PAPERS

Circadian gastric acidity in *Helicobacter pylori* positive ulcer patients with and without gastric metaplasia in the duodenum

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Abstract

Background—The presence of gastric metaplasia allows *Helicobacter pylori* to colonise the duodenum and this condition is thought to be acquired as a response to acid hypersecretion. This functional disorder, however, is present only in a subgroup of duodenal ulcer patients and, in addition, surface gastric metaplasia has been frequently found in the proximal duodenum of normal subjects and patients with non-ulcer dyspepsia, who cannot be certainly considered as acid hypersecretors.

Aims—To clarify the role of acid in inducing gastric type epithelium in the duodenum. This study aimed at assessing whether the pattern of circadian gastric acidity differs between *H pylori* positive duodenal ulcer patients with and without duodenal gastric metaplasia.

Patients—Seventy one patients with duodenal ulcer confirmed by endoscopy and who were found to be positive for *H pylori* infection by histology on antrum biopsy specimens were enrolled into this study.

Methods—Gastric type epithelium in the duodenum was found in 49 of 71 ulcer patients (69%). Continuous 24 hour gastric pH metry was performed in 50 healthy subjects and in the two subgroups of duodenal ulcer patients with and without gastric metaplasia in the duodenum. Gastric acidity was calculated for 24 hours (1700–1659), night (2000–0759) and daytime (0800–1959).

Results—Ulcer patients without gastric metaplasia showed a significantly higher gastric acidity ($p < 0.001$) than controls for every time interval considered, while the ulcer subgroup with gastric metaplasia was more acid than healthy subjects ($p < 0.001$) during the whole 24 hour period and the daytime. There was no difference between the two subgroups of duodenal ulcer patients with and without gastric metaplasia during the various time segments analysed.

Conclusions—The findings confirm that the circadian gastric acidity of duodenal ulcer patients is higher than that of controls. As there is no difference in

gastric pH between duodenal ulcer patients with and without gastric metaplasia, gastric hyperacidity is not specific to patients with duodenal gastric metaplasia. It is probable that this histological change is a non-specific response to mucosal injury resulting from various factors and not exclusively to acid.

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Keywords: duodenal gastric metaplasia, duodenal ulcer, gastric acidity, *Helicobacter pylori*, pH monitoring.

It is now generally accepted that *Helicobacter pylori* infection causes type B chronic gastritis and is frequently associated with peptic ulceration.¹ The pathogenetic link between *H pylori* and duodenal ulcer, however, is still not clear. As the germ colonises only gastric type epithelium, many authors^{2–4} have hypothesised that it contributes to ulceration by growing on areas of gastric metaplasia in the duodenum. When these areas are infected, chronic duodenitis develops and then duodenal ulcer may occur.⁵

The development of duodenal gastric metaplasia is believed to be a protective mechanism secondary to acid injury.⁶ The responsibility of acid in this process seems to be supported by experimental^{7–8} and human studies.^{9–12} However, this evidence is countered by the following findings. Epithelium with gastric metaplasia has been found in up to 22%–64% of normal subjects,^{13–14} who cannot be defined as acid hypersecretors. In addition, patients with duodenal ulcer certainly represent a population secreting, on average, more acid than normal,¹⁵ but it is well known that only one third of these patients have peak acid output above the upper limit of normal.¹⁶ Although a rapid gastric emptying may also produce an increased acid load to the duodenum with subsequent possible mucosal injury, only a subgroup of duodenal ulcer patients shows this functional disorder.¹⁷ Finally, duodenal gastric metaplasia has been found in a high proportion of patients with non-ulcer dyspepsia,^{6–11–18} who have a basal acid output comparable to that of normal subjects¹⁹ and a circadian gastric acidity significantly lower than normal.²⁰ Apart from data obtained in animal studies, the

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number of papers that correlated directly gastric acid with duodenal gastric metaplasia in human beings are few.^{11 12 21} More importantly, the evaluation of gastric acidity in these studies is highly questionable, because pH was measured in single samples of gastric juice collected during unphysiological endoscopy. For instance, some authors¹¹ chose pH 2.5 as the threshold below which gastric juice was considered consistently acid and this allowed them to correlate the presence of high acidity with gastric metaplasia. It should be remembered, however, that a pH value of 2.5 units is poorly representative of the low pH values commonly found in basal gastric juice of both normal subjects and duodenal ulcer patients.^{22 23} The physiological recording of gastric pH is now possible by means of modern computerised devices that allow us to describe accurately all the time related acidity variations within the stomach over the circadian cycle.²⁴

As the relation between gastric acid and the formation of duodenal gastric metaplasia is still controversial, we carried out this study to assess whether the pattern of circadian gastric acidity differs between *H. pylori* positive duodenal ulcer patients with and without gastric metaplasia in the duodenum.

