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Helicobacter pylori Infection in Never-Smoking Male Patients with Chronic Obstructive Pulmonary Disease and its Relation to Lung Function

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ABSTRACT

There is a recent epidemiologic and serologic evidence for relationship between *Helicobacter pylori* (*H. pylori*) infection and Chronic Obstructive Pulmonary Disease (COPD). In order to assess the relationship between *H. pylori* infection and COPD and its impact on lung function we performed a cross-sectional study including 84 never-smoking male patients with COPD and an equal number of never-smoking males without chronic respiratory disease matched to the COPD patients by age. Evaluation of the study subjects included evaluation of *H. pylori* serological status, baseline and post-bronchodilator spirometry. We found significantly higher *H. pylori* seropositivity in COPD patients than in controls (76.2 Vs 34.5%, p = 0.041). The prevalence of *H. pylori* seropositivity did not differ significantly between patients with mild, moderate and severe COPD. Borderline significance was registered for the difference of the forced expiratory volume in one second (FEV_1) mean value between seropositive and seronegative COPD patients (56.4 vs. 59.2, p = 0.063). The mean degree of FEV_1 reversibility did not differ significantly between seropositive and seronegative COPD patients. Our findings indicate that in cross-sectional analysis there is higher prevalence of *H. pylori* seropositivity in COPD than in non-COPD patients, as well as that *H. pylori* infection has not significant impact on lung function in COPD patients.

Keywords: Baseline Spirometry, Chronic Obstructive Pulmonary Disease, *Helicobacter Pylori*, Never-Smokers, Post-Bronchodilator Spirometry

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) becomes one of the most important global public health problems in the last decades affecting 9-10% of the adults aged over 40 years (Halbert *et al*., 2006). COPD is the fourth leading cause of death in adults in the United States and is projected to be the third most common cause of death by 2020 (Petty, 2003). Between 1970 and 2002, in the United States death rates due to stroke and heart disease decreased (63 and 52%, respectively), while death rates due to COPD increased 100% (Jemal *et al*., 2005).

On the other side, exposure to microbes may result in the modulation of immune system and an increase in the risk of obstructive airways diseases (Fullerton *et al*., 2009). *Helicobacter pylori* (*H. pylori*) is a micro-aerophilic spiral-shaped gram negative bacterium that chronically infects the stomach of more than 50% of the human population (varying from over 70% in developing countries to less than 40% in developed countries) and represents the major cause of gastroduodenal pathologies

(e.g., chronic active gastritis, peptic ulcer, B-cell lymphoma and gastric carcinoma) (Wotherspoon *et al*., 1999; Parsonnet *et al*., 1991; D'Elios *et al*., 1997). Some recent epidemiologic and serologic studies have reported a relationship between *H. pylori* seropositivity, especially of the high virulent cytotoxin-asssociated gene A (CagA) positive strains and extra-gastroduodenal diseases, such as vascular (coronary artery disease and stroke), metabolic (autoimmune atrophic thyroiditis), rheumatic (Henoch-Schönlein purpura), dermatologic (chronic urticaria and rosacea), as well as respiratory diseases (chronic bronchitis, COPD, bronchiectasis, asthma and lung cancer) (Whincup *et al*., 1996; Luis *et al*., 1998; Tsang *et al*., 1998; Roussos *et al*., 2006; Jun *et al*., 2006; Behroozian and Moradkhan, 2010). The activation of inflammatory mediators as a result of systemic immune response induced by *H. pylori* infection may be potential explanation for these associations (Kanbay *et al*., 2007).

In addition, results from some cross-sectional studies indicated gender-dependent difference in the decline in lung function associated with *H. pylori* infection. Fullerton *et al*. (2009) reported lower lung function, i.e., significantly lower Forced Expiratory Volume in one second (FEV_1) and Forced Vital Capacity (FVC) values, in men with positive serology for *H. pylori* as compared to seropositive women. On the other side, controversial results have been reported regarding *H. pylori* prevalence and smoking (considered as a major risk factor for COPD): Higher, normal and lower seropositivity were stated for smokers (Brenner *et al*., 1997; Parasher and Eastwood, 2000; Ogihara *et al*., 2000).

The present study is aimed at assessment of the relationship between *H. pylori* infection and COPD and its impact on lung function in never-smoking male patients.

2. MATERIALS AND METHODS

2.1. Study Design and Setting

A cross-sectional study was carried out in the Department of Cardiorespiratory Functional Diagnostics at the Institute for Occupational Health of R. Macedonia, Skopje-WHO Collaborating Center for Occupational Health and GA^{2}LEN Collaborating Center in the period March 2011-June 2012.

