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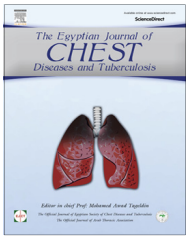

ORIGINAL ARTICLE

Study of the *Helicobacter pylori* infection in chronic obstructive pulmonary disease

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Abstract *Background:* COPD may be associated with other systemic diseases including cardiovascular diseases, diabetes, osteoporosis and peptic ulceration and *Helicobacter pylori* infection seems to be the main cause of PUD.

Aims: The aim of this work is to study the association of *H. pylori* infection in chronic obstructive pulmonary disease (COPD).

Subject and methods: This study was performed on 80 subjects. They were classified into two groups: **Group I:** 65 COPD patients. **Group II:** 20 healthy control subjects. COPD was diagnosed according to the Global Initiative for chronic obstructive pulmonary disease admitted at chest department of Benha University Hospital.

Results: It shows that seropositivity of anti-*H. pylori* IgG and anti-CagA IgG was higher in COPD patients than in controls with a highly statistically significant difference ($p = 0.009$ and 0.047 respectively). Also the IgG level of *H. pylori* positive cases and CagA positive cases was higher in the COPD group than in the control group with a highly statistically significant difference ($p = 0.027$ and 0.0001 respectively).

Conclusion: The present study suggests that patients with COPD have an increased seroprevalence of Hp infection.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease. It is characterized by persistent airflow limitation that is usually progressive. It is associated with abnormal chronic inflammatory response to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients [1].

Helicobacter pylori is a slow growing, microaerophilic, gram-negative spiral shaped bacterium. It colonizes gastric mucosa and elicits both inflammatory and lifelong immune responses with release of various bacterial and cytotoxic

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substances [2]. 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 [3].

COPD had been associated with gastroduodenal ulcer, many years before the identification of *H. pylori* infection as a cause of peptic ulcer disease [3]. 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 pathogenetic role of *H. pylori* [4]. Data in the literature on the relationship between *H. pylori* infection and chronic obstructive pulmonary disease (COPD) are poor [3].

Subjects and methods

The present study is a cohort prospective study. It was conducted in the period extending from January 2014 to January 2015 after obtaining informed patients' consent.

Subjects

This study was performed on 85 subjects. They were classified into two groups:

- **Group I** included 65 COPD patients.
- **Group II** included 20 healthy control subjects.

Inclusion criteria: COPD was diagnosed according to the Global Initiative for chronic obstructive pulmonary disease (GOLD) admitted at chest department of Benha University Hospital. Severity of COPD will be classified by spirometric data according to guidelines of Global Initiative for chronic obstructive lung disease [1]. The studied groups were complaining of dyspeptic symptoms (as abdominal pain related to meals, fullness, early satiety and nausea) or history of peptic ulcer.

Exclusion criteria: Patients with exacerbation of COPD in the preceding month, as in those cases pulmonary function does not represent baseline levels, prior *H. pylori* eradication therapy, history of taking of acid suppressive drugs or antibiotics in the preceding 6 months, and history of vagotomy or operation on the upper gastrointestinal tract.

All patients were submitted to:

(1) Full history and thorough clinical examination (stress on dyspeptic symptoms and history of peptic ulcer).
(2) Radiological examination: plain postero-anterior and lateral chest X-ray.
(3) Ventilatory function test (spirometry) before and after bronchodilatation.
(4) *H. pylori* antibody level positive detection was measured by ELISA using specific kits for anti-*H. pylori* IgG (Catalog No. E-HL G-K08) and anti-CagA *H. pylori* IgG [DIA. PRO (Diagnostic Bioprobes) SrlVia G. Carducci no 27 20099 Sesto San Giovanni (Milano)- Italy]. Purified antigens are coated to a microwell plate. Antibodies in the patient samples bind to the antigens and were determined during the second incubation step using enzyme-labeled antihuman antibodies (the conjugate). All unbound materials are removed by washing. The bound enzyme converts the colorless substrate (H_2O_2/TMB) to a blue end product.

