The Libyan International Medical University

Faculty of Basic Medical Science

The Association Between Barrett's Esophagus and Helicobacter pylori

Name : Ali Hassan 1785

Supervised by: Dr khadija mansur

Assisted by: Mohamed haj

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Abstract

Helicobacter Pylori (*H.pylori)* is a curved gram negative bacterium that mainly infects the stomach mucosa , it is urease positive and can neutralize the gastric mucosa and is associated with gastric carcinomas and peptic ulcers. The urease can also break Urea to Ammonia and that in turn can neutralize stomach acid, allowing the organism to survive and multiply in the mucosa. The decrease in acid can have positive effects despite the complications and effects of infection by *H.pylori,* mainly by reversing the progression of Barrett's metaplasia which is caused by gastric acid secretion to the epithelium of distal one third of esophagus, causing a change in cellular structure to a metaplastic columnar shape that is more resistant to gastric reflux as a result of Gastroesophageal reflux or GERD, but can also lead to Adenocarcinoma. The incidence of Barrett's esophagus lies between 5 to 15% of patients with long standing GERD, and many patients do not show any symptoms, in addition to reflux esophagitis which is characterized by inflammation and is caused by GERD. *H.pylori* is inversely related to diseases caused by GERD such as Barrett's metaplasia and in turn Adenocarcinoma, and studies have been conducted to investigate the mechanisms behind the effect of GERD over the decrease of BE and Adenocarcinoma.

Introduction

Helicobacter Pylori (*H.pylori*) particularly the cytotoxin associated A gene (CagA) producing strain is associated with decreased levels of adenocarcinoma and Barrett's esophagus, mainly due to corpus atrophy and decreased gastric acid secretion, which is a predisposing factor for epithelial change in the esophagus (Barrett's esophagus) and then to adenocarcinoma. There were early reports in the 90s suggesting that with the eradication of *H.pylori* there would be an increase in Gastroesophageal reflux symptoms(GERD) and Barrett's esophagus.[(1)] With the trend mainly seen in western societies that have low rates of *H.pylori* infection and higher rates of Barrett's esophagus and Adenocarcinoma, far east countries such as China showed negative association.[(2)] While the inverse relationship between Barrett's esophagus and Adenocarcinoma are well founded, the mechanisms behind it are still under the microscope, with a possible ethnic relationship and the incidence of Barrett's metaplasia[(3)] There are some studies that suggest the protective role of *H.pylori* is mediated by the decrease in GERD symptoms and hence the lower risk of metaplastic change in BE.[(4)] The main limitations in

previous studies are that the cohort were not examined for foregut diseases or that the diagnosis of GERD was placed on the basis of endoscopic esophagitis, while the majority of GERD patients exhibit no erosive esophagitis [1] The aim of the study is to discuss the possible role of CagA strain of *H.pylori* within a group exhibiting GERD symptoms, erosive esophagitis and Adenocarcinoma

Materials and Methods

Male colorectal patient between the ages of 50-79 were sampled and divided to groups with GERD, Barrett's metaplasia and erosive esophagitis, and the control groups were colorectal patients exhibiting none of the symptoms of GERD, BE or erosive esophagitis. The sample group were queried on whether they had taken proton pump inhibitors(PPis) or Histamin 2 receptor antagonists (H2RA) and if so were separately queried on the frequency of intake and duration of symptoms while the group that hadn't taken any medication were only asked about the duration of symptoms. Patients first had undergone colonoscopy and then endoscopy, if BE was suspected, then a biopsy was taken and examined by a pathologist. If esophagitis was suspected, then patients were instructed to take PPis and a repeat biopsy would be taken to determine BE. Blood samples were then drawn in separator serum tubes, 150 blood samples from BE patients, 153 blood samples from GERD patients before antisecretory medication use, and 222 blood samples from patients with erosive esophagitis regardless of medication use. Blood was also taken from 177 controls without any of the 3 conditions. The blood was then tested by using IgG immunoassay for *H.pylori* twice, and if positive, was then assayed for CagA by IgG immunoassay against the CagA. For description of effect of CagA, 328 patients with GERD, BE and esophagitis were taken and had the effects of CagA estimated by logistical means and was compared to the control group, adjusting for age, weight to hip ratio, smoking, education level [1]

Results

Out of 822 male colorectal patients who underwent upper endoscopy, 328 were randomly selected and 73 (22.3%) were found to have antibodies against *H.pylori* and 36 of those(49.3%) were found to be seropositive for CagA antibodies. Of those equivocal or had 2 sample assays against *H.pylori* were 6 (1.8%) none of whom were seropositive against CagA.

Those who were seropositive were more likely to be smokers and have less income or education. 225 CRC patients were selected (27.4%) and 222 had serum assay available, CagA seropositivity was inversely correlated to incidence of erosive esophagitis, with an adjusted odd's ratio of 0.47 and a confidence interval of 95%. In addition. 70 patients with CRC who reported BE (8.5%) were assayed for CagA positivity, and 80 patients newly diagnosed with BE were enrolled in the study, in comparison to the 177 CRC patients without BE, GERD or erosive esophagitis, CagA seropositivity was also inversely correlated to BE, with 50% of BE patients not having antibodies against *H.pylori* and 70% not having antibodies against CagA. 155 CRC patients reported GERD based on weekly symptoms and 153 without prior PPis or H2RA intake were taken and assayed for CagA seropositivity, there was no evidence of a correlation between CagA seropositivity and GERD symptoms, adjusting for Abdominal girth (OR 1.75 CI 95% 1.14-2.68) Smoking (OR 1.74 CI 95% 1.14-2.64) Hiatal Hernia (OR 1.95 CI 95% 1.21-3.14) Barrett's esophagus (OR 2.41 CI 95% 1.42-4.08) and without prior PPi use, esophagitis (OR 1.87 CI 95% 1.11-3.14). Lastly a comparison between men who had erosive reflux disease and nonerosive reflux disease, of the 36 who had nonerosive reflux disease without prior PPi compared to the men who had erosive reflux disease were less likely to be CagA seropositive and *H.pylori* seropositive overall. [(1)]

