Impact of H. Pylori on Severity of Chronic Obstructive Pulmonary Disease

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Background and aim of the work: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Many studies reported a high prevalence of Helicobacter pylori (H. pylori) infection in COPD patients and this may have a role on severity of COPD. To estimate impact of H. pylori infection on exacerbation and severity of COPD.

Patients and Methods: A prospective observative study was conducted for one year and included 142 well controlled COPD patients. Participants were classified into two groups; group 1 which included 72 COPD patients with +ve H. pylori infection and group 2 which included 70 COPD patients with -ve H. pylori infection. All participants were submitted to full clinical examination, routine laboratory investigations, CXR, arterial blood gases analysis, spirometry, H. pylori serology and stool antigen and COPD assessment test (CAT). Patients were followed monthly for at least three months.

Results: High significant statistical differences were found between both groups regarding; FEV1, FVC, PH, PaO2, which were lower in group 1 when compared to group 2. While CRP, CAT score, PCO2, HCO3 were significantly higher in group 1. COPD severity was higher in group 1 when compared to group 2 where the sever and very sever COPD cases were more abundant in group1.

Conclusion: H. pylori infection adds an inflammatory burden in the COPD patients by increasing their CAT and number of COPD exacerbations per year.

INTRODUCTION

Helicobacter pylori *(H. pylori*) is a gram-negative anaerobic spiral-shaped rods. It develops several mechanisms for its survival and replication in the acidic environment of the stomach. H. pylori synthesizes urease enzyme which catalyze the hydrolysis of urea to ammonia, which in turn decreases the stomach pH and produces a neutral environment around the bacteria **[1]**. H. pylori was reported globally to colonizes the gastric mucosal lining of ~50% to 60% of the world population, with increased prevalence in those patients with other inflammatory diseases including autoimmune, vascular and skin diseases **[2]**. In Egypt, prevalence of H. pylori is much higher in the healthy asymptomatic population both in adults and in pediatric populations**.** Low socioeconomic status, low body mass index, living in rural areas and low educational status were multiple risk factors for the acquisition of H. pylori in most of the Egyptian studies **[3]**. Chronic obstructive pulmonary disease (COPD) represents an important public health challenge and is a major cause of chronic morbidity and mortality worldwide **[4]**. Gastro-oesophageal reflux disease (GERD) is one of the most common causes of chronic cough and a potential risk factor for COPD exacerbation **[5,6]**. GERD is a relatively common condition, affecting ~10 to 29% of the western population **[7]**. Gastro-oesophageal reflux (GER) can heighten bronchial reactivity and micro-aspiration **[8]**. Abnormal GER was associated to lung diseases **[9]**. Moreover, most COPD

patients have flat diaphragm and increased intra-abdominal and negative intra-thoracic pressure, which could aggravate GER **[10]**. GERD is more common in patients with COPD than in those without COPD **[11]**. Also, it has been suggested that an increase in the frequency of COPD exacerbation can be associated with GERD **[12]**. The possible mechanisms for the relationship between *H. pylori* and COPD might be the systemic effect of certain gastrointestinal peptides as gastrin, somatostatin, and cytokine release or due to direct injury and chronic inflammation of airways due to aspiration and/or inhalation, most probably activation of inflammatory mediators by H. pylori is the pathogenic mechanism of extragastric manifestations of H. pylori infection **[13]**.The aim of our work was to estimate impact of H. pylori infection on the severity of COPD and clarifying a role for H. pylori infection in COPD exacerbation.

PATIENTS AND METHODS

Study design and settings

This observative prospective study was conducted at Tropical medicine, Internal medicine and Chest departments, Zagazig university hospitals, Egypt, through a twelve months period from *October 2017* to *October 2018.*

Target population

Out of 300 well controlled COPD patients attending our outpatient clinics, one hundred forty-two patients fulfilling inclusion and exclusion criteria were randomly chosen to participate in this study.

