

## Effects of *Helicobacter pylori* infection on spirometry in patients with chronic obstructive pulmonary disease in Basrah, south of Iraq

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**Abstract**— This study aimed to demonstrate the effect of *Helicobacter pylori* (*H. pylori*) infection on spirometric parameters and to highlight the prevalence of *H. pylori* infection in patients with chronic obstructive pulmonary diseases (COPD) as well as to study the association between *H. pylori* infection and severity of COPD. One hundred and fifty adult COPD patients aged 20-75 years of both genders were included in the study, patients were divided into two groups; the first group (cases) included 60 *H. pylori* positive COPD patients, the second group (control) included 90 *H. pylori* negative COPD patients. Assessment of pulmonary function by measurement of spirometric parameters and detection of *H. pylori* infection by stool rapid antigen test were done to all patients in both groups. Patients in both groups were comparable with regard to demographic characters. Moreover, the predicted values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, peak expiratory flow rate (PEF) and forced expiratory flow rate in mid expiration (FEF25-75) were not significantly different between the two groups ( $P > 0.05$ ). A significantly lower FEV1, FEV1%, FVC and FVC%, FEV1/FVC, PEF, PEF%, FEF25-75 and FEF25-75% were noticed in case group compared with control group ( $P < 0.05$ ). While, FEV1/FVC % was not significantly different between the two groups ( $P > 0.05$ ). The severity of air way obstruction and cough symptom was significantly more in case group compared with control group ( $P < 0.05$ ). It could be concluded that *H. pylori* infection is associated with lower spirometric parameters, more severity of airway obstruction and cough symptom which may be related to exacerbation of chronic airway inflammation secondary to systemic response to *H. pylori* infection.

**Keywords:** *H. pylori*; COPD; spirometry; Basrah; Iraq

### 1. Introduction

Chronic obstructive pulmonary disease (COPD) is preventable and treatable respiratory disease characterized by persistent, partially reversible airflow obstruction and lung hyperinflation with significant extra pulmonary complications and comorbidities, that may affect the outcome of the disease in individual patients. It is mostly caused by smoking and heavy exposure to chemicals, and noxious gases [1, 2]. The initial symptoms are mild and include dyspnea and intermittent cough with or without sputum production. While in moderate stage of the disease, the symptoms worsen with increased cough, mucus production and dyspnea on walking and during exercise [3]. A purulent sputum indicates exacerbation of inflammatory process due to bacterial infection [4]. In severe stages, the symptoms get more frequent and worsening of dyspnea that occurs even at rest. An exacerbation is a complex phenomenon caused by any of the risk factors that trigger severe airway inflammation and lead to more hyperinflation, reduced expiratory flow and shortness of breath [5]. Frequent exacerbation fastens the decline in lung function, therefore affecting the progression of the disease and reducing health quality [6].

#### 1.1 Risk factors for COPD

The main risk factor for COPD is tobacco smoking. WHO's smoking and Tobacco Use Policy defines smokers as anyone who smokes tobacco products daily (even once every day) or from day to day in his or her lifetime and nonsmokers are those who never smoke tobacco products. In addition, passive exposure to cigarette smoke (environmental tobacco smoke) or second-hand smoke leads to inhalation of irritant particles and gases which results in respiratory symptoms and COPD. Occupational exposure to noxious particles and chemicals and burning fuels are other risk factors for COPD [4, 7].

### **1.2 Prevalence of COPD**

In Iraq, the prevalence of COPD among adult smokers aged  $\geq 35$  years was 15.1% [8]. In developing countries, indoor air pollution by traditional fuels used in cooking was associated with COPD in female gender [9, 10, 11].

