

## Relationship between *Helicobacter pylori* Infection and Chronic Obstructive Pulmonary Disease

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**Abstract-** There is some evidence indicating the role of *Helicobacter pylori* infection in pathogenesis of extragastrointestinal diseases including skin, vascular, and autoimmune disorders, as well as some respiratory diseases. The aim of this study was to investigate the association between *H. pylori* and chronic obstructive pulmonary disease (COPD). In a case-control study, 90 patients with COPD and 90 age- and sex- matched control subjects were included. Serum samples were tested for anti-*H. pylori* and anti-CagA IgG by ELISA. A physician completed a questionnaire including demographic characteristics, habitual history, and spirometric findings for each patient. Of 90 patients with COPD 66 (51%) had mild, 31 (34.4%) moderate, and 13 (14.4%) severe disease. There was no significant association between *H. pylori* IgG seropositivity and COPD. Serum levels of anti-CagA IgG were significantly higher in patients with COPD than in the control subjects ( $P < 0.001$ ). No association was observed between *H. pylori* infection and severity of COPD. The results suggest that there is an association between CagA-positive *H. pylori* infections and COPD. Further studies should be planned to investigate the potential pathogenic mechanisms that might underlie these associations.

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**Keywords:** COPD; *Helicobacter pylori*; Infection

### Introduction

*Helicobacter pylori* is a major causative agent of peptic ulcer disease and a risk-factor for gastric cancer. Persistent *H. pylori* colonization may be associated with nonulcer dyspepsia (1). An increased seroprevalence of *H. pylori* has also been reported in various extragastrointestinal disorders including skin, vascular, and autoimmune disorders, as well as in some respiratory diseases such as bronchial asthma, bronchiectasis, chronic bronchitis, and lung cancer (2). The association between *H. pylori* and chronic obstructive pulmonary disease (COPD) has been described in recent studies (3). Moreover, a high prevalence of COPD has been found in patients with peptic ulcer (4). It is believed that the release of proinflammatory cytokines stimulated by *H. pylori* may play a role in chronic inflammation of bronchi. Cytotoxin-associated gene-A (CagA) is the most

important virulence factor for *H. pylori* that affects cytokine production. Thus, CagA-positive *H. pylori* strains may induce more inflammatory response in COPD and other inflammatory disorders (5).

The aim of this study was to compare the seroprevalence of *H. pylori* and particularly of CagA-positive strains between COPD patients and control subjects, and to evaluate the association between *H. pylori* seropositivity and severity of COPD.

### Materials and Methods

This study has been approved by the Ethical Committee of Hamedan University of Medical Sciences, Hamedan, Iran.

In a case-control study, from May 2009 to January 2010, 90 consecutive patients with COPD who referred to the outpatient clinic of respiratory diseases in Shahid Behaeshhti Hospital were included.

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**Table 1.** Seroprevalence of *H. pylori* infection in COPD patients and controls

	COPD patients n (%)	Controls n (%)	P-value
Anti- <i>H. pylori</i> IgG positive (N=90)	32 (35.6)	30 (33.3)	P>0.05
Anti-CagA IgG positive (N=90)	43 (47)	14 (15)	P<0.001

**Table 2.** Seroprevalence of *H. pylori* infection according to severity of COPD

Severity	Anti- <i>H. pylori</i> IgG positive n (%)	Anti-CagA IgG positive n (%)
Mild	23 (50)	18 (39.1)
Moderate	14 (45.2)	10 (32.3)
Sever	7 (53.8)	6 (46.2)

Shahid Behaeshti Hospital is a referral center for pulmonary diseases located in Hamedan, west of Iran.

Diagnosis of COPD was established by spirometry in all patients with a clinical suspicion of COPD. Exclusion criteria for COPD patients were: *a.* exacerbation of COPD in the last month, *b.* history of antibiotic use in the last month, *c.* history of *H. pylori* eradication, *d.* full reversibility in spirometric findings. Full reversibility was defined as a 12% increase in FEV1 after using two puff of short-acting bronchodilator. The severity of COPD was classified by spirometric data according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (6).

The control group consisted of 90 age- and sex-matched patients with pulmonary diseases other than COPD (bronchial asthma, lung cancer, sarcoidosis) who referred to the hospital during the period of the study. Those with known history of COPD, gastrointestinal disorders due to *H. pylori* infection, or antibiotic use in the last month were excluded. After taking informed consent, a questionnaire including demographic characteristics, history of cigarette smoking, and pulmonary function test results was fulfilled for each subject, and a serum sample was obtained and stored at -20°C until use. *H. pylori* antibody titers were measured by ELISA using specific kits for anti-*H. pylori* IgG (IBL, Homburg, Germany) and anti-CagA *H. pylori* IgG (Diapro, Milan, Italy). Anti-*H. pylori* IgG titers more than 25 U/ml and anti-CagA IgG titers more than 7.5 U/ml were considered as positive.