Methods

Patients

Seventy one patients with duodenal ulcer confirmed by endoscopy and found to be *H. pylori* positive were enrolled into this study. Patients receiving non-steroidal anti-inflammatory drugs or longterm treatment with powerful antisecretory drugs were excluded. *H. pylori* infection was verified by histology on two biopsy specimens taken from the antrum, fixed in formalin, and stained with the well established Warthin-Starry and modified Giemsa methods. Two additional biopsy specimens were taken from the duodenum at the margins of the ulcer crater to detect areas of gastric metaplasia, which have been shown frequently in this site.²⁵

Gastric metaplasia was defined as the occurrence of foci of gastric epithelial cells containing apical PAS positive neutral mucine together with the absence of a brush border. Forty nine patients (69%) were found to have surface gastric metaplasia (31 male, mean (SD) age 47 (12)) and 22 patients (31%) were found to be devoid of gastric metaplasia in the duodenum (14 male, mean (SD) age 44 (15)). There was no significant difference between the two subgroups with and without gastric metaplasia with regard to ulcer size (12.1 (2.6) mm *v* 10.9 (2.2)), length of history (10.8 (9.9) years *v* 11.3 (12.2)), and number of ulcer relapses (8.8 (9.7) *v* 7.6 (7.8)). All patients gave their informed consent to the study, which was also approved by the local ethical committee.

pH Monitoring

All duodenal ulcer patients underwent 24 hour

continuous gastric pH metry within three days of the endoscopic diagnosis of the ulcer niche. During this interval they were asked to take only antacids for symptom control, if necessary, and these drugs were withdrawn the day of examination. No patient was being treated with antisecretory drugs during the two weeks preceding the test or had undergone previous gastric surgery. The examination was performed with two closely adjacent pH electrodes that were positioned about 10 cm below the cardia, using a well established procedure.^{26 27} This method removes noise, interference, and artefacts superimposed to the endoluminal pH tracings, thus improving the accuracy of 24 hour pH metry in every clinical condition. The 24 hour mean pH profile obtained in each patient by averaging the pH tracings of the two channels every minute is calculated for final analysis. Obviously, tracings where pH readings vary for more than one hour over 24 hours cannot be considered valid and were repeated.²⁷ The test was also performed in 50 healthy subjects (30 male, mean (SD) age 47 (10)) who were asymptomatic and had no history of relevant gastroenterological or systemic disease and were used as controls. The search for *H. pylori* infection was not performed in them, but it has been shown that there is no difference in 24 hour gastric acidity between *H. pylori* positive and negative normal subjects²⁸ and chronic *H. pylori* infection does not change the circadian pattern of gastric acidity.^{22 29} In total, four tests had to be repeated because of discrepancies lasting for more than one hour over the entire circadian cycle between the two simultaneous tracings of each examination. Patients and controls were fully ambulatory and smoking was permitted, because it has been shown not to affect the gastric pH pattern.³⁰ During the test day, the time of the meals (dinner at 1800, breakfast at 0800, and lunch at noon), and composition³¹ were standardised. Extra food or water or alcoholic and carbonated beverages were forbidden.

Data processing and statistical analysis

At the end of each run, experimental data were downloaded into a calculator (Compaq, Proliant) using service routines. The pH readings of the two channel tracings of each patient were averaged every minute,²⁷ so that 1440 datapoints/24 hours were obtained. Acidity data were expressed as mean pH (SD) values^{31 32} for three different time intervals: 24 hours; night (2000–0759) and daytime (0800–1959). These findings were compared by means of two way ANOVA and p values were corrected for multiple testing. The density distribution of 24 hour pH values were also calculated for each population. Patient characteristics were compared by means of Student's *t* test. Statistical significance was set at *p* < 0.05.

Results

Figure 1 shows the 24 hour mean pH profiles obtained in normal subjects and in duodenal

Figure 1: 24 Hour mean pH profiles of the three populations studied. Meals were given at 1800, 0800, and 1200.

ulcer patients with and without gastric metaplasia. The curves pertaining to the two subgroups of duodenal ulcer patients are rather superimposed and run below that of controls during almost the whole 24 hour period. The difference between ulcer patients and normal subjects is particularly evident during the first half of the night and the postprandial periods.

