

Duodenal ulcer, *Helicobacter pylori*, and gastric secretion

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Abstract

Patients with chronic dyspepsia were categorised by macroscopic appearance at oesophagogastroduodenoscopy as having duodenal ulceration (DU), other diagnosed lesions such as reflux oesophagitis, carcinoma of stomach, etc, or no organic lesion (non-ulcer dyspepsia, NUD). Material was collected to identify gastric infection with *Helicobacter pylori* (*H pylori*) by CP urease test, culture, and histological examination and to make the microscopic diagnosis of active chronic gastritis. Each patient in the DU and NUD categories was then invited to volunteer for a gastric secretion study in which maximal gastric secretion in response to histamine was measured. Sixty two gastric secretion tests were performed (31 DU, 31 NUD). The presence of *H pylori* was associated with active chronic gastritis (100%). DU patients secreted more acid than the NUD patients. *H pylori* positivity was associated with decreased maximal gastric secretion in both groups. There was a positive correlation between smoking and maximal acid output shown only in *H pylori* negative but not in *H pylori* positive patients. These findings were clear cut when all corrections of maximal gastric secretion were made for pyloric loss, duodenogastric reflux, and stature. This study failed to show any aetiological link between *H pylori* and DU by increased maximal gastric secretion.

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Duodenal ulcer (DU) is a multifactorial disease, but since 1983 several studies have shown an association between duodenal ulcer and *H pylori*.¹⁻³ Two unproved hypotheses have been put forward to link *H pylori* with the pathogenesis of duodenal ulcer. One suggests that high gastric acidity or rapid gastric emptying, or both by creating a low duodenal pH, results in gastric metaplasia in the duodenum.⁴ This permits *H pylori* from an area of antral active chronic gastritis to colonise the duodenum leading to duodenitis and thence to DU.⁵⁻⁹ The other hypothesis is that urease produced by *H pylori* splits urea in the gastric juice into ammonia, which neutralises the acid in contact with the mucosa overlying the G cells. This impairs the normal inhibition of gastrin release by intraluminal acid leading to an inappropriate secretion of gastrin in response to food and thereby an increase in acid output that leads to the ulcer.¹⁰⁻¹⁶

Maximal acid secretion in a subject has been shown to be related to the risk that the subject had a DU.¹⁷ Other agents postulated to be risk factors for DU can be assessed against the background of acid related risk.¹⁸ Thus patients with high acid secretion might not need to have any other risk factor present to express the ulcer, whereas patients with low gastric secretion will probably not develop an ulcer unless they are exposed to the putative factor. It follows that the link between maximal gastric secretion and the risk factor might not be the simple one of duodenal ulcer, *H pylori*, and high maximal secretion.

The purpose of this study was to find out if *H pylori* was one of the risk factors necessary to cause DU in patients with low gastric acid output, or if it was associated with an increased parietal cell mass.

Subjects and methods

From January 1988 to July 1990 two of the authors (KC and DV) undertook 206 diagnostic endoscopies in the department of gastroenterology, The Middlesex Hospital. Forty six further patients had an endoscopy at two neighbouring centres.

Patients were divided into three groups based on the endoscopic findings: (1) DU (76 subjects), (2) any other macroscopic lesion (53 subjects), and (3) no macroscopic lesion of oesophagus, stomach or duodenum (non-ulcer dyspepsia (NUD), 123 subjects). Duodenitis was not specified nor was a biopsy specimen taken from the duodenum to attempt a histological diagnosis of duodenitis.

Each patient in the DU and NUD categories was told the macroscopic diagnosis and invited to volunteer for a gastric secretion study. Patients who had taken steroids, non-steroidal anti-inflammatory drugs, antibiotics or colloidal bismuth subcitrate within the previous three months or who had had gastric surgery were excluded. Of the volunteers who finally attended for gastric secretion studies, there were 31 of 76 in the DU group, 31 of 123 in the NUD group. The study had the approval of the clinical investigations panel of The Middlesex Hospital.

