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ORIGINAL PAPER

Helicobacter pylori Infection and Severity of Reflux-Induced Esophageal Disease in a Cohort of Patients with Columnar-Lined Esophagus

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Abstract The relationship between *Helicobacter pylori* infection and reflux-induced esophageal diseased is controversial. We examined esophageal disease severity in patients with columnar-lined esophagus and compared results between patients with and without *Helicobacter pylori* infection. Medical records of 1000 patients diagnosed with columnar-lined esophagus were examined. Endoscopic and histological findings of reflux-induced esophageal disease were compared between *H. pylori*-positive and *H. pylori*-negative patients. Four hundred twenty-nine patients (42.9%) showed evidence of *H. pylori* status, of whom 239 (55.7%) were positive and 190 (44.3%) negative. There were no significant differences in length of columnar-lined segment ($P = 0.305$), frequency of associated esophagitis ($P = 0.583$), or presence of gastroduodenal inflammation ($P = 0.335$, $P = 0.131$) between the two groups. Histological grade of esophageal disease severity was similar between them, with no statistically significant differences ($P = 0.231$).

We conclude that in patients with established columnar-lined esophagus, there appears to be no difference in severity of reflux-induced esophageal disease between those with and those without *H. pylori* infection.

Keywords Esophagus · Barrett's · *Helicobacter pylori* · Dysplasia · Eradication

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Introduction

The association between *Helicobacter pylori* (HP) and reflux-induced esophageal disease is controversial. Whereas some authors have proposed various mechanisms by which HP may be detrimental to esophageal mucosa [1–4], others have not been able to demonstrate such a relationship and some have suggested that HP may even be protective for this type of disease [5, 6].

There is a well-documented relationship among HP infection, peptic ulcer disease (PUD), and noncardia gastric cancer [7–11], and the vast decrease in prevalence of HP infection over the last 20–30 years has coincided with a rapid decrease in these diseases. Over this same time frame, however, the incidence of gastroesophageal reflux disease (GERD) and esophageal adenocarcinoma has risen dramatically and has led many authors to speculate on the possible association between this and this observed decrease in HP prevalence [12–15].

Some studies have also suggested that patients with previous PUD who have their HP eradicated are much more likely to develop GERD at a later stage [16] and support the theory that HP may be playing some protective role against the development of reflux-induced esophageal pathology.

Many studies have looked at the effect of HP on gastric acid output [17–19], which has led to theories of mechanisms of subsequent effect on esophageal mucosa. Authors have suggested that the distribution of HP within the stomach, with resultant varying patterns of gastritis, has different effects on gastric acid output. A predominant antral distribution may cause an increase in acid production via its effect on somatostatin levels, whereas a corpus distribution resulting in chronic gastric atrophy may lead to a subsequent reduction in acid production. There appear to be very few studies, however, comparing this relationship and the resultant effect

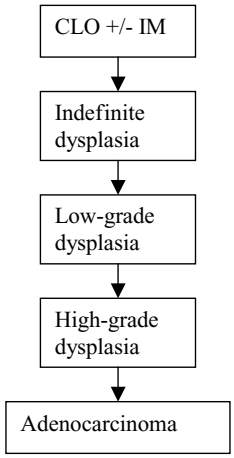

Fig. 1 Sequence of progression of reflux-induced esophageal disease

on esophageal mucosa directly. There is also little known about the direct effect of HP on esophageal mucosa itself, although some studies have observed HP only adhering to areas of gastric metaplasia in esophageal mucosa, and not to intestinal metaplasia, and have therefore concluded that it is unlikely to have any direct malignant potential [20].

The aim of this study was to examine the prevalence of HP infection in a cohort of patients with established columnar-lined esophagus (CLO) and ascertain any differences in severity of their esophageal disease compared to patients who were HP negative (HP^-).

Patients and methods

Medical records of 1000 patients diagnosed with CLO and registered with the U.K. National Barrett's Esophagus Registry were examined. Information was extracted and entered onto the research database situated at the Royal Free Hospital, London.

Specific medical information including patient demographics—age, gender, follow-up—and endoscopic and histological findings were used for this study and patients were divided into two cohorts based on documented HP status as defined below.