The Table shows the mean pH values of each population calculated for three different time intervals. The two subgroups of *H pylori* positive duodenal ulcer patients have significantly higher acidity than normal subjects ($p < 0.001$) during the whole 24 hour period and the daytime. Patients without gastric metaplasia maintain higher acidity than normal also during the night ($p < 0.001$), while those with gastric metaplasia do not differ from controls in this period. On the other hand, the acidity patterns of the two subgroups of duodenal ulcer patients with and without gastric metaplasia do not differ for every time segment considered.

The analysis of the density distribution of 24 hour pH values (Fig 2) shows that the peaks at the lowest pH values, denoting the highest acidity, are much more evident for the two subgroups of duodenal ulcer patients than for normal subjects.

Discussion

Our study shows that ulcer patients with and without gastric metaplasia in the duodenum have a similar pattern of gastric acidity and both subgroups are significantly more acid than normal subjects over the 24 hour period. The existence of higher acidity in patients with duodenal ulcer than in healthy subjects is a well established finding in pathophysiological

Mean pH values (SD) during three different time intervals for each population

Time period	Normal subjects	Duodenal ulcer with metaplasia	Duodenal ulcer without metaplasia
1700–1659	1.9 (0.4)	1.6 (0.5)	1.4 (0.4)
2000–0759	1.6 (0.5)	1.4 (0.6)	1.2 (0.3)
0800–1959	2.2 (0.5)	1.8 (0.5)	1.7 (0.5)

Figure 2: Density distributions of pH values over the whole 24 hour period for the three populations that were analysed.

studies with continuous longterm pH monitoring.^{22 23} On the other hand, the similar pattern of gastric acidity in *H pylori* positive ulcer patients with and without duodenal gastric metaplasia casts some doubts about the responsibility of acid in inducing the development of gastric type epithelium in the duodenum of these patients. Using traditional acid secretory tests, Patrick³³ also observed the lack of correlation between gastric hyperacidity and duodenal gastric metaplasia, while Kreuning³⁴ found that superficial gastric metaplasia in the duodenum was directly correlated to gastric acid secretion. Our technique measuring gastric pH over the entire circadian cycle provides us with information on both fasting and meal related gastric acidity and it is certainly more accurate than that achievable by only assessing the pH of a single gastric juice sample collected during an unphysiological manoeuvre, such as endoscopy.^{11 12 21} It is probable that the direct correlation of acid with the extent of gastric type epithelium in the duodenum is the best way to define its role in inducing this histological change. If acid is the most important factor, it is to be expected that it increases in parallel with the degree of gastric metaplasia. We have recently evaluated this relation in 47 *H pylori* positive duodenal ulcer patients, in whom gastric metaplasia was graded by assessing four biopsy specimens from the duodenal bulb (personal unpublished observations). We found that there is a progressive, although not significant, reduction of 24 hour gastric acidity as the extent of gastric metaplasia increases: pH 1.4 (0.4) *v* gastric metaplasia <5% (n=19); pH 1.6 (0.4) *v* gastric metaplasia 5–20% (n=14); pH 1.7 (0.3) *v* 20–50% (n=8); pH 2.0 (0.5) *v* gastric metaplasia >50% (n=6). These findings seem to confirm further that acid cannot be considered the only factor implicated in the formation of duodenal gastric metaplasia.

Using two biopsy specimens from the duodenum, we found gastric metaplasia in 69% of our *H pylori* positive ulcer patients. This proportion is in keeping with average data published in medical literature on this type of patient and ranging from 39% to 92%.⁶ It is noteworthy that even a single biopsy specimen taken from the edge of a consecutive series of duodenal ulcers allowed some authors to show

the presence of gastric metaplasia in 92% of cases.²⁵ More recently, however, a large number of duodenal biopsy specimens has been recommended to improve the detection of gastric metaplasia,¹² which is generally patchily distributed. Yang³⁵ found duodenal gastric metaplasia in 83% of Chinese duodenal ulcer patients by examining four biopsy specimens taken from the ulcer margins. In the light of this study, we may have missed some patients with gastric metaplasia because of the small number of biopsy specimens, but, if so, we think that the reflections on the overall results of our study should only be marginal. Our experimental findings, in fact, show a clear tendency towards higher acidity in ulcer patients without duodenal gastric metaplasia compared with those who have gastric metaplasia and therefore moving some of the patients from the first group to the second group would only result in a major equivalence between them.