Three antral biopsy specimens were taken during the endoscopy procedure. The CP urease test (CP Test, Gist-Brocades Farma, Spa, Italy) was performed in the endoscopic suite using the method described by Vaira *et al.*¹⁹ The presence or absence of active chronic gastritis was determined in histological sections of biopsy specimens stained with haematoxylin and eosin, using the classification

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TABLE I Relation between maximal gastric secretion, expressed in four different ways for (a) DU v NUD and (b) *H pylori* negativity and positivity

Group	MAO (mmol h ⁻¹)	MAO (ht std) (mmol h ⁻¹)	Vg (ml h ⁻¹)	Vg (ht std) (ml h ⁻¹)
DU (n=31)	47.90	49.60	383	395
NUD (n=31)	25.75	27.31	188	203
% Difference	46.24	44.93	50.9	48.6
Wilcoxon	S	S	S	S
<i>H pylori</i> negative (n=21)	39.68	42.13	323	339
<i>H pylori</i> positive (n=41)	34.34	36.58	267	274
% Difference	13.45	13.17	17.3	19.1
Wilcoxon	NS	NS	NS	S

MAO=maximal acid output, Vg=corrected volume of gastric secretion, ht std=height standardised (for 170 cm). NS=not significant (p>0.05); S=significant (p<0.05).

TABLE II Relation between maximal gastric secretion and *H pylori* state in the DU group: influence of corrections for the measurement of gastric secretion

	MAO (mmol h ⁻¹) mean (SD)	MAOs (mmol h ⁻¹) mean (SD)	Vg (ml h ⁻¹) mean (SD)	Vgs (ml h ⁻¹) mean (SD)
<i>H pylori</i> positive (n=21)	45.28 (15.12)	47.82 (14.08)	361 (68)	374 (73)
<i>H pylori</i> negative (n=10)	53.41 (13.75)	53.35 (14.94)	429 (79)	439 (100)
% Reduction	15.0	10.3	15.8	14.8
Wilcoxon	NS	NS	S	S

Abbreviations as in Table I.

criteria of Whitehead²⁰ as modified by Warren and Marshall.²¹ *H pylori* was identified microscopically in sections with Giemsa staining and in culture on blood agar medium with 6 mg/ml of amphotericin.²² Gastric secretion studies were performed by a standard technique.^{18, 23} The salient features were that the studies started at 0830, the patient had fasted for at least eight hours, and smoking and alcohol had been proscribed for 12 hours. Also, for 72 hours before the test the subjects were asked to stop taking H₂ antagonists and any other treatment known to change the gastric secretion or motility, or both. After a basal one hour period, an intravenous infusion of histamine acid phosphate, 40 µg kg⁻¹ h⁻¹ was started and 10 minute samples were analysed for volume and titratable acidity; corrections were made for pyloric losses and duodenogastric reflux, and allowance made for stature (height). Gastric

TABLE III Relation between maximal gastric secretion and *H pylori* state in the NUD group: influence of corrections for the measurement of gastric secretion

	MAO (mmol h ⁻¹) mean (SD)	MAOs (mmol h ⁻¹) mean (SD)	Vg (ml h ⁻¹) mean (SD)	Vgs (ml h ⁻¹) mean (SD)
<i>H pylori</i> positive (n=20)	22.86 (10.90)	24.77 (11.67)	168 (75)	188 (74)
<i>H pylori</i> negative (n=11)	31.01 (12.86)	31.92 (10.11)	225 (51)	230 (46)
% Reduction	26.2	22.3	25.3	18.2
Wilcoxon	S	S	S	S

Abbreviations as in Table I.