Statistical analysis

Data obtained from the present study were computed using SPSS versions 17 under the platform of Microsoft Windows XP, Professional Edition. Continuous data were expressed in the form of mean ± SD while categorical data were expressed in the form of count and percent. Comparison of continuous data was performed utilizing student *t* test, while categorical data were done using Chi-square test. *P* value less than 0.05 was considered statistically significant.

Results

Table 1 shows a highly significant difference between them as regards smoking ($p = 0.0001$).

Table 2 shows that seropositivity of anti-*H. pylori* IgG and anti-CagA IgG were higher in COPD patients than controls with a highly statistically significant difference ($p = 0.009$ and 0.047 respectively). Also IgG level of *H. pylori* positive cases and CagA positive cases were higher in the COPD group than in the control group with a highly statistically significant difference ($p = 0.027$ and 0.0001 respectively).

Table 3 shows no statistically significant differences between COPD patients with anti-*H. pylori* +ve and −ve IgG regarding pulmonary functions.

Table 4 shows there is significantly lower FEV1 in anti-CagA +ve patients when compared with anti-CagA −ve patients with a statistically significant difference and ($p = 0.011$).

Table 5 shows the majority of anti-CagA +ve patients had a significantly higher frequency of severe disease 26 (72.2%) with a highly statistically significant difference between 2 groups ($p = 0.02$).

Table 6 shows a statistically significant correlation between anti-CagA seropositivity and both disease severity and FEV1.

Discussion

The pulmonary component of chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible [5]. *H. pylori* is a major causative agent of peptic ulcer disease and a risk-factor for gastric cancer [6]. 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

Table 1 Demographic data in COPD patients and controls.

Variables		Group (I) (COPD patients) $n = 65$	Group (II) (Controls) $n = 20$	*P* value
Age (years)		62.2 ± 9.3	60.6 ± 6.4	0.22
Gender	Male	63 (96.9%)	18 (90%)	0.31
	Female	2 (3.1%)	2 (10%)	
Smoking		50 (76.9%)	5 (25%)	0.0001*

* Means significant.

Table 2 Serological parameters in the studied subjects.

Variables	Group (I) (COPD patients) $n = 65$	Group (II) (Controls) $n = 20$	P
Anti-*H. pylori* IgG seropositivity (%)	41 (63.1%)	6 (30.0%)	0.009*
Anti-*H. pylori* IgG level (U/ml)	29.3 ± 21.8	17.1 ± 12.3	0.027*
Anti-CagA IgG seropositivity (%)	36 (55.4%)	6 (30.0%)	0.047*
Anti-CagA IgG level (U/ml)	25.3 ± 18.3	12.4 ± 9.8	0.0001*

* Means significant.

Table 3 Comparison between anti-*H. pylori* +ve and −ve IgG COPD patients regarding pulmonary functions.

Variables	Anti-*H. pylori* +ve $n = 41$	Anti-*H. pylori* −ve $n = 24$	P
FEV1	48.1 ± 12.4	51.5 ± 16.3	0.35
FVC	51.9 ± 15.2	54.2 ± 17.5	0.57
FEV1/FVC	58.9 ± 12.9	60.5 ± 13.9	0.64
MVV	33.6 ± 13.2	35.7 ± 18.1	0.59

Table 4 Comparison between anti-CagA IgG +ve and −ve patients regarding pulmonary function tests.

	Anti-CagA + ve $n = 36$	Anti-CagA –ve $n = 29$	P
FEV1	45.2 ± 13.4	53.5 ± 14.5	0.011*
FVC	52.2 ± 15.0	53.2 ± 17.1	0.79
FEV1/FVC	60.5 ± 13.3	58.6 ± 13.3	0.56
MVV	35.1 ± 14.5	33.7 ± 15.8	0.7

* Means significant.

Table 5 Comparison between anti-CagA IgG +ve and −ve patients regarding disease severity.

Degree of disease severity	Anti-CagA +ve $n = 36$	Anti-CagA −ve $n = 29$	P
Mild	1 (2.8%)	4 (13.8%)	0.02*
Moderate	8 (22.2%)	14 (48.3%)	
Severe	26 (72.2%)	11 (37.9%)	
Very severe	1 (2.8%)	−(0%)	

* Means significant.

cytokine production. Thus, CagA-positive *H. pylori* strains may induce more inflammatory response in COPD and other inflammatory disorders [7].