If gastric hyperacidity is not specific to patients with duodenal gastric metaplasia compared with those without this histological alteration, an augmented load of acid to the duodenum may be proposed as alternative cause of this type of injury. We have already emphasised that an accelerated gastric emptying is only characteristic of a subgroup of duodenal ulcer patients¹⁷ and, therefore, other mechanisms may be involved, such as a defective buffering of duodenal acid on the part of bicarbonates secreted by the pancreas or duodenal mucosa. A reduced secretion of pancreatic bicarbonates has been already described in duodenal ulcer,³⁶ but the impairment of duodenal bicarbonates should also be taken into account. In another study, Rapier³⁷ showed that *H. pylori* diminishes proximal duodenal mucosal bicarbonate secretion in patients with duodenal ulcer and, more importantly, this reduction returns to normal after *H. pylori* is eradicated. It is also true, however, that the important role of the neutralisation process of acid within the duodenal bulb has been highly questioned in another study.³⁸ These authors measured simultaneously gastric and duodenal pH and showed that bulb acidity does not significantly differ between healthy subjects and patients with duodenal ulcer. Moreover, there was no difference between normosecretor controls and hypersecretor ulcer patients and this seems to further exclude the pathogenetic relevance of acid in causing increased duodenal aggression. An additional study on the pattern of intra-duodenal acidity³⁹ confirmed that bulb pH is similar in patients with active ulceration and controls, even though a higher bulb acidification can be seen in patients with healed ulcers. Further support for an incomplete correlation between excess secretion of acid and duodenal gastric metaplasia comes from the finding that the extent of gastric type epithelium is not affected by the longterm use of powerful antisecretory drugs, such as H₂ receptor antagonists,^{6 40 41} and from the conflicting results on its reversal after parietal cell vagotomy.^{40 42} It has been preliminarily seen,

however, that the more profound acid inhibition achievable with the proton pump inhibitor omeprazole may favour the regression of gastric metaplasia,⁶ but this must be confirmed in an appropriate number of patients. In our opinion, an important elucidation of the role of acid in inducing gastric metaplasia in the duodenum would also come from the assessment of the prevalence of duodenal gastric type epithelium in patients with chronic atrophic gastritis and complete impairment of acid secretion.

It is also unclear whether the development of duodenal gastric metaplasia is a reaction to inflammation or a primary phenomenon. Fitzgibbons¹³ found that gastric metaplasia often occurs in the distal duodenal bulb of normal subjects in the absence of severe duodenal inflammation and Noach *et al*⁶ excluded any significant change in duodenal gastric metaplasia one year after *H. pylori* eradication and the probable improvement of the organism related inflammatory process. More recently, however, Khulusi⁴¹ showed that the extent of gastric metaplasia in duodenum declines 10 months, on average, after *H. pylori* eradication. Thus, the bacterium itself and its related duodenal inflammation seems to be responsible for the formation or, at least, the further stimulation of gastric type epithelium in the duodenum.¹² On the other hand, the role of chronic inflammation in inducing gastric metaplasia seems to be also confirmed by the detection of this histological abnormality in patients with chronic inflammatory disease, such as Crohn's disease at different sites in the gastrointestinal tract and intestinal tuberculosis.^{6 43 44} It is also true that gastric metaplasia has been found in many areas of the gastrointestinal tract, including the rectum, pancreas, and gall bladder,³ where the contact of acid can be absolutely excluded and therefore this factor is not required for its development.

Further confirmation that factors other than acid can be implicated in the genesis of gastric metaplasia in the duodenum derives from two studies,^{18 45} which have shown that heavy alcohol consumption is associated with the formation of duodenal gastric type epithelium. This finding and the above considerations seem to highlight the fact that gastric metaplasia is a non-specific response to mucosal injury and many factors can be responsible for this process, including acid and other substances or events.

In conclusion, our study shows that circadian intragastric acidity does not differ between *H. pylori* positive duodenal ulcer patients with and without gastric metaplasia in the duodenum. Thus, an increased gastric acidity cannot be considered an essential factor in the development of duodenal gastric metaplasia. As this can be considered a non-specific response to mucosal injury, it is probably associated with many factors and not exclusively to acid.

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