TABLE IV Correlation between smoking factor (square root of cigarettes per day multiplied by years of smoking) with maximal gastric secretion in DU and NUD patients (Kendall's rank correlation coefficient τ)

Helicobacter pylori negative patients only				
	MAO (mmol h ⁻¹) mean (SD)	MAOs (mmol h ⁻¹) mean (SD)	Vg (ml h ⁻¹) mean (SD)	Vgs (ml h ⁻¹) mean (SD)
DU (n=10)	53.41 (13.75)	53.35 (14.94)	429 (79)	439 (100)
	$\tau=0.198$	$\tau=0.188$	$\tau=0.288$	$\tau=0.301$
	NS	NS	S	S
Non-DU (n=11)	31.01 (12.86)	31.92 (10.11)	225 (51)	230 (46)
	$\tau=0.303$	$\tau=0.361$	$\tau=0.410$	$\tau=0.441$
	NS	NS	S	S

Abbreviations as in Table I.

secretion was thus expressed in four different ways – as the raw data of plateau average maximal acid output obtained as the product of titratable acidity and volume, as Vg – the pyloric loss corrected, reflux corrected volume of pure gastric juice,²³ and as each of these standardised to a height of 170 cm.²⁴

STATISTICAL ANALYSIS

Data were expressed in means and standard deviations. Gastric secretion groups were compared by a non-parametric test, the Wilcoxon signed rank test, because gastric secretion was not normally distributed in the population. Contingency table analysis with χ^2 or Fisher's exact test was used depending on the numbers within the smallest cells. Kendall's τ was used to assess the correlation between smoking and gastric secretion. A value of p<0.05 was considered to be statistically significant.

Results

Two hundred and fifty two patients (100 men, 152 women; average age 50.8 years, range 16–79) had an endoscopy. Fifty three patients had miscellaneous macroscopic findings other than duodenal ulcer. These 53 patients were not approached for gastric secretion studies. A duodenal ulcer was diagnosed in 76 (30%) and no abnormality, that is no ulcer disease (NUD) was found in 123 (49%). The CP urease test was positive in 145 (58%) and negative in 107 (42%). All CP urease positive patients were also positive by culture or sensitivity or both.

The final decision for *H pylori* infection in the stomach was made according to whether culture or sensitivity (or both) was (were) positive: by these criteria, 159 patients (63%) were *H pylori* positive. In the DU group, 9 of 17 patients below the age of 36 and 44 of the 59 patients aged 36 or more were *H pylori* positive.

Active chronic antral gastritis was present in sections of mucosa in all *H pylori* positive subjects but was absent in all *H pylori* negative patients.

Maximal gastric secretion was higher in patients with DU than in those without DU whichever method was used to show secretion (Table I). Within each of these main groups maximal gastric secretion was 15–18% lower in those with *H pylori* compared with those without (Tables II and III). This second statement was correct when secretion was expressed as height standardised Vg. Tables II and III show the effect of using the less accurate indices (Vg unstandardised, acid output unstandardised, and standardised).

Of the two subjects who attended for gastric secretion studies, 33 (18 men, 15 women) were smokers, 29 (21 men, 8 women) were non-smokers. In smokers, positive correlations between smoking factor, that is the square root of the product of the number of cigarettes smoked per day and the number of years smoked, and maximal gastric secretion were shown in *H pylori* negative (both ulcer and non-ulcer) groups, but once again only if the

secretion was expressed as Vg (Table IV). In patients who were *H pylori* positive, however, there was no correlation between gastric secretion and smoking, however secretion rate was expressed or whether the patient had a DU.

In the range of standardised Vg of 270–321 ml there was an overlap between the DU and NUD groups consisting of six DU and six NUD subjects. All six of the DU group, but also four of the NUD, were *H pylori* positive. Subdividing the DU group into those lying within the normal range previously reported from this department,²³ that is below 425 ml, and those above this range and therefore statistically hypersecretors, there were 23 in the normal range and eight hypersecretors. The *H pylori* positive subjects were distributed as 17 of 23 in the normal range (74%) and four of eight in the hypersecretors (50%). This difference is not significant (Fisher's exact test, $p=0.1731$). If it is accepted that *H pylori* reduces gastric secretion by 17% and we increase the secretion values of the *H pylori* positive DU patients by about 17%, they now split as 11 hypersecretors and 10 hypo-secretors. This emphasises the fact that *H pylori* is not apparently summing with low gastric secretion to produce a DU.