Data collected on smoking habits and alcohol consumption were analyzed as a comparison between cohorts. Scores were calculated based on frequency of consumption of alcohol and usage of tobacco as used in previous studies [21]. Severity of esophageal disease on histology was based on grade reported by the pathologists and assumed a sequence of progression from *Campylobacter*-like organism (CLO) ± intestinal metaplasia (IM) to indefinite dysplasia (ID) to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to adenocarcinoma (AC) (see Fig. 1).

Data were examined and classified as the most pathological findings for that patient. On endoscopy this meant the greatest length of CLO recorded and the presence of esophagitis, gastritis, or duodenitis if documented at any stage for those patients; and on histology the most severe pathology attained as per Fig. 1. This was considered a more useful indication of disease severity than follow-up endpoint to negate the process of any possible disease regression that may have resulted over the follow-up period due to pharmacological intervention.

All endoscopic and histological findings used in the analysis were documented after HP status for the patient was noted.

Definition of the cohorts

Two cohorts were defined from information extracted from the database.

Helicobacter pylori positive (HP+) Patients with documented evidence of HP infection on CLO test, breath test, or serology or observed at histology (stomach or esophagus), and with no subsequent documentation of HP− status were taken as being HP+ for the purpose of the study. Patients who had undergone eradication therapy but who on repeat testing remained HP+ (i.e., unsuccessful eradication) were also included in this cohort.

Helicobacter pylori negative (HP−) All patients with documented evidence of HP− status on CLO, breath test, or serology were included in the HP− cohort, except for patients who had received successful eradication therapy having been previously noted to be HP+. Patients who had received eradication therapy but had no posttreatment status documented were also excluded from the study.

Demographic, endoscopic, and histological data were compared between the HP+ and the HP− groups, with statistical analyses undertaken using SPSS version 11.0. The chi-square test of association was used to compare categorical data between the groups, and the independent *t*-test and Mann-Whitney *U* to examine differences between continuous variables.

Results

Prevalence of HP infection

Of the 1000 patients examined, 429 (42.9%) had documented evidence of HP status. Of these, 239 (55.7%) had evidence of being HP+ or had documentation of having had eradication therapy at some time over their follow-up. Sixty-six (27.6%) had eradication therapy, with 20 having a documented HP− status posttreatment; 6 remained HP+ and 40 had no HP status documented in the notes posttreatment.

HP+ cohort One hundred seventy-nine patients were included in the HP+ cohort. Seventy-two (40%) were diagnosed as being HP+ on their first endoscopy that was diagnostic for CLO; 99 (55%) were diagnosed after their initial diagnosis of CLO (an average of 5.36 years postdiagnosis) and 8 (5%) before their diagnosis.

HP− cohort One hundred ninety patients had documented evidence of being HP− (not including the 20 successfully eradicated patients). One hundred four (55%) were diagnosed on the same endoscopy as their initial diagnostic for CLO endoscopy; 68 (36%) were diagnosed after their initial diagnosis of CLO (an average of 4.71 years postdiagnosis) and 18 (9%) before their diagnosis (an average of 2.17 years before).

Comparison between HP+ and HP− Cohorts

Demographics/patient characteristics The ratio of males to females in the HP+ group was 2.1:1 (121:57) and 1.6:1 (117:73) in the HP− group, with no significant differences between them ($P = 0.199$, χ^2 test).

The mean age at diagnosis of CLO was also similar between the two cohorts, being 60.45 years in the HP+ group and 58.42 years in the HP− group ($P = 0.148$, *t*-test).

The mean endoscopic follow-up period was longer for the HP+ group (5.39 years) compared to the HP− group (3.35 years) ($P < 0.001$).

Of the patients who were diagnosed as being HP+, 48 (19.6%) were detected on CLO test alone, 49 (20.0%) on histology, 53 (21.6%) on serology, 3 (1.2%) on breath test, and the rest on a combination of these tests. Of the patients included in the HP− cohort, 124 (65.3%) were detected by CLO test alone, 52 (27.4%) on serology, 5 (2.6%) on breath test, and the rest on a combination of these tests.

There were no significant differences in smoking habits ($P = 0.796$, χ^2) or in overall alcohol consumption ($P = 0.067$) between the two cohorts.

