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Helicobacter pylori and gastro-oesophageal reflux disease: a cross-sectional epidemiological study

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ABSTRACT

Background: *H. pylori* infection is accompanied by a lower prevalence of reflux disease. There is still an ongoing debate as to whether *H. pylori* actually protects against the development of reflux oesophagitis or is merely an epiphenomenon. A cross-sectional study was performed to study the relation of *H. pylori* with reflux oesophagitis, hiatus hernia and Barrett's oesophagus.

Material and methods: Consecutive patients undergoing upper gastrointestinal endoscopy in a period of ten years were studied. Included were patients with active reflux oesophagitis and/or hiatus hernia and/or Barrett's oesophagus. As a reference group, patients without macroscopic abnormalities were included. *H. pylori* was detected applying routine diagnostic modalities.

Results: In the ten years 11,691 consecutive patients were studied. Reflux oesophagitis was seen in 1535 patients, 307 patients had Barrett's oesophagus and a hiatus hernia was present in 2116 patients. The reference group consisted of 5341 patients. *H. pylori* was significantly less often detected in patients with reflux oesophagitis or Barrett's oesophagus compared with the reference group, 20 *vs* 29% (p<0.001). Also presence of *H. pylori* was significantly lower in patients with hiatus hernia 20 *vs* 29% (p<0.0001).

Conclusion: The present study confirms, in a very large group of patients studied in one single centre, the findings of earlier papers. Patients without *H. pylori* gastritis suffer more often from reflux disease. There is a relation between *H. pylori* and reflux disease. However, the consequence of this relation will not be the same in every patient.

INTRODUCTION

The discovery of *H. pylori* has been a major breakthrough in understanding and treatment of gastritis and ulcer disease. Despite the effects of *H. pylori* infection on the gastric acid production,[1,2] the bacterium does not play a role in the pathogenesis of reflux disease. On the contrary, presence of *H. pylori* is accompanied by a lower prevalence of reflux disease.[3-7] There is still an ongoing debate as to whether *H. pylori* actually protects against the development of reflux oesophagitis or is merely an epiphenomenon.[8-10] In earlier studies, it was shown that patients with reflux disease exhibit *H. pylori* infection less often than a reference group of patients without signs of reflux oesophagitis or Barrett's oesophagus.[6,11] These findings have been confirmed in many other papers. In most studies relatively small populations of patients were studied. Significant differences in study design were present (prospective, retrospective case control or trial). In the present cross-sectional study the number of patients was extended considerably and the relation of *H. pylori* with reflux oesophagitis, hiatal hernia and Barrett's oesophagus in a large population of patients undergoing upper gastrointestinal endoscopy for various reasons was studied.

MATERIAL AND METHODS

All consecutive patients undergoing upper gastrointestinal endoscopy in a period of ten years were included. Endoscopies carried out as follow-up because of newly developed or recurrent symptoms were excluded. Included in the study were patients with active reflux oesophagitis and/or hiatus hernia and/or Barrett's oesophagus. As a

reference group, patients without macroscopic abnormalities in oesophagus, stomach or duodenum, with the exception of endoscopic signs of gastritis, were included. Biopsy specimens were taken from the gastric antrum if judged necessary by the endoscopist or if a clinical reason for detection of *H. pylori* was present. *H. pylori* was detected using Gram's stain with culture, standard haematoxylin and eosin stain, and immunoperoxidase stain. Culture has been used since 1994 as a standard diagnostic method. A patient was judged *H. pylori*-positive if one or more of the applied methods were positive. A patient was considered *H. pylori*-negative if all methods failed to detect the bacterium.

All endoscopy results were noted in a standardised endoscopy report.

A hiatus hernia was defined as a distance of more than 2 cm between the oesophageal gastric junction and the diaphragm. Barrett's epithelium was judged to be present if the typical coloured metaplastic mucosa was seen in the tubular oesophagus.

Statistical analysis was done with chi-square test for contingency tables. A result was judged statistically significant if the value was below 0.05.

RESULTS

In the ten-year period 14,909 consecutive diagnostic upper gastrointestinal endoscopies were performed in 11,691 patients. A total of 3218 endoscopies were excluded because these procedures were carried out as follow-up after previously diagnosed abnormalities (peptic ulcer, cancer) or because of recurrent or newly developed upper gastrointestinal symptoms in the same patient.

Four groups of patients were seen. Group 1 consisted of 1535 patients with active reflux oesophagitis; Barrett's oesophagus was seen in 307 patients (group 2). A hiatus hernia was diagnosed in 2116 patients (group 3) and, finally, group 4 consisted of 5341 patients without any macroscopic abnormalities in oesophagus, stomach or duodenum or with signs of endoscopic gastritis (reference group). *Table 1* shows details of the different groups. Patients in group 4 (reference group) were significantly younger than all other groups ($p<0.001$); however, overlap in age cohorts is present.

H. pylori was significantly less often detected in patients with reflux oesophagitis or Barrett's oesophagus compared with the reference group, 20 *vs* 29% ($p<0.001$). Also presence of *H. pylori* was significantly lower in patients with hiatus hernia (group 3), 20 *vs* 29% ($p<0.0001$) (*table 2*). Unfortunately the *H. pylori* status was not known in all patients. There was no difference in the number of missing biopsy specimens in the different groups of patients. Assuming that *H. pylori* was present in 30 or 40% of the missing specimens (this is a normal prevalence of the bacterium in the Western world), than the numbers in each group would have been higher but the final significant differences would not change.

Table 3 shows the differences in *H. pylori* presence in three major age cohorts.