Discussion

We studied *H pylori* in relation to DU, NUD, and a group of miscellaneous diagnoses. We decided not to include duodenitis in our diagnostic categories because this condition is difficult to diagnose/quantify.^{25,26}

The presence of *H pylori* was 100% associated with active chronic gastritis and vice versa. Culture and histological examination for *H pylori* gave almost identical results, and the specificity of the urease test in relation to the others suggests that all three methods used were reliable and at least comparable with the results of other workers.^{27–30} The accuracy of gastric secretion results in our laboratory is high and the evidence has been published elsewhere.¹⁸

The most notable positive finding of our study was that *H pylori* infection was associated, both in the DU and NUD groups, with decreased maximal gastric secretion. The effect was only clear cut when all corrections had been made for pyloric loss, duodenogastric reflux, and stature and emphasises the importance of taking these factors into account, especially when small numbers of subjects have been studied. Failure to make such corrections probably accounts for the discrepancies in published works; Brady *et al*,³¹ Hui *et al*,³² and Kang *et al*³³ found no consistent relation between *H pylori* and acid secretion, Wanger *et al*³⁴ found no difference in intragastric acidity in *H pylori* positive and negative patients but acidity was higher in DU subjects, Levi *et al*^{11–13} and McColl *et al*¹⁴ claimed *H pylori* increased gastric secretion and in contrast Steer studied 17 DU patients and showed a negative correlation between the number of *H pylori* and acid output.³⁵ Our data are consistent with the findings of Steer but not with those of others.

The patients in the DU and NUD groups who had overlapping gastric secretion showed no evidence of any predilection of the organism for the DU group. Again, this argues against an aetiological role for *H pylori* but we accept that the numbers were small. There was a disproportionately large incidence of *H pylori* in the DU normosecretors compared with the hypersecretors. At first glance this finding fits the suggestions made previously¹⁷ that aetiological factors other than acid might have an additive effect so that smaller acid outputs might in their presence be sufficient to produce an ulcer compared with the amount of acid needed in their absence. In the light of all our evidence, however, we believe that the likelier explanation of this phenomenon is that *H pylori* reduces gastric secretion. If we increase the maximal acid output by 17% (that is the figure by which *H pylori* on average reduces gastric secretion) of all DU and NUD *H pylori* positive patients then the asymmetry of *H pylori* positivity between normosecretors and hypersecretors vanishes.

The comparative antral hypoacidity produced by *H pylori* could fit the observed tendency to hypergastrinaemia, and in this respect the effect of *H pylori* is similar to that of acute cigarette smoking.³⁶ Chronic cigarette smoking, however, gives rise to an increased parietal cell mass and hyperacidity.^{36–39} This does not occur with *H pylori*. The reason is possibly that *H pylori* produces its hypoacidity not pharmacologically (as smoking does) but pathologically, that is by destroying parietal cells^{40–42} and so there is no chance for the increase in parietal cells to develop. This suggestion is supported by our finding that the increase in maximal gastric secretion with overall dose of cigarettes (smoking factor) was demonstrable in *H pylori* negative subjects, but not in *H pylori* positive subjects. The regressions between smoking and maximal secretion were only statistically significant with Vg standardised for height, yet another reason that all gastric secretion studies should be corrected for pyloric loss and duodenogastric reflux and standardised for stature, if useful information is not to be lost.

We failed to show any evidence of an aetiological link acting by raised maximal gastric secretion between DU and *H pylori*: indeed, the predominant aetiological factor for DU in our series was increased maximal gastric secretion and the association of *H pylori* with reduced gastric secretion makes it unlikely that the organism is an aetiological factor.

The hypothesis that *H pylori* is an important factor in the aetiology of duodenal ulcer rests upon three lines of evidence: (1) an increased incidence of *H pylori* in patients with duodenal ulcer compared with controls; (2) the claim that *H pylori* increases gastric secretion; and (3) the well documented reports from several centres that eradicating the organism results in healing with longer relapse free interval than H₂ antagonists and proton pump inhibitors can achieve. We present in this paper evidence that seems to deny the acid link, at least as far as the parietal cell mass is concerned.

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