The present study aimed to study the association of *H. pylori* infection in chronic obstructive pulmonary disease (COPD) and its relation to severity of the disease. As shown in Table 1, there was an immense dominance of males in the COPD patients (96.9%) with no statistically significant differences between patients and controls regarding age and gender distribution.

Also there is a highly significant difference between patients and control as regards smoking ($p = 0.0001$). Cigarette smoking is by far the most important risk factor for development of COPD. Earlier studies reported that 15% up to 20% of smokers develop COPD, although this number may reach 50% in elderly smokers [8].

Table 6 Correlation between anti-CagA seropositivity and all studied parameters.

	Anti-CagA seropositivity	
	R	P
Age	−0.1	0.41
Disease severity	0.43	0.0001*
FEV1	−0.34	0.005*
FVC	−0.06	0.6
FEV1/FVC	0.028	0.28
MVV	−0.4	0.75

* Means significant.

As shown in Table 2 we found that the seropositivity of anti-*H. pylori* IgG and anti-CagA IgG was higher in COPD patients than in controls with a highly statistically significant difference ($p = 0.009$ and 0.047 respectively). Also IgG level of *H. pylori* positive cases and CagA positive cases were higher in the COPD group than in the control group with a highly statistically significant difference ($p = 0.027$ and 0.0001 respectively).

The higher prevalence of H pylori infection in COPD patients in comparison with controls was also noted by the study of Prónai et al. [9], who found that the prevalence of *H. pylori* compared to the age-matched controls is significantly higher in patients with chronic obstructive pulmonary disease.

Also this coordinates with the study of Gencer et al. [10], they aimed to investigate seroprevalence in *H. pylori* patients with COPD and to determine whether there is an association between *H. pylori* infection and COPD. Forty-nine voluntary patients with COPD and 50 healthy control subjects of similar age and sex were included in the study. Serum levels of *H. pylori* specific IgG and *H. pylori* IgG seropositivity were significantly higher in the patients with COPD than in the control subjects.

In addition to the study of Roussos et al. [3], in which they searched for the seroprevalence of *H. pylori* and in particular of CagA-positive virulent strains in patients with chronic obstructive pulmonary disease (COPD), 126 COPD patients (88 males and 38 females, aged 61.3 ± 8.1 years) and 126, age and sex-matched, control subjects were investigated. The prevalence of *H. pylori* infection in patients and controls was 77.8% and 54.7%, respectively ($P < 0.001$) and that of CagA-positive *H. pylori* infection was 53.9% and 29.3%, respectively ($P < 0.001$).

But in Hashemi et al'. [4] study, when they investigated the association between *H. pylori* and chronic obstructive pulmonary disease (COPD). In this 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* IgG and anti-CagA IgG by ELISA. There was no significant association between *H. pylori* IgG seropositivity and COPD

while Serum levels of anti-CagA IgG were significantly higher in patients with COPD than in the control subjects ($P < 0.001$).

Several studies found that *H. pylori* infection was associated with extragastroduodenal pathologies characterized by activation of inflammatory mediators or induction of autoimmunity. This arose the interest of researchers to search for *H. pylori* to recognize its role in several diseases outside GIT. They found that *H. pylori* seroprevalence was high in certain diseases as IHD, vascular, rosacea, skin and even in some chest diseases as active bronchiectasis. In 1998 a pilot study in a small number of Italian patients showed that *H. pylori* per se, might be related to a high risk of developing chronic bronchitis [5]. Also the prevalence of COPD in peptic ulcer patients increases 2–3-folds compared with findings in ulcer free controls as proved by epidemiological study done between 1968 and 1986 [11,12]. Moreover, eradication of *H. pylori* leads to normalization of serum cytokines levels [13], these cytokines are also thought to be involved in the pathogenesis of COPD [14]. Therefore, *H. pylori* infection in general and CagA positive strains in particular may play a proinflammatory role and co-trigger COPD with other more specific environmental, genetic and unknown factors.