### **1.3 *Helicobacter pylori* (*H. pylori*)**

*Helicobacter pylori* (*H. pylori*) is spiral shaped bacteria that grow in human gastric mucosa, it can penetrate the gastric mucosa and causing the infection [12, 13]. It affects half of the population worldwide [14]. *H. pylori* colonization of gastric mucosa triggers immune response and inflammation of gastric and duodenal epithelial lining [15]. It also stimulates gastrin secretion by induction of proinflammatory cytokines affecting G cells which causes acid secretion by gastric glands, this eventually results in development of peptic ulcer [16, 17]. The relationship between COPD and *H. pylori* infection has been explained by the systemic effect of the infection, which causes chronic airway inflammation due to the release of gastrointestinal peptides like gastrin, somatostatin, and proinflammatory cytokine [interleukin-1 (IL-1), IL-8, IL-17, IL-23] and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) into the blood. Furthermore, the direct effect on the airway due to aspiration of *H. pylori* exotoxins which causes bronchial mucosal injury [18, 19, 20].

### **1.4 Tests for *Helicobacter pylori* (*H. pylori*) infection**

Tests used for diagnosis of *H. pylori* are either invasive or non-invasive. Invasive tests required endoscopy and includes histological assessment, culture, rapid urease test, and polymerase chain reaction. Non-invasive tests include urea breath test, serological tests and stool antigen (Ag) test. Stool Ag test is a lateral flow immunoassay for the qualitative detection of *H. pylori* antigen in human fecal specimen. This test is reliable test, easily performed, does not need special laboratory equipment's and with sensitivity (94%) and specificity (97%) [21, 22].

### **1.4 Spirometry**

Spirometry is an important pulmonary function test in diagnosing of many respiratory diseases. It is an essential test in diagnosing, follow up and evaluation of treatment in COPD. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, peak expiratory flow rate (PEF), forced expiratory flow rate in mid expiration (FEF25-75) are the common spirometric parameters, their values are evaluated by comparison with predicted values calculated by the spirometer according to age, height, weight, sex, and race of subjects [23].

Chronic obstructive pulmonary disease is diagnosed when FEV1/FVC < 70%, the severity (staging) of the severity of airway obstruction were classified according to post bronchodilator FEV1 into mild (FEV1  $\geq 80\%$  predicted), moderate ( $50\% \leq$  FEV1 <  $80\%$  predicted), severe ( $30\% \leq$  FEV1 <  $50\%$  predicted), very severe (FEV1 <  $30\%$  predicted) [1].

### ***1.5 Aim of the study***

A controversy still exists about the effect of *H. pylori* infection on spirometric parameters in COPD patients. Therefore, this study aimed to investigate the effect of *H. pylori* infection on pulmonary function by spirometry in COPD patients.

### ***2. Subjects and Method***

A case control study is conducted during the period from October 2020 to October 2021 in College of medicine, University of Basrah, Iraq. The study included 150 adult COPD patients of both genders, aged more than 20 years, COPD is diagnosed according to the Global Initiative for Obstructive Lung Disease guidelines [1]. All patients were referred by internists in outpatient clinic of AL-Sadder Teaching hospital. Spirometry and stool examination for *H. pylori* antigen were done to all patients. The study was approved by the College council and ethical committee in the College of Medicine, University of Basrah. The aim of the study, all relevant details, and importance of the study was explained to all participants and a written informed consent was taken from all of them.

#### ***2.1 Inclusion and exclusion criteria***

All patients with signs and symptoms or those who previously diagnosed as COPD (FEV1/FVC% <70%) aged more than 20 years were included in the study. Airway obstruction in patients was classified according to postbronchodilator FEV1% from predicted FEV1 into mild (FEV1  $\geq$ 80%), moderate (50%  $\leq$  FEV1 <80%), severe (30%  $\leq$  FEV1 <50%), and very severe (FEV1 <30%) [1].

Patients with bronchial asthma, other respiratory illnesses, and chronic diseases (diabetes, hypertension), Acute exacerbation of COPD in the preceding month, drugs intake that affecting the results of spirometry (beta blockers, beta agonists) and those who take proton pump inhibitor and/orantibiotics were excluded from the study.

