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HELICOBACTER PYLORI

Long-term follow-up of gastric histology after *Helicobacter pylori* eradication

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Abstract *Helicobacter pylori* causes chronic active gastritis and is thought to be associated with the development of gastric atrophy, intestinal metaplasia and carcinoma. As the effect of *H. pylori* eradication on this process is poorly understood, we sought to determine the long-term effects of *H. pylori* eradication on gastric histology. Fifty-four patients with duodenal ulceration associated with *H. pylori* infection received *H. pylori* eradication therapy in 1985/86 and either remained infected ($n = 22$) or had the infection eradicated ($n = 32$); patients were followed up by endoscopy with gastric antral biopsy for 7.1 years (mean). Histopathological analysis of gastric antral mucosa from patients rendered *H. pylori*-negative revealed a marked decrease in both inflammatory cells within the lamina propria and intra-epithelial neutrophils and an increase in epithelial mucinogenesis. Gland atrophy remained unchanged in both *H. pylori*-positive and -negative patients. When examined for the presence and severity of intestinal metaplasia, there was neither a difference between the two patient groups nor a change with time. These data demonstrate that significant long-term improvements in gastric histology accompany *H. pylori* eradication when compared with histology in patients with persistent infection. Whether this confers a protective effect by reducing the risk of gastric carcinoma remains unknown.

Keywords: eradication, follow-up, gastric atrophy, gastric carcinoma, *Helicobacter pylori*, histology, metaplasia.

INTRODUCTION

Helicobacter pylori causes chronic active gastritis and is strongly associated with the development of duodenal and gastric ulceration. Numerous studies have demonstrated that eradication of *H. pylori* reduces the recurrence rate of duodenal ulcer over a 1 and 2 year follow-up period; more recently, this protective effect has been shown to extend to 7 years after treatment.[1] The benefit of *H. pylori* eradication therapy in patients with gastric ulceration probably exists,[2,3] but is less well established. Of greater controversy is the relationship between *H. pylori* infection and gastric carcinoma and, hence, the role of eradication therapy in protecting against carcinoma.

Helicobacter pylori infection is an independent risk factor for the development of gastric carcinoma,[4] and one large multinational study suggested that this risk is six-fold when compared with subjects not infected by *H. pylori*.[5] The putative mechanisms linking primary *H. pylori* infection ultimately to gastric carcinoma are unproven, but may relate to the development of chronic gastritis, mucosal atrophy and intestinal metaplasia[6-8] as precursor lesions to malignancy.[9-12] Eradication of *H. pylori* is accompanied by resolution or improvement in the histological severity of gastritis in the short term,[13] but the effects of *H. pylori* eradication on gastric mucosal histology are unknown for periods greater than 2 years.[14] In the present study we examined the long-term histological outcome of *H. pylori* eradication and compared this with patients who remained infected.

METHODS

One hundred patients with duodenal ulceration associated with gastric antral *H. pylori* infection were enrolled in a double-blind trial of *H. pylori* eradication therapy in 1985/86, and were prospectively followed by endoscopy with gastric antral biopsy for up to 12 months.[15] Of 78 patients available in 1992/93 for

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clinical and endoscopic follow-up, 63 (81%) agreed; the details of that study have been reported previously.[1]

At the time of each endoscopy, three gastric antral biopsies were taken for histological examination, which was undertaken by a single experienced histopathologist (JRW) blinded to the clinical details of each patient and without reference to previous pathological specimens. Formalin-fixed paraffin-embedded sections stained with haematoxylin and eosin, Giemsa and combined periodic acid-Schiff and alcian blue were examined for the following features, derived from the Whitehead classifications of gastritis:[16] (i) lamina propria inflammatory cell infiltrate; (ii) neutrophil infiltration of epithelium; (iii) reduction in epithelial mucinogenesis; (iv) gland atrophy; and (v) intestinal metaplasia.