The study protocol was approved by the ethics committee of the institution and each subject gave an informed consent before entering the study.

2.2. Study Subjects

The study protocol underwent 84 never-smoking males aged 39 to 74 years with COPD. Exclusion criteria for COPD patients were exacerbation of COPD in the last month, history of antibiotic use in the last month, history of *H. pylori* eradication and/or presence of other chronic respiratory disease.

In addition, an equal group of never-smoking males without chronic respiratory disease matched to the COPD patients by age was studied as a control. Exclusion criteria for controls were history of antibiotic use in the last month and history of *H. pylori* eradication.

Never-smoker was defined as a non-smoker who has never smoked at all, or has never been daily smoker and has smoked less than 100 cigarettes in his lifetime (WHO, 1998; Leffondre *et al*., 2002).

2.3. Questionnaire

A questionnaire including demographic characteristics, family history of COPD and Chronic Bronchitis (CB) (taking into account the first-degree relatives), exposure to Environmental Tobacco Smoke (ETS), as well as presence of accompanying diseases, was completed by all study subjects.

Exposure to ETS or passive smoking was defined as an exposure to tobacco combustion products from smoking by others (at home, workplace), i.e., as a presence of at least one smoker in the household and/or in the workplace (DHHS, 1984; Janson *et al*., 2001). In addition, passive smokers were divided in two groups regarding the number of hours per day they were exposed to ETS (less or more than 4 h per day).

2.4. H. Pylori Serological Status

H. pylori serological status, i.e., quantitative detection of serum Immunoglobuline G (IgG), was evaluated using the Siemens Immulite^R 1000 assay (a solid-phase, chemiluminiscent IgG assay) (Siemens, Germany). Seropositivity was considered in the case of finding of specific IgG concentration equal or more than 1 U/mL, while the subjects with serum concentration of specific IgG equal or less than 0.9 U/mL were considered as seronegative Immulite^{R,} 1000 Chemiluminiscent Technology, 2012.

2.5. COPD Diagnosis

The diagnosis of COPD was established according to the actual GOLD recommendations (GSD, 2012), i.e., COPD was considered in any study subject who had

dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease (tobacco smoke, smoke from home cooking and heating fuels and/or occupational dusts and chemicals). The diagnosis was proved by the presence of a post-bronchodilator FEV_1/FVC less than 0.70 suggesting persistent airflow limitation.

The severity of the disease in the COPD patients was categorized according to the GOLD 2010 (GSD, 2012) spirometric classification as a mild COPD ($FEV_1/FVC < 0.70$; $FEV_1 \leq 80\%$ predicted), a moderate COPD ($FEV_1/FVC < 0.70$; $50\% \leq FEV_1 < 80\%$ predicted) and a severe COPD ($FEV_1/FVC < 0.70$; $30\% \leq FEV_1 < 50\%$ predicted).

2.6. Baseline Spirometry

The baseline spirometry, including measures of FVC, FEV_1, FEV_1/FVC and maximal expiratory flow at 25-75% of FVC (MEF_{25-75}), was performed in all subjects using spirometer Ganshorn SanoScope LF8 (Ganshorn Medizin Electronic GmbH, Germany) with recording the best result from three measurements the values of FEV_1 of which were within 5% of each other. The results of spirometry were expressed as percentages of the predicted values according to the actual recommendations of European Repsiratory Society (ERS) and American Thoracic Society (ATS) (Miller *et al*., 2005). The combined reference equations for people aged 18 to 70 years, with a height range of 155-190 cm in males, published in the 1993 ERS statement (Quanjer *et al*., 1993) were used for deriving predicted values.

2.7. Bronchodilator Reversibility Testing

Bronchial reversibility testing was performed according to the actual GOLD spirometry guide. Spirometric measurements were performed before and 20 min after administration of 400 μg salbutamol by metered dose inhaler through spacer. Fixed airflow narrowing characteristic for COPD was considered if post-bronchodilator FEV_1/FVC remained less than 0.70. The degree of FEV_1 reversibility was expressed as % FEV_1 reversibility ([post-bronchodilator FEV_1 -pre-bronchodilator FEV_1]/pre-bronchodilator $FEV_1 \times 100$). Significant FEV_1 improvement (a change more than 12% and more than 200 mL) in the presence of fixed airflow limitation did not negate a diagnosis of COPD.

2.8. Statistical Analysis

Continuous variables were expressed as mean values with Standard Deviation (SD) and the nominal variables as numbers and percentages. Analyses of the data involved testing the differences in prevalence and comparison of the means. Chi-square test (or Fisher's exact test where appropriate) was used for testing difference in the prevalence. Comparison of spirometric measurements was performed by independent-samples *T*-test. A *P*-value less than 0.05 were considered as statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows.