#### ***2.2 Patients' classification***

Patients were classified into two groups according to the result of *H. pylori* stool antigen test. Case group: included 60 COPD patients who were positive for *H. pylori* stool antigen test, aged from 20-to 75 years, 27 of them were males and 33 were female and control group included 90 COPD patients who were negative for *H. pylori* stool antigen test, aged 20 to 75 years, 42 of them were males and 48 were female.

#### ***2.3 Demographic characters (weight, height, BMI)***

Body weight (Kg), and height (cm) were measured by the electronic device (kinLee, china). Body mass index (BMI)in meter square was calculated according to the equation weight (Kg) /[height (m)]<sup>2</sup>.

#### ***2.4 Spirometry***

Pulmonary function tests (PFT) were done by spirometry (spirolab IV MIR) to all patients in outpatients of Al-Sadder teaching hospital, the test was done in sitting position at 8-12 a.m. The best results of at least three technically accepted maneuvers were selected by the spirometer for further analysis. Predicted values of spirometric parameters (FEV1, FVC, FEV1/FVC, PEF and FEF25-75) were calculated automatically by the spirometer depending upon patients age, gender, height, weight, and ethnic group.

### 2.5 Stool examination for *H. pylori* infection

All patients were subjected to stool antigen test for detection of *H. pylori* infection using Onsite *H. pylori* Ag Rapid Test (manufactured by CTK Biotech, Inc. San Diego, USA).

### 2.6 Statistical Analysis

The study results were analyzed by Computerized SPSS program, version 26 program. Continuous data were tabulated as mean  $\pm$  standard deviation (SD), the significant difference between the experimental groups was determined by independent-samples T-test. Qualitative data are tabulated as number (%), the significant difference between the groups were determined by chi-square ( $\chi^2$ ) and Fisher's exact test. A significant difference is considered if  $P < 0.05$ .

## 3. Results

The two studied groups were comparable in demographic characters (age, height, weight, BMI, gender distribution and duration of symptoms as shown in Table 1. Moreover, the mean predicated values of FEV1, FVC, FEV1/ FVC, PFR, and FEF 25 were not significantly different between control and case groups.

The results in Table 2 show a significantly more FEV1, FEV1%, FVC, FVC%, FEV1/FVC, PEF, PEF%, FEF and FEF25-75% were noticed in control group compared with case group.

The severity of airway obstruction according to the results of FEV1% by spirometry were significantly less in control group compared with case group (Table 3). Significantly more patients complaining from cough in case group than in control group; While no significant difference exists in sputum production between control and case groups and all patients of both groups were complaining from dyspnoea (Table 4).

No significant difference noticed in percentage of smoking between control and case groups (Table 5).

**Table 1. Demographic distribution of COPD patients (mean  $\pm$  SD and % for gender)**

Parameter	Control group n=90	Case group n=60
Age (year)	44.4 $\pm$ 13.5	47.3 $\pm$ 13.5
Gender Male	42 (46.7%)	27 (45%)
Female	48 (53.3%)	33 (55%)
Height (cm)	166.6 $\pm$ 9.4	165.4 $\pm$ 9.0
Weight (kg)	82.2 $\pm$ 14.9	83.5 $\pm$ 16.5

BMI (kg/m <sup>2</sup> )	2.32±0.84	2.32±0.84
Duration of symptoms	36.3±32.8	34.3±28.8

Independent sample T test for continuous data and Chi square ( $\chi^2$ ) test for categorical data (gender): BMI= body mass index.