Table 1
Numbers of men and women and H. pylori*-positives and negatives in the four groups of patients*

	MEN	WOMEN	HP+		HP-		NO BIOPSY SPECIMEN		MEAN AGE
			n	%	n	%	n	%	
Group 1	937	598	312	20	770	50	453	30	56
Group 2	193	114	55	18	124	40	128	42	65
Group 3	938	1178	416	20	994	47	706	33	58
Group 4	2159	3182	1550	30	2425	45	1366	25	50

Hp means no biopsy specimens available, the numbers in brackets indicate percentages. Age of the different groups is compared. Group 1 vs group 2: p = ns, group 1 vs group 3: p = ns, group 1 vs group 4: p<0.001, group 2 vs group 3: p = ns, group 2 vs group 4: p = 0.03, group 3 vs group 4: p<0.0001.

Table 2
Numbers of H. pylori*-positive and negative patients*

	HP+		HP-		HP NOT KNOWN	
	n	%	n	%	n	%
Group 1 + 2	367	20	894	49	581	31
Group 3	416	20	994	47	706	33
Group 4	1550	29	2425	45	1366	26

Table 3
Presence of H. pylori *in three different age cohorts of patients in the four different groups*

PATIENTS >50 YEARS	HP+		HP-		NO BIOPSY SPECIMEN	
	n	%	n	%	n	%
Group 1 + 2	247	20	489	41	465	39
Group 4	747	29	988	38	863	33
	p<0.001					

PATIENTS 30 TO 50 YEARS	HP+		HP-		NO BIOPSY SPECIMEN	
	n	%	n	%	n	%
Group 1 + 2	94	18	326	63	99	19
Group 4	534	29	940	52	340	19
	p<0.001					

PATIENTS <30 YEARS	HP+		HP-		NO BIOPSY SPECIMEN	
	n	%	n	%	n	%
Group 1	26	21	75	65	17	14
Group 4	269	29	497	53	163	18
	p = 0.04					

DISCUSSION

The present study confirms, in a very large group of patients studied in one single centre, the findings of earlier papers. Patients without *H. pylori* gastritis suffer more often from reflux disease. This observation has led to the hypothesis that *H. pylori* protects against reflux oesophagitis. There is an ongoing debate in the literature as to whether reflux disease actually develops after successful anti-*H. pylori* therapy.[12-15] Is *H. pylori* protective or is this merely coincidence? A point of criticism can be that in the reference group patients are included with endoscopy negative reflux disease. The so-called typical reflux symptoms are not very specific for reflux disease. They are also present in ulcer disease and patients with functional dyspepsia. In addition, pH monitoring in the oesophagus, often considered as gold standard, can produce false-negative results. The only true gold standard for reflux disease is the presence of reflux oesophagitis or Barrett's metaplasia.
The major problem in all studies on *H. pylori* and reflux disease is that many different types of patients have been studied: patients treated with maintenance acid suppressive therapy because of peptic ulcer disease or reflux disease, patients with peptic ulcer disease with coexisting reflux disease and patients with newly developed disease without ever having been treated before. This makes comparisons difficult. Also many patients with functional dyspepsia or genuine reflux oesophagitis have been included.[16-18]
Patients with a chronic *H. pylori* associated corpus gastritis induced by the use of acid suppressive therapy started for whatever reason will have higher acid production once *H. pylori* has been eradicated compared with patients without corpus gastritis.[19,20] Obviously the presence of corpus gastritis, induced by acid suppressive therapy, in a studied patient population is a confounding factor.
The most likely mechanism by which *H. pylori* may protect against reflux is by decreasing the potency of the gastric refluxate in patients with corpus predominant gastritis.[21] It has been shown that colonisation with CagA-positive *H. pylori* provides significant protection against the development of reflux disease and its long-term complications.[4] While *H. pylori* infection itself does not cause or really protect against developing reflux disease, it may protect certain susceptible individuals from developing the condition and its possible complications.[23]
The prevalence of reflux disease and oesophageal adenocarcinoma is rising, while the prevalence of *H. pylori* infection has been decreasing[24] in the Western world. Since it is known that the acquisition of *H. pylori* at young age is decreasing this could be an explanation. The rising prevalence of reflux disease can also be explained by changes in dietary habits and body mass index. *H. pylori* in the stomach is possibly responsible for other feeding habits. Recent studies indicate that *H. pylori* has effects on production of leptin and plasma ghrelin levels. Leptin is produced in the mucosa of the gastric fundus. Gastric distension due to eating will lead to a decrease of fundic leptin.[24] Eradication of *H. pylori* does not change plasma leptin levels. However, leptin immunoreactivity in the gastric fundus significantly decreases after successful

eradication of the bacterium. In the studied patients, this was accompanied by a significant correlation with changes in body mass index. Since the serum leptin levels did not change this must be due to a local effect.[24]

Ghrelin, a newly discovered gastric hormone, is an important factor in appetite. After *H. pylori* cure plasma levels increase significantly.[25] This could lead to increased appetite and hence weight gain. Whether these levels are also higher in people who were always *H. pylori* negative is yet to be determined. The concept, however, is appealing.

It is conceivable to assume that individuals without *H. pylori* have more appetite resulting in increase in body weight, more transient lower oesophageal sphincter relaxation and hence induction of reflux disease. It is also possible that dietary habits change after eradication of *H. pylori* to such an extent that the BMI rises. Together with healing of corpus gastritis, this may be a risk factor in developing reflux disease.

A rising body mass index takes time. It is well known that the majority of people gain weight with rising age. Since patients with reflux disease are older then patients in the reference group it is tentative to assume that reflux patients could have a higher body mass index. This observation could be an extra argument in favour of a relation of dietary habit and body mass index.

Long-term prospective studies on the prevalence of reflux disease with information of dietary habits, body mass index and presence of *H. pylori* are mandatory.

It can be concluded that there is a relation between *H. pylori* and reflux disease. However, the consequence of this relation will not be the same in every patient.

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