3. RESULTS

Demographic characteristics were similar in both examined groups (**Table 1**).

The mean baseline values of all spirometric parameters were significantly lower in COPD patients (**Table 2**).

Table 1. Demographics of the study subjects

Characteristic	COPD patients (n = 84)	Controls (n = 84)
Age (years)	54.7±7.6	55.6±8.1
BMI (kg/m^2)	25.8±3.9	26.4±4.0
Family history of COPD or CB	10 (11.9%)	7 (8.3%)
Exposure to ETS	39 (46.4%)	44 (52.4%)
Exposed less than 4 h	18 (21.4%)	23 (27.4%)
Exposed more than 4 h	21 (25.0%)	21 (25.0%)
Accompanying diseases		
Arterial hypertension	10 (11.9%)	12 (14.3%)
Diabetes mellitus type 2	6 (7.1%)	4 (4.8%)

Numerical data are expressed as mean value with standard deviation; frequencies as number and percentage of study subjects with certain variable

Table 2. Mean baseline values of spirometric parameters in the study subjects

Spirometric parameter	COPD patients (n = 84)	Controls (n = 84)	P-value*
FVC (%pred)	70.1±12.3	96.4±9.2	0.000
FEV_1 (%pred)	57.3±9.2	88.1±11.2	0.000
FEV_1/FVC	0.62±0.05	0.78±0.07	0.000
MEF_{25-75} (%pred)	44.7±14.8	73.6±16.7	0.000

Data are expressed as mean value with standard deviation. COPD: Chronic Obstructive Pulmonary Disease; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in one second; MEF_{25-75}: Maximal Expiratory Flow at 25-75% of FVC; % pred: % of predicted value. *Compared by Independent-samples *T*-test.

Table 3. Characteristics of the disease in the COPD patients

Characteristic	COPD patients (n = 84)
Mean COPD duration (years)	9.2±3.4
COPD severity	
Mild COPD	32 (38.1%)
Moderate COPD	28 (33.3%)
Severe COPD	24 (28.6%)

Numerical data are expressed as mean value with standard deviation; frequencies as number and percentage of study subjects with certain variable. COPD: chronic obstructive pulmonary disease.

Table 4. Mean baseline values of spirometric parameters in *H. pylori* seropositive and seronegative COPD patient

Spirometric parameter	*H. pylori* seropositive COPD patients (n = 64)	*H. pylori* seronegative COPD patients (n = 20)	*P*-value*
FVC (%pred)	69.2±10.8	70.9±11.3	0.127
FEV_1 (%pred)	56.4±8.4	59.2±10.6	0.063
FEV_1/FVC	0.61±0.02	0.62±0.06	0.098
MEF_{25-75} (%pred)	45.3±12.9	43.9±15.8	0.104

Data are expressed as mean value with standard deviation. *H. pylori*: *Helicobacter pylori*; COPD: Chronic Obstructive Pulmonary Disease; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in one second; MEF_{25-75}: Maximal Expiratory Flow at 25-75% of FVC; % pred: % of predicted value. *Compared by Independent-samples *T*-test

Table 5. Mean post-bronchodilator values of spirometric parameters in *H. pylori* seropositive and seronegative COPD patients

Spirometric Parameter	*H. pylori* Seropositive COPD patients (n = 64)	*H. pylori* seronegative COPD patients (n = 20)	*P*-value*
FVC (%pred)	70.3±11.6	71.4±12.1	0.188
FEV_1(%pred)	58.7±10.4	60.5±11.8	0.074
FEV_1/FVC	0.62±0.04	0.62±0.07	0.109
MEF_{25-75}(%pred)	46.9±14.2	45.2±13.9	0.131

Data are expressed as mean value with standard deviation. *H. pylori*: *Helicobacter pylori*; COPD: Chronic Obstructive Pulmonary Disease; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in one second; MEF_{25-75}: Maximal Expiratory Flow at 25-5% of FVC; % pred: % of predicted value. *Compared by Independent-samples *T*-test

Characteristics of the disease in the COPD patients are presented on **Table 3**.

The prevalence of *H. pylori* seropositive subjects was significantly higher in the group of COPD patients (76.2% Vs. 34.5%, P = 0.041; Chi-square test) (**Fig. 1**).