**Table 2. Results of spirometry in COPD patients (mean ±SD).**

Parameter	Control group n=90	Case group n=60
FEV1 (L)	1.93±0.72	1.58±0.63**
FEV1 predicted (L)	3.17±0.73	3.04±0.76
FEV1%	60.4±15.8	51.4±15.4**
FVC (L)	3.29±1.04	2.86±1.04*
FVC predicted (L)	3.82±0.89	3.68±0.91
FVC %	85.8±17.6	77.2±18.3*
FEV1/FVC	58.8±10.4	54.88±10.4*
FEV1/FVC predicted	83.1±2.6	82.6±2.6
FEV1/FVC %	70.1±12.2	66.3±12.7
PEF (L/sec)	2.66±1.09	2.36±1.04**
PEF (L/sec) predicted	7.31±1.5	7.11±1.6
PEF %	36.1±11.9	33.2±12.9**
FEF 25-75 (L/sec)	1.46±0.7	1.05±0.5*
FEF 25-75 (L/sec) predicted	3.45±0.73	3.30±0.79
FEF 25-75 %	41.4±15.4	31.3±14.4*

Independent sample T test: FVC=forced vital capacity, FEV1=forced expiratory volume in one second, PEF= peaked expiratory flow, FEF25-75=forced expiratory flow in mid expiration.\*P <0.05 and \*\*P <0.01.

**Table 3. Severity of airway obstruction in COPD groups [no. (%)].**

Parameter	Control group n=90	Case group n=60	P-value
Mild (FEV1%: ≥80%)	4 (4.4%)	2 (3.3%)	<b>0.006**</b>
Moderate (FEV1:50-<80%)	65 (72.2%)	28 (46.7%)	
Severe(FEV1%: 30-<50%)	16 (17.8%)	25 (41.7%)	
Very severe (FEV1:<30%)	5 (5.6%)	5 (8.3%)	

Fisher's Exact Test: A significant difference (2-sided) is considered if P <0.05.

**Table 4. Dyspnea, cough, and sputum in COPD groups [no. (%)].**

Symptom	Control group n=90	Case group n=60	P value
Dyspnea	Present	90 (100%)	60 (100%)
	Absent	0 (0%)	0 (0%)

<b>Cough</b>	Present	70 (77.8%)	59 (98.3%)	<b>&lt; 0.001***</b>
	Absent	20 (22.2%)	1 (1.7%)	
<b>Sputum</b>	Present	17 (18.9%)	18 (30%)	<b>0.121</b>
	Absent	73 (81.1%)	42 (70%)	

Fisher's Exact Test: A significant difference (2 sided) is considered if P <0.05, no P value for dyspnea because it's constant.

**Table 5. smoking distribution in COPD patients [no. (%)]**

<b>Parameter</b>	<b>Control group n=90</b>	<b>Case group n=60</b>	<b>P-value</b>
<b>Smoker</b>	17 (18.9%)	7 (11.7%)	<b>0.265</b>
<b>Non-smoker</b>	73 (81.1%)	53 (88.3%)	

Chi square ( $\chi^2$ ) test: A significant difference (2-sided) is considered if P <0.05.

**Table 6. smoking distribution in male and female COPD patients [No. (%)]**

<b>Parameter</b>	<b>Male n=69</b>	<b>Female n=81</b>	<b>P-value</b>
<b>Smoker</b>	24 (34.8%)	0 (0%)	<b>&lt;0.001</b>
<b>Non-smoker</b>	45 (65.2%)	81 (100%)	

Chi square ( $\chi^2$ ) test: A significant difference (2-sided) is considered if P <0.05.