Inclusion criteria

COPD patients diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease guidelines(**14**). For patients with airway obstruction according to the American Thoracic Society/The European Respiratory Society (ATS/ ERS) guidelines (Forced expiratory volume (FEV1) at the end of the first and second/Forced vital capacity (FVC) <70%), detection of COPD severity was performed according to the following criteria ; stage 1: FEV1 ≥80% predicted, stage 2: 50% ≤FEV1 <80% predicted, stage 3: 30% ≤FEV1 <50% predicted and Stage 4: FEV1 <30% predicted.

Exclusion criteria

Those patients with asthma, known peptic ulcers, acute exacerbation of COPD, used antibiotics within and PPIs within the last month, histamine-2-receptor antagonists within the last week, an antacid within the last 24 hours and those having H. pylori eradication treatment within the last 6 months were excluded from beginning of the study.

Patients classification

According to presence of *H. pylori*, participants were classified into two groups; group 1 which included 72 COPD patients with positive H. pylori infection and group 2 which included 70 COPD patients with negative H. pylori infection.

Study tools

All patients under went regular history taking, full physical examination and routine laboratory work up including serum high sensitive C-reactive protein (hsCRP) level and arterial blood gases (ABGs). Diagnosis of H. pylori infection was done by detection of serum antibodies against H. pylori using rapid anti H. pylori test. It is simple visual qualitative test that detect antibodies in human whole blood, serum or plasma. The test based on immune chromatography and can give result within 15 minutes **[15]**. Stool antigen test for H. pylori was done for using rapid antigen test (lateral flow immune chromatographic test with a monoclonal antibody). It has a positive line to indicate a positive reading accompanied by a control line. The test has been reported sensitivity and specificity (94% and 98% respectively. Interpretation of H. pylori testes was as follow **[16]** :

- Patient with negative antibody are considered negative for *H.* pylori infection**.**
- Patient with positive antibody and negative antigen indicate history of H. pylori infection.
- Patient with positive antibody and positive antigen are infected participants.

Spirometry pulmonary function tests (PFTs) were done by (Winspear PRO 5.0.0) including FVC% of predicted, FEV1% of predicted, FEV1/ FVC and PEF. Pre- and post-bronchodilator spirometry was also performed. At least three technically accepted maneuvers were performed, and the best value was recorded (ZAN100). The COPD Assessment Test (CAT) is a questionnaire for people with COPD. It is designed to measure the impact of COPD on a person's life, and how this change over time. The CAT is a standard and validated test containing eight items for the evaluation of the impact of COPD on health status **[17]**.

Data processing and analysis

All statistical calculations were done using the computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA version 20.0). Data were statistically described in terms of mean ± SD, median and range, or frequencies and percentages when available. To determine the significant independent predictors for the occurrence of EVs, the grade and occurrence of significant EVs, univariate and multivariate regression models were constructed. P values <0.05 was considered statistically significant.

RESULTS

There were no significant differences between both groups regarding mean age, gender, smoking pattern and the prevalence of co-morbidities. (Table 1). The frequencies of H. pylori (stool antigen & serum antibody) in both studied groups were; 62 patients were H. pylori stool Ag +ve &H. pylori serum Ab +ve, 10 patients wereH. pyloristool Ag +ve &H. pylori serum Ab-ve, 42 patients wereH. pylori stool Ag –ve &H. pylori serum Ab +ve and lastly 28 patients wereH. pyloristool Ag –ve &H. pylori serum Ab –ve (Table 2). High significant statistical differences were found between both groups regarding; FEV1, FVC, PH, PaO2, which were lower in group 1 when compared to group 2. While CRP, CAT score, PCO2, HCO3 were significantly higher in group 1 (Table 3).Moreover, there was a high significant statistical difference in the severity of COPD which was higher in group 1 when compared to group 2 where the sever and very sever COPD cases were more abundant in group 1 (Table 4). At number of COPD exacerbation (1-3), COPD patients with positive H. pylori infection (group 1) had less frequent exacerbations than those of group 2 (43% Vs 77 %) respectively, while at number of exacerbation (4-7), group 1 has more frequent exacerbation than those of group 2 (57% Vs 21.5%) respectively with high significant statistical difference (Table 5).