This was performed for biopsies taken at entry to the 1985/86 study (time = 0), upon completion of that study (mean t = 0.8 years) and at the time of the 1992/93 study (mean t = 7.1 years). These histological parameters were graded semiquantitatively according to a 10 point grading system as outlined in Table 1; the results for patients who were initially rendered *H. pylori* negative and remained so over the 7.1 years of follow-up were compared with those patients who remained infected throughout. Statistical analysis of the difference in histological grade from t = 0 to 7.1 years between *H. pylori*-positive and -negative patient groups was performed using the Mann-Whitney *U*-test.

Table 1 Grading of the five histological parameters

Lamina propria inflammatory cell infiltrate/reduction in epithelial mucinogenesis/ gland atrophy		Neutrophil infiltration of epithelium/intestinal metaplasia	
0–3	Normal	0	None
4–5	Mild	1–3	Mild
6–7	Moderate	4–6	Moderate
8–9	Marked	7–9	Marked

RESULTS

Of 63 patients followed between 1985 and 1993, nine were excluded from histological study because they either received *H. pylori* eradication therapy ($n = 6$) or they became reinfected with *H. pylori* ($n = 3$) during the interval period between studies. Twenty-two patients who remained *H. pylori*-positive (15 male, seven female; mean age 52 years; range 30–83 years) and 32 patients who remained *H. pylori*-negative (23 male, nine female; mean age 52 years; range 24–78 years) had a mean histological follow-up over 7.1 years (range 6.0–7.9). Six (27%) *H. pylori*-positive patients and five (16%) *H. pylori*-negative patients ($\chi^2 = 1.09$; NS) received histamine H_2-receptor antagonists during follow-up (continuously in three patients: two *H. pylori*-positive and one *H. pylori*-negative). No patient received proton pump inhibitors.

The histological results are summarized in Table 2. Before *H. pylori* eradication was attempted, both groups had similar histological features with the exception of gland atrophy, which was more marked in the group for whom eradication failed ('*H. pylori*-positive' group; $P = 0.006$, Mann-Whitney *U*-test). However, this difference was no longer present at the 0.8 year (mean) follow-up. In patients who remained *H. pylori*-positive over the next 7.1 years, there was no change in the grade of inflammatory cell infiltrate in the lamina propria, neutrophil infiltration of the epithelium, intestinal metaplasia, gland atrophy or epithelial mucinogenesis.

By contrast, patients who remained *H. pylori*-negative showed a marked reduction in both inflammatory cells in the lamina propria and intraepithelial neutrophils at 0.8 years and this persisted to follow-up at 7.1 years. There was some return of epithelial mucinogenesis, but no change in gland atrophy, which remained mild to moderate in severity in the *H. pylori*-negative group. Overall, the grade of intestinal metaplasia was mild and there was no difference in severity between *H. pylori*-positive and -negative patients.

Table 2 Histological grading of patients who remained *H. pylori*-positive compared with those rendered *H. pylori*-negative

	LP infiltrate	Epithelial PMN	Metaplasia	Atrophy	Mucin
Hp+ patients					
t = 0	7.6 ± 1.0	5.0 ± 1.4	0.7 ± 1.4	5.0 ± 1.5	6.0 ± 1.7
t = 0.8	6.8 ± 1.4	4.6 ± 1.7	0.7 ± 1.3	4.5 ± 1.3	6.9 ± 1.6
t = 7.1	7.0 ± 0.8	4.9 ± 1.6	0.9 ± 1.3	4.7 ± 1.0	5.6 ± 1.7
Hp − patients					
t = 0	7.3 ± 1.3	5.3 ± 1.6	0.8 ± 1.3	3.8 ± 1.4	5.7 ± 1.2
t = 0.8	3.7 ± 1.5	0.3 ± 0.5	0.5 ± 1.2	4.4 ± 1.8	4.6 ± 1.5
t = 7.1	1.9 ± 0.8	0.3 ± 1.1	0.7 ± 1.4	3.8 ± 1.6	4.0 ± 1.5
P value	< 0.0001	< 0.0001	NS	NS	0.0004

All patients were *H. pylori*-positive at t = 0; *H. pylori*-negative patients were all negative for *H. pylori* at 0.8 and 7.1 years.