#### **4. Discussion**

Chronic obstructive pulmonary disease (COPD) is one of the most public health challenges in the world [24, 25]. *H. pylori* infection affects the pathogenesis of COPD by a systemic effect, through the release of gastrointestinal peptides and proinflammatory cytokines and a local effect, due to chronic airway inflammation and damage due to aspiration of gastric juice [18, 26]. In this study, age, gender, height, weight, BMI were not significantly different between *H. pylori* negative and positive COPD groups (Table 1), this indicates that the studied groups were well matched. Lower spirometric parameters in *H. pylori* positive COPD patients (FEV1, FEV1%, FVC, FVC%, and FEV1/FVC) may result from *H. pylori* induced exacerbation of airway inflammation and obstruction. This is caused by different mechanisms that lead to systemic inflammation and local airway damage [18, 27]. Our results are in agreement with the result of Abdelmagied et al. [28] who reported lower FEV1 and FVC in COPD patients with positive *H. pylori* stool antigen test. Another study in Saudi Arabia reported a significantly less FEV1, FVC, FEV1/FVC, FEF25-75 in *H. pylori* seropositive COPD patients compared with control subjects [29]. While Lee et al. [30] mentioned that there was no relationship between *H. pylori* infection and severity of airway limitation in COPD patients. In this study, PEF, PEF%, FEF25-75 and FEF25-75% were significantly less in *H. pylori* positive compared with *H. pylori* negative COPD patients. Reduction in FEF25-75% indicates small airway obstruction, it is a better indicator than FEV1 in detecting small airway disease [31]. The reduction in FEF25-75% and PEF in

*H. pylori* infected COPD patients may result from increased severity of airway inflammation and obstruction in small airways of those patients. Narrowing and obstruction of small airways in COPD results from inflammatory process, increased mucus production and smooth muscle spasm. Airway resistance to airflow is inversely proportional to the fourth power of the airway radius. Therefore narrowing or decrease in number of patent small airways causes a marked increase in airway resistance [32, 33]. Contrary to our results, Nahla, *et al.* [34] reported insignificant difference in FEF25-75% between *H. pylori* seropositive and seronegative COPD patients.

A significantly more COPD patients in *H. pylori* negative group have mild and moderate severity of airway obstruction (FEV1%) than in *H. pylori* positive group (Table 3). *Helicobacter pylori* induces the release of cytokines such as IL-1, IL-8, and Tumor necrosis factor alpha, these exacerbate the inflammation process and severity of airway obstruction [35]. Abdelmagied *et al.* [28] also found that *H. pylori* infection in COPD patients is associated with more severe stages of airway obstruction. Gencer *et al.* [36] found that *H. pylori* IgG levels were correlated with severity of airway obstruction in COPD patients. However, other studies did not find a significant relation between *H. pylori* infection and severity of airway obstruction in COPD patients [37, 38, 39]. In this study all COPD patients of both groups had exertional dyspnoea. While significantly less COPD patients in *H. pylori* negative had cough compared with *H. pylori* positive group. Whereas, no significant difference with regard to sputum production exist between control and case groups of COPD patients (Table 4). Chronic airway inflammation causes persistent airway irritation and chronic cough which result in progressive decline in lung functions and consequently increased incidence of obstructive or restrictive pulmonary diseases [40, 41], airway irritation is aggravated by active *H. pylori* infection [42, 43]. Comparable results were reported by Heet *et al.* [44], whom mentioned that cough is significantly more in *H. pylori* positive than in *H. pylori* negative individuals.

Table 5 shows that the percentage of smokers is not significantly different between *H. pylori* negative and positive COPD patients. Our results are agreed with results of Abdelmagied *et al.* [28] and Kanbay *et al.* [45]. Although cigarette smoking is a major causative agent for pathogenesis of COPD but its influence on *H. pylori* infection was uncertain [26]. The results of our study show significantly more smoker in male than in female COPD patients (Table 6). In non-smoker individuals, occupational and environmental exposure to dust and fumes and the usage of gases in cooking and indoor air pollution are other important risk factors for development of COPD [46, 47]. Moreover, old age, asthma, female gender and low educational level are associated with high risk for development of COPD in non-smoker individuals [48].

## 5. Conclusions and Recommendations

*Helicobacter pylori* infection is associated with significant reduction in spirometric parameters of COPD patients and with severe form of COPD. Further longitudinal studies are recommended to explore the effect of *H. pylori* eradication on pulmonary function in patients with COPD.

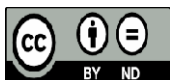
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