eradicating *H pylori* in patients with NUD have produced conflicting results and this is consistent with the infection playing a role in only a subgroup of NUD patients.[23–25] The challenge now is to find a means of identifying the subgroup of patients with NUD whose symptoms are secondary to their *H pylori* infection and who are therefore most likely to benefit from its eradication. Assessment of GRP stimulated acid secretion might provide a means of identifying these patients.

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