Data were analysed using SPSS statistical package version 15, and a P<0.05 was considered statistically significant. Student’s t-test was used for quantitative variables and Chi-Square test for qualitative variables.

## Results

Ninety patients with COPD (65 males and 25 Females, mean age 67.7±1.2) and 90 age- and sex- matched control subjects (53 males and 37 Females, mean age 61.6±1.2) were included in the study. According to GOLD classification, 66 (51%) of patients with COPD had mild, 31 (34.4%) moderate, and 13 (14.4%) severe disease. No patient was found to have very severe COPD.

Table 1 shows the seroprevalence of *H. pylori* infection in COPD patients and control subjects. There was no significant difference in anti-*H. pylori* IgG seropositivity between the study and control groups. The frequency of anti-CagA IgG seropositivity was significantly higher in COPD patients than in controls (P<0.001).

The frequency of anti-*H. pylori* IgG and anti-CagA IgG seropositivity in different stages of COPD is shown in Table 2. No significant association was found between the severity of COPD and the frequency of anti-*H. pylori* IgG and anti-CagA IgG seropositivity.

## Discussion

The role of *H. pylori* in pathogenesis of extragastric diseases remains controversial (7). Recent seroepidemiological studies suggest a relationship between *H. pylori* and respiratory diseases (8). In this study, we found a significant association between anti-CagA IgG but not anti-*H. pylori* IgG and COPD. In addition, we did not found any association between the *H. pylori* infection and the severity of COPD.

Some previous studies have shown increased seroprevalence of *H. pylori* IgG in patients with COPD

(3,4). A recent study also reported the association between anti-*H. pylori* IgG and COPD, and correlation of anti-*H. pylori* IgG levels with the severity of COPD (9). The controls in these studies were consisted of healthy subjects. However, the controls in our study were selected from other chronic respiratory diseases. This selection was done to match the control group for nonspecific affects of chronic inflammation and biochemical mediators released in these diseases. Although our study does not support any specific relation between *H. pylori* IgG and COPD, but finding the association between seroprevalence of anti-CagA IgG and COPD suggests the role of more virulent strains of *H. pylori* in developing the disease. Another recent study conducted by Fullerton *et al.* (10) reported no association between *H. pylori* serologic status and either COPD, asthma, allergic disease or decline in lung function. However, anti-CagA IgG status was not measured in their study.

Despite the fact that the role of *H. pylori* in pathogenesis of COPD remains controversial, the activation of inflammatory mediators by *H. pylori* infection and during the course of COPD may explain the potential ethiopathogenetic role of *H. pylori*. It is well known that CagA+ *H. pylori* strains stimulate the release of proinflammatory cytokines including IL (interleukin) -1, IL-8, and tumor necrosis factor-  $\alpha$  (11). CagA+ strains also cause severe gastric inflammation in association with increased serum levels of IL-17 and IL-23 (12). Moreover, serum levels of cytokines normalize following eradication therapy of *H. pylori* (13). On the other hand, It is known that inflammation is the main pathologic lesion in COPD which is associated with activated macrophages and neutrophils in airway mucosa and increased inflammatory mediators (14,15). Previous studies have shown that cytokines resemble those stimulate by *H. pylori* release in the course of COPD and its exacerbation (4,11,16). Accordingly, this probability strengthen that *H. pylori* infection have a proinflammatory and stimulatory role for COPD.

Previous epidemiologic and serologic studies have shown the association between *H. pylori* and extragastrointestinal diseases (17). The effect of systemic inflammatory response induced by *H. pylori* was the main explanation for these associations. Kowalski *et al.* (18) have reviewed the relationship between *H. pylori* infection and coronary artery diseases and discussed the role of toxic materials including proinflammatory cytokines, CagA cytotoxins and endotoxins in the development of atherosclerosis. A number of studies which have reported the relationship between *H. pylori* and respiratory diseases including

chronic bronchitis, bronchiectasia and lung cancer emphasised that the inflammation similar to that in gastric mucosa, can occur in tracheobronchial mucosa (9,11). This effect is triggered by systemic inflammatory mediators. On the other hand, Bayraktoroughlu *et al.* (19) reported that despite the increased production of cytotoxins following inflammatory response due to *H. pylori*, serum levels of IL-6, IL-8, and TNF- $\alpha$  do not increase. They explained that these cytokines might release only locally in bronchial secretion.

Moreover, detection of *H. pylori* in bronchial secretion may further support its relationship with respiratory diseases. In a previous study, it has been detected in tracheobronchial secretions of mechanically ventilated patients (20). Another study in which the role of *H. pylori* in the pathogenesis of bronchiectasis was investigated, failed to detect *H. pylori* DNA in the bronchoalveolar lavage fluid and even in lung tissue samples (21). As yet no similar study has been carried out in COPD patients. More studies for detection of specific *H. pylori* DNA, histological changes of bronchial tissue, and the role of eradication therapy of *H. pylori* in the course of COPD are needed to confirm the role of *H. pylori* infection in developing COPD.

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