	GERD Adjusted OR (CI 95%)	Erosive Esophagitis Adjusted OR (CI 95%)	Barrett's Esophagus Adjusted OR (CI 95%)
H.Pylori negative	(Reference)1	(Reference)1	(Reference)1
H.Pylori Positive	0.55-)0.95 (1.64	0.37-)0.63 (1.08	(0.29-0.97)0.53
H.Pylori positive CagA negative	0.46-)0.93 (1.88	0.40-)0.78 (1.54	(0.30-1.36)0.64

H.Pylori Positive CagA Positive	0.46-)0.97 (2.03	0.21-)0.47 (1.03	(0.14-0.90)0.36

Discussion

There is a strong negative association between *H.pylori* CagA strain and erosive esophagitis and Barrett's metaplasia demonstrated while no negative association between GERD symptoms and *H.pylori* CagA strain was found ,which goes against the hypothesis that the prevention of BE and erosive esophagitis is mainly by reduction of GERD symptoms, while the eradication of *H.pylori* generally does not increase GERD either[(1)]Other factors which can increase BE such as central obesity and metabolic disorders were evaluated in a group of Asian patients and it was found that wider waist circumference or central obesity generally increased the chance of BE(odds ratio [OR], 2.53; 95% confidence interval [CI], 1.78-3.60) in addition to metabolic disorders(OR, 2.02; 95% CI, 1.38-2.96) or negative *H.pylori*(OR, 0.50; 95% CI, 0.34-0.74) (2) which correlates with the probable effect of CagA strain in decreasing BE and erosive esophagitis even in the presence of central obesity given there is an infection by *H.pylori*. The reason behind this is that *H.pylori* infections in Asians tend to be corpus dominated leading to a decrease in gastric acid, while the same trend cannot be seen in western countries where mainly the infection is antral dominated, increasing gastric acid secretion(1) in a large based study on 1308 patients with BE, 1388 control based and 1775 with GERD were evaluated and measured for Body Mass Index, smoking status and waist to hip ratio, BE was inversely associated with *H.pylori* (OR 0.44 CI 95% 0.36-0.45) with no evidence of interaction between *H.pylori* with smoking status, BMI and hip to waist ratio and having BE, patients with BE and *H.pylori* were compared to GERD controls and no association was found between *H.pylori* infection and prevention in GERD patients (3) The finding correlates with the primary study indicating GERD is generally not increased by the absence of infection nor decreased by it once BE intervenes, but rather decreases the risk of BE and erosive esophagitis development in patients with GERD and exhibiting associated risk factors(smoking, obesity) (1) The occurrence of BE is generally higher with northern Europeans, in an analysis comprising 596479 patients with whom 76475 had BE, northern

Europeans had a higher rate of BE and generally lower rate of *H.pylori* infection compared to other ethnic groups showing lower rates of BE and higher rates of *H.pylori* infection, in tune with the hypothesis that infection by the bacterium decreases BE (4) A meta analysis from multiple studies in Europe, United States, China, Peru, Malaysia and Pakistan showed a relative risk of 0.46(CI 95% 0.35-0.60) indicating an overall protective role for *H.pylori* in a large set of studies conducted in different geographical locations regardless of ethnicity, adjusting for selection bias and classifying populations with appropriate levels of *H.pylori* occurence, and in seven studies evaluated, six showed the role of CagA antigen of *H.pylori* with OR of 0.38 (CI 95% 0.19 0.78), consistent with the results of the main study showing the role of CagA in particular in preventing BE. The results also indicated that as a result of corpus inflammation and atrophy, there was a decrease in acid production by the parietal cells and decreased acid secretion, hence preventing BE and erosive esophagitis.(5)

Conclusion

The role of the CagA strain can be seen mainly in reversing the effects of BE and erosive esophagitis by decreasing corpus gastric acid secretion, controlling for various factors such as central obesity, abdominal girth, smoking and *H.pylori* infection status, with a strong geographical trend seen in oriental countries, while it has no effect in altering the symptoms of GERD in patients with both diseases, or in other words there is no decrease or increase in GERD symptoms depending on *H.pylori* infection, particularly with the CagA strain, mainly because GERD is caused by a variety of factors such as sliding hiatal hernias, reduced esophageal clearance of refluxed content and decreased functional ability of the cardiac esophageal opening, regardless of the amount of acid secretion.

Future work

Establishing the role of *H.pylori* and the CagA strain in reversing the effect of BE and erosive esophagitis has been well established, however, further research behind the mechanism as to why GERD is not as easily reversed as BE and erosive esophagitis remains to be discovered, and more studies encompassing cross regional groups with GERD should be conducted to explore if geographical tendencies and ethnicity have a correlation with decreased GERD symptoms concurrent with *H.pylori* carrier status.

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