Another potential mechanism could be the spilling or inhalation of *H. pylori* or its toxins into the respiratory tract which also might lead to chronic airway inflammation such as COPD [12]. However, as far as we know, neither identification of *H. pylori* species in human bronchial tissue, nor isolation of *H. pylori* from bronchoalveolar lavage fluid has been achieved yet [15]. Certain studies found that *H. pylori* was not found in bronchial biopsies of patients with various respiratory diseases, which suggested that *no direct evidence supporting the theory that H. pylori may cause pulmonary disease and no relation with GERD was detected* [16,17].

Also this coordinate with the study of Shams-Hosseini et al. [18] *they perform study on* 32patients with any pulmonary disease undergoing bronchoscopy and biopsy samples were obtained from them. Three bronchial mucosa biopsy specimens were obtained by fenestrated biopsy forceps for pathologic assessment from carina, using a fiberoptic bronchoscope. One of these samples was used to determine urease activity. They used hematoxylin-eosin staining for histopathological evaluation of the presence of *H. pylori* in the second mucosa sample and the third specimen was used for histopathological diagnosis, they found that no correlation was detected between histopathological evaluation and urease test for *H. pylori* in lung specimens. *However, a possible indirect role could not be excluded.*

As regards our study in comparison between patients with anti-CagA +ve and anti-CagA −ve regarding pulmonary functions it revealed significantly lower FEV1 in anti-CagA +ve patients when compared with anti-CagA −ve patients. Also, there was a statistically significant inverse correlation between FEV1 and anti-CagA titer ($p = 0.005$), while no statistically significant differences between COPD patients with anti-*H. pylori* +ve and −ve IgG regarding pulmonary functions as shown in Tables 3 and 4 it revealed that disagreement with Gencer et al. [10] as they found that FEV 1, which is one of the respiratory parameters indicating airway damage and the severity of inflammation, was lower in Hp-seropositive COPD patients, than in seronegative ones ($p = 0.014$) suggesting that Hp is associated with airway inflammation.

This incoordinates with the study of Roussos et al. [2], in which the spirometric values showed that no statistically significant difference, as regards the values, was detected between *H. pylori* infected COPD patients and uninfected ones as the spirometric values did not differ significantly between COPD patients infected with CagA-positive strains of COPD patients in relation with *H. pylori* infection.

Moreover, as shown in Tables 5 and 6 we found that the majority of anti-CagA +ve patients had a significantly higher frequency of severe disease 26 (72.2%) with a highly statistically significant difference between 2 groups ($p = 0.02$), although there were no statistically significant differences between 2 groups regarding anti-*H. pylori* IgG. There is a statistically significant correlation between anti-CagA and both disease severity and FEV1.

This result coordinates with another study which showed that the prevalence of positive *H. pylori* serology in a group of COPD patients stratified according to disease severity and in a control group matched for age, socioeconomic class and pack year smoking history. The prevalence of positive *H. pylori* serology was significantly higher in patients with COPD (54.7%) compared with the control group (23.5%; $p = 0.026$) [19].

While in the study of Hashemi et al. [4] they found that no significant association was found between the severity of COPD and the frequency of anti-*H. pylori* IgG and anti-CagA IgG seropositivity. As explanation for positive results they found that CagA positive are those strains that induce increased local and systemic, humoral and cellular inflammatory response [20]. With regard to the potential etiopathogenic role of *H. pylori* infection in COPD, the chronic activation of inflammatory mediators induced by *H. pylori* infection might lead to the development of COPD, the increased prevalence of CagA positive strains further supports this hypothesis, it is well known that these virulent strains stimulate the release of a variety of proinflammatory cytokines, including interleukin-1 (IL-1), IL-8 and tumor necrosis factor-alpha [21,22].

Fedorova et al. [23], found a significant increase in the incidence of gastritis in patients with COPD and emphasized the effect of *H. pylori*. They also detected a correlation between the duration of COPD, hypoxia and the degree of bronchial obstruction and the severity of gastritis. *H. pylori* seropositivity may be an important factor that should be kept in mind while approaching and treating dyspeptic symptoms in patients with COPD. Conclusively, the present study found a significant link between COPD and *H. pylori* infection and a significant association between disease severity and anti-CagA +ve cases. Further studies assessing the effect of Hp infection on the pathogenesis of COPD and on the effect of Hp eradication on COPD are required.

Conflict of interest

Authors have no conflict of interest to declare.

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