Table (1) : The demographic data and co-morbidities of both groups

Demographic data	Group 1 (H. pylori stool Ag +ve) (n=72)		Group 2 (H. pylori stool Ag -ve) (n=70)		p
Age (years)					
Mean ± SD	54.35 ± 11.8		48.06 ± 12.04		0.075
Sex					
Male	49	68.1%	48	68.6 %	0.94
Female	23	31.9%	22	31.4%	
Smoking					
Smokers	36	25.35%	29	20.4%	0.31
Ex-smokers	9	6.3%	14	9.8%	
Non-smokers	27	19%	27	19%	
Co-morbidity					
+ve	61	84.7%	58	82.9%	0.76
-ve	11	15.3%	12	17.1%	

Table (2) : Frequencies of H pylori (stool antigen & serum antibody) among studied patients

	N	%
H.pylori stool Ag +ve &H. pylori serum Ab +ve	62	43.6
H. pyloristool Ag +ve &H. pylori serum Ab -ve	10	7
H. pylori stool Ag –ve &H. pylori serum Ab +ve	42	29.5
H. pyloristool Ag –ve &H. pylori serum Ab –ve	28	19.7
Total	142	100

Table (3) : Comparison between Forced expiratory volume (FEV1), forced vital capacity (FVC), FEV1/ FVC ratio, CRP, CAT score and ABG parameters in both groups

	Group 1 (H. pylori stool Ag +ve) (n=72)		Group 2 (H. pylori stool Ag -ve) (n=70)		t	p
	Mean	Std. Deviation	Mean	Std. Deviation		
FEV1	50.7500	±17.40548	67.2143	±12.14155	6.520	0.00
FVC	75.1389	±22.80431	94.2571	±16.66436	5.691	0.00
FEV1/FVC	65.9403	±4.10093	66.3927	±8.60482	0.402	0.689
CRP	41.5833	±32.79976	15.0000	±17.43476	6.006	0.00
CAT score	20.6528	±9.72170	17.0571	±8.32472	2.364	0.019
PH	7.3743	± .05566	7.4067	± .02723	-4.388	0.00
PCo2	61.1250	±11.92575	50.8286	±5.86557	6.499	0.00
Pao2	52.3194	±7.88085	56.6000	±6.70799	-3.481	0.001
HCo3	37.7403	±4.62941	34.3386	±3.90775	4.725	0.00

Table (4) : The severity of COPD in both groups

		Group 1 (H. pylori stool Ag +ve)		Group 2 (H. pylori stool Ag -ve)		Total		x2	p
		No	%	No	%	No	%		
No. of exacerbation/ year	0	0	0.0%	1	3.4%	1	0.7%	32.09	0.00**
	1 -3	31	43.05%	54	77.1%	85	59.85%		
	4 – 7	41	56.95%	15	21.5%	56	39.45%		
Total		72	100%	70	100%	142	100%		

Table (5): The frequency of COPD exacerbations per year in both groups

		Group 1 (H. pylori stool Ag +ve)		Group 2 (H. pylori stool Ag -ve)		Total		x2	p
		No	%	No	%	No	%		
No. of exacerbation/ year	0	0	0.0%	1	3.4%	1	0.7%	32.09	0.00
	1 -3	31	43.05%	54	77.1%	85	59.85%		
	4 – 7	41	56.95%	15	21.5%	56	39.45%		
Total		72	100%	70	100%	142	100%		

DISCUSSION

The chronic and the progressive course of COPD is often punctuated by "exacerbations" and is defined clinically as episodes of increasing respiratory symptoms, particularly dyspnea, cough and sputum production with increased its purulence. COPD exacerbations have a negative impact on the quality of life of COPD patients, accelerate disease progression, and can result in repeated hospital admissions and even death **[18,19].**