LP infiltrate, the lamina propria inflammatory cell infiltrate; epithelial PMN, neutrophil infiltration of the epithelium; metaplasia, intestinal metaplasia; atrophy, gland atrophy; mucin, reduction in epithelial mucinogenesis; NS, not significant; *P* value, analysis of the difference in histological grade from 0 to 7.1 years between Hp+ and Hp − patient groups.

DISCUSSION

The present study has shown that successful eradication of *H. pylori* is accompanied by long-term improvement in the histological abnormalities that occur with this infection. In patients rendered *H. pylori*-negative there was a marked reduction in the lamina propria inflammatory cell infiltrate, almost complete loss of intraepithelial neutrophils and an improvement in the amount of epithelial mucinogenesis. By contrast, in patients who remained *H. pylori*-positive, there was no improvement in any of these histological features.

In neither *H. pylori*-positive nor *H. pylori*-negative patients did the amount of glandular atrophy change over the 7.1 year follow up. Furthermore, none of the *H. pylori*-positive patients developed histological features of 'gastric atrophy': the combination of severe gland atrophy, extensive metaplasia and negligible inflammation.[17] Proposals that *H. pylori* infection leads ultimately to gastric atrophy stem from longitudinal population based studies,[11] which suggest that chronic gastritis eventually progresses to atrophic gastritis. Further support for this sequence of events comes from a recent 11.5 year follow-up study of a group of untreated *H. pylori*-positive patients who developed atrophic gastritis and intestinal metaplasia more frequently than did a group of patients never infected.[6] This was an important observation in light of the association between gastric atrophy and carcinoma.[12] Intestinal metaplasia is also thought to be a precursor lesion for gastric carcinoma.[10,11] If chronic *H. pylori* infection does lead to gland atrophy, intestinal metaplasia and ultimately, in certain individuals, gastric carcinoma, this process is likely to occur over several decades. Hence, longer duration of follow up of our patients may be needed to detect progression of potentially premalignant histological abnormalities.

A further limitation of our study is that only three gastric antral biopsies were taken at each endoscopy, hence creating the possibility of histological sampling error. Overall, intestinal metaplasia was generally mild or absent, both in patients who remained *H. pylori*-positive throughout the study period and those in whom *H. pylori* was eradicated. Our preliminary histological studies[18] were not undertaken using the combined periodic acid-Schiff and alcian blue stain to examine for intestinal metaplasia. This resulted in an overestimation of the presence of intestinal metaplasia in our initial studies, especially when persistent *H. pylori* infection was present, and illustrates the importance of this tissue stain.

Future long-term studies of this type may be difficult to undertake in view of the link between *H. pylori* and gastric carcinoma[19,20] and the recent World Health Organisation classification of *H. pylori* as a class I carcinogen. It is unknown whether successful *H. pylori* eradication therapy results in lessening of the gastric cancer risk to levels seen in subjects who have never been infected. Previous follow-up studies of up to 2 years suggested that eradication of *H. pylori* results in incomplete[21] or no improvement in intestinal metaplasia or gland atrophy.[14] These observations and the present study suggest that if *H. pylori* eradication is associated with a lessened risk for gastric carcinoma, this reduced risk may not be to the level seen in subjects never infected.

In conclusion, previous data suggest that *H. pylori* infection results in a progressive form of chronic gastritis, which may predispose to gastric cancer.[6,8–12] Our data indicate that *H. pylori* eradication is accompanied by long-term improvement in the histological severity of gastritis, but whether this is reflected in clinical practice by a reduced incidence of gastric carcinoma is unknown and may be difficult to show.

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