Endoscopic findings The mean length of CLO segment at worst pathology was 6.13 cm for the HP+ group and 5.91 cm for the HP− group, with no significant differences on statistical analysis ($P = 0.269$, Mann-Whitney *U*).

There was no significant difference in the frequency of associated esophagitis ($P = 0.583$, χ^2 test) or in associated gastroduodenal inflammation or ulceration ($P = 0.335$, inflammation; $P = 0.131$, ulceration, χ^2) between the two cohorts.

Histological findings Distribution of grades of histology at worst pathology were very similar between the two groups, with no significant differences overall ($P = 0.231$) or when proportions of nondysplastic and dysplastic disease were analyzed more closely ($P = 0.386$).

Endoscopic and histological findings are summarized in Table 1.

Table 1 Findings at worst pathology for the two cohorts

Finding	HP positive	HP negative
Endsoscopic		
Mean length of CLO	6.13 cm	5.91 cm
Esophagitis	141 (78.8%)	146 (76.8%)
Gastritis/ulceration	48 (26.8%)	43 (22.6%)
Duodenitis/ulceration	38 (21.2%)	29 (15.3%)
Histological (frequency of grades of disease)		
CLO	21 (11.7%)	32 (16.8%)
CLO + IM	65 (36.3%)	76 (40.0%)
ID	33 (18.4%)	24 (12.6%)
LGD	50 (27.9%)	43 (22.6%)
HGD	3 (1.7%)	7 (3.7%)
AC	7 (3.9%)	8 (4.2%)
Total	179	190

Note. CLO, *Campylobacter*-like organism; IM, intestinal metaplasia; ID, indefinite dysplasia; LGD, low-grade dysplasia; HGD, high-grade dysplasia; AC, adenocarcinoma.

Discussion

Reports of the prevalence of HP infection in esophageal disease vary from 14% to 40% in GERD/esophagitis and 25% to 62% in CLO [22–27], although the prevalence of HP in esophageal adenocarcinoma seems to be much lower and reports have suggested anything from 0% to 20% [23, 25, 28]. From our study of a cohort of patients with CLO, the prevalence of HP infection in patients that had been tested was fairly high, at 55.7%. Even if the remaining 571 patients who were not tested for HP were found to be negative, this would give an overall prevalence of HP infection of 24.5%. As we would reasonably predict this to be higher, it may be that the prevalence of HP in the entire cohort would have been greater than the reported prevalence of HP infection in normal/control populations, which ranges from 17% to 36% [24, 28]. Whether it would have reached reported prevalence rates seen in patients with PUD, 48–94% [24, 28], however, seems unlikely.

Demographics and patient characteristics were similar between the two groups. Follow-up in the HP− group, however, was significantly shorter, and whether more dysplastic disease may have developed over a longer period of time is debatable. Overall, patterns of disease distribution and

endoscopic findings relating to esophageal disease severity were remarkably similar between the two groups, with no significant differences in any of the parameters examined. This seems to support the theory that HP may play little or no role in the progression of reflux-induced esophageal disease. However, that the predicted high prevalence of HP infection in the entire cohort could suggest a role in the initial pathogenesis of the disease is a possibility.

An unexpected finding of this study was that the frequency of associated gastroduodenal inflammation and ulceration did not seem to be higher in the HP+ group. This may reflect the fact that the vast majority of these patients would have been on long-term acid suppression treatment and therefore would be expected to have limited clinical evidence of gastroduodenal disease. There is also evidence that HP+ patients on proton pump inhibitors or H_2 receptor antagonists show a greater level of acid suppression [29, 30], an observation that has added weight to the argument that HP need not be eradicated in patients with esophageal disease.

On the other hand, long-term proton pump inhibitor therapy has also been shown consistently to alter the distribution of HP from an antral- to a corpus- or fundus-predominant pattern, an alteration that enhances the progress of atrophic gastritis and thus the risk of gastric cancer [31].

Whether or not to treat HP infection in these patients, therefore, is still controversial and there remains to be any current consensus over this. Interestingly, in our study, 571 of 1000 (57.1%) patients with CLO were *not* tested for HP at any time over their follow-up, and of those who were, only 27.6% of patients who were HP+ underwent eradication therapy.

Conclusion

In this study of patients with established CLO, there were no significant differences in esophageal disease severity between those who were HP+ and those who were HP−.

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