Prevention of COPD exacerbations is a key for disease management. Many patients with COPD are prone to suffer from recurrent exacerbations **[5]**. Mechanisms that link *H. pylori* infection and lung diseases may be attributed to both systemic and local effects; the systemic effect comes from gastrointestinal peptides (gastrin and somatostatin),

cytokine release from the gastric mucosa and systemic effects of the adaptive immune system, and the local effect comes from damage and chronic airway inflammation by aspiration or inhalation of gastric contents. *H. pylori* has been isolated from tracheal secretion of intubated patients, however, it has never been detected in human bronchial tissue or isolated from bronchoalveolar lavage fluid **[20]**.

In this study, no statistically significant differences were found as regard participants age, gender, smoking and associated co-morbidities between the two groups. Gencer et al., reported the same results regarding age, gender, smoking between the study and the control groups **[21]**.

We use *H. pylori* stool Ag as the main diagnostic test for *H. pylori* infection. Stool antigen test (SAT) is a non-invasive test with good sensitivity and specificity; 94% and 97% respectively in most global meta-analysis **[22]**. SAT seems to provide more reliable results in diagnosis of *H. pylori* infection. SAT and UBT have higher accuracy than serological or urinary antibody-based tests **[23]**. While UBT has been considered the most reliable non-invasive test for the diagnosis of *H. pylori* infection, it has several limitations. UBT cost is still relatively high because of the price of C^{13}-urea and cost of measuring CO2 **[13]**. By contrast, SAT do not require expensive chemical agents and special equipment and hence are less expensive. In addition, patients are required to fast before UBT testing, but not before doing SAT **[24]**.

Both *H. pylori* infection and COPD development are linked to older age, male sex and low socioeconomic status. COPD patients were well matched for all parameters. However, as *H. pylori* infection is usually acquired during childhood, matching for socioeconomic status should be performed for childhood and not for the time of study. Therefore, inappropriate matching for socioeconomic status should be regarded as a limitation of all mentioned studies. Cigarette smoking could be another confounding factor. It is well known that tobacco smoking represents the major cause of COPD. On the other hand, data on the relation between *H. pylori* infection and smoking habits are controversial **[20]**.

H. pylori infection might play a proinflammatory role and co-trigger COPD with other more specific environmental, genetic and yet, unknown factors. The association between *H. pylori* infection and COPD is based only on serologic case-control studies with low socioeconomic status and tobacco abuse as confounding factors **[20]**.

In this work, *H. pylori* seropositivity was found in 73.2% of participants and *H. pylori* stool Ag were positive in 50.7%. The frequencies of *H. pylori* stool Ag & *H. pylori* Ab among the studied population were the presence of negative results of both Ag &Ab in 28 patient (19.7%). Several studies confirmed our results; in 1998, Caselli et al., carried out a prospective pilot study in a sample of 60 bronchitis patients and found an increased *H. pylori* seroprevalence (81.6 vs. 57.9% in controls) **[25]**. A large epidemiological study in a Danish adult population showed that COPD might be much more prevalent in *H. pylori* IgG seropositive women than in uninfected ones **[26]**. Moreover, two case-control Greek studies studied a cohort of 144 patients with chronic bronchitis and 120 control subjects, and they found that *H. pylori* seropositivity in COPD patients was significantly higher than that in controls **[27]**. Kanbay et al. found that *H. pylori* seropositivity in bronchitis patients was significantly higher than that in controls (66.1 vs. 57.7%, respectively) **[28]**. Moreover, Gencer et. al., showed that *H. pylori* IgG levels might be correlated with the severity of COPD **[21]**.

No studies in the literature focused on the potential etiopathogenetic role of *H. pylori* infection in COPD patients. It is well known that *H. pylori* prevalence in COPD patients is extremely increasing that stimulate release of a variety of proinflammatory cytokines, including IL-1, IL-8 and tumor necrosis factor-α **[29]**. Chronic inflammation is a prominent feature of COPD, as shown by the presence in the airway of activated neutrophils and macrophages and the increased number of inflammatory mediators **[30]**. Recent studies showed that cytokines identical to those stimulated by *H. pylori* are released during the course and COPD exacerbations.IL-8 might also be implicated in the disease pathogenesis **[31]**. The previous statements may explain our results of significant increasing hsCRP level in COPD patients infected with *H. pylori* that may reflect more inflammation with subsequent more exacerbation rate of COPD.

Our study showed negative correlation between *H. pylori* positive Ag COPD patients on one limb and pH and PaO2 on the other limb. There was positive relationship between *H. pylori* positive Ag COPD patients and PaCO2 and calculated bicarbonate levels. These results reflect the non-

spirometry parameters of severity. Fedorova et al. detected a positive correlation between the duration of COPD, hypoxia andthe 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 **[32]**.

Regarding COPD severity according to their post-bronchodilator FEV1%, patients in the present research were classified into; mild COPD {19 patients (13.4%)}, moderate COPD {77 patients (54.2%)}, Severe COPD {33 patients (23.2%)} and very sever COPD {13 patients (9.2%)}. Spirometry parameters in both groups showed that FEV1 and FVC were significantly lower in *H. pylori* positive group when compared with these of *H. pylori* negative status. There was a high significant statistical difference in COPD severity in group 1 when compared with group 2, evident with more cases of sever and very sever COPD cases in group 1.

The CAT and FEV1 are both reliable methods for assessing treatment response and progression of disease severity in COPD patients **[33]**. Our study showed significant statistical difference positive correlation between CAT and COPD severity. This finding agreed with Hassan et al., (2012) who determined the relationship between CAT scores and severity of airflow obstruction in stable COPD patients. In their study, the correlation between mean FEV1%predicted and mean score of CAT groups 1, 2, 3, and 4 was statistically significant. In our study, CAT score was 20.6 ±9.7 in group 1, while, was 17±8 in group 2.FEV1 1that indicating airway damage and severity of inflammation, was lower in *H. pylori* stool Ag positive COPD patients, suggesting that *H. pylori* infection may be associated with airway inflammation **[34]**. This goes in agreement with Gencer et al., who reported a negative relationship between FEV1and *H. pylori* serum IgG levels in all patients with COPD **[21]**. A second study of Nahla F. Khattab, et al. compared pulmonary function tests of *H. pylori* seropositive COPD patients and controls. Pulmonary functions were significantly lower among COPD patients with *H. pylori* when compared to those of the controls **[35]** which agree with our results. These findings suggesting that *H. pylori* infection is associated with more severe airway inflammation. Fullerton et al. attributed similar findings of FEV1 among seropositive COPD patients to the ability of *H. pylori* to produce a lot of enzymes, including urease, catalase, protease, lipase and phospholipase, and its ability to release pro-inflammatory mediators that cause gastric mucosa inflammation **[36]**. Inhalation of *H. pylori* or *H. pylori* exotoxins may cause tissue damage in the bronchial system and hence can affect the pulmonary function tests especially FEV1 **[37]**. Roussos et al., found higher serum *H. pylori* seropositivity and serum *H. pylori* IgG levels in COPD patients, but they could not detect an association with lung function parameters (**27**).

CONCLUSION

This study clearly demonstrated that *H. pylori* infection may play a role in COPD initiation and exacerbation in predisposed patients, due to high prevalence of both *H. pylori* and COPD. More randomized controlled studies are needed before confirming this interplay as a tight relation of just co-association.

Ethical consideration

Ethical clearance was obtained from the Ethical Board of the faculty of medicine, Zagazig University, Egypt. Oral consent was obtained from the study participants after the consent form was developed by the research team and approved by the ethical committee of Zagazig University. Similarly, all the information gathered from the clients was handled confidentially, and it was used only for research purpose.

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Conflict of interest

There is no conflict of interest.

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