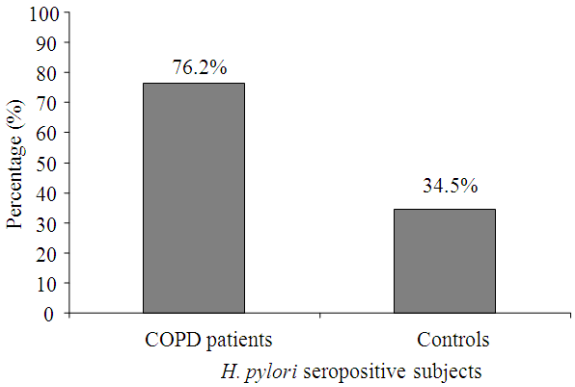

Fig. 1. Prevalence of *H. pylori* seropositivity in the examined groups

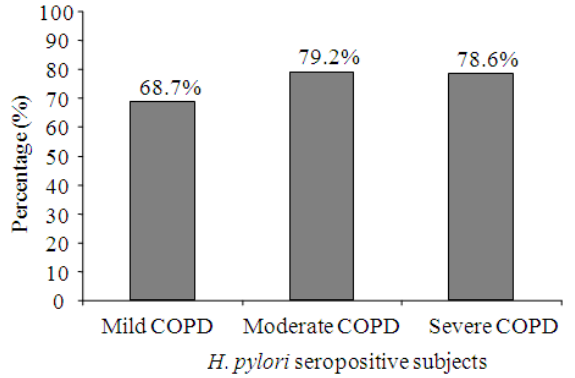

Fig. 2. Prevalence of *H. pylori* seropositivity in the patients with mild, moderate and severe COPD

The prevalence of *H. pylori* seropositive subjects in the patients with mild, moderate and severe COPD is shown on **Fig. 2**. There was no significant difference in the prevalence of *H. pylori* seropositivity between patients with mild and moderate COPD (68.7% vs. 79.2%, p = 0.104; Chi-square test), mild and severe COPD (68.7% vs. 78.6%, p = 0.112; Chi-square test), as well as between patients with moderate and severe COPD (79.2% vs. 78.6%, p = 0.279; Chi-square test).

With exception of the mean FEV_1 baseline value where a borderline significance was registered, there was no significant difference in the mean baseline values of the other spirometric parameters between seropositive and seronegative COPD patients (**Table 4**). The mean baseline spirometric values did not differ significantly between seropositive and seronegative controls.

Similar results were registered regarding the mean post-bronchodilator spirometric values in seropositive

and seronegative COPD patients (**Table 5**). The mean post-bronchodilator spirometric values did not differ significantly between seropositive and seronegative controls.

The degree of FEV_1 reversibility expressed as % FEV_1 reversibility was significantly higher in COPD patients than in controls (10.2±2.3 Vs 4.7±2.1, p = 0.000; Independent-samples T-test). The mean value of % FEV_1 reversibility in H. pylori seropositive COPD patients was similar to its mean value in seronegative COPD patients (10.7±3.1 vs. 9.9±2.9, P = 0.119; Independent-samples *T*-test).

4. DISCUSSION

COPD remains frequent and costly disease representing one of the principal demands of the public health worldwide. Inhaled tobacco smoke and other noxious particles, such as occupational exposures and smoke from biomass fuels, are the most important exogenous factors that influence disease development and progression (GSD, 2012; Chatila *et al*., 2008). On the other side, *H. pylori* infection, a lifelong and often asymptomatic infection of the stomach, profoundly alters gastric immune response that may lead to systemic effects. *H. pylori* persistence leads to chronic inflammation and immune stimulation, which could contribute to several extra-gastroduodenal pathologies (Pellicano *et al*., 1999; Kowalski *et al*., 2006; Islami and Kamangar, 2008; Najafizadeh *et al*., 2007).

As it is mentioned above, the results of several studies emphasis the relationship between *H. pylori* infection and chronic bronchial inflammatory disorders, e.g., chronic bronchitis, COPD and bronchiectasis. It is believed that the release of proinflammatory cytokines, e.g., Interleukin-1 (IL-1), IL-8, IL-17, IL-23 and Tumor Necrosis Factor-ά (TNF-ά), stimulated by *H. pylori* infection plays a role in the chronic inflammation of bronchi (Roussos *et al*., 2006; Jafarzadeh *et al*., 2009; Cornwell *et al*., 2010). Moreover, serum levels of these cytokines normalize following eradication therapy of *H. pylori* (Kountouras *et al*., 2000). There is a need of further studies to assess whether eradication therapy of *H. pylori* may modify the course of COPD (Hashemi *et al*., 2011). The impact of chronic infections, e.g., *H. pylori*, *Chlamidia pneumoniae* (*C. pneumoniae*) and *Cytomegalovirus* (CMV) infections, on COPD development and severity actually is investigated in the United States in a large population-based sample in a MESA-Lung study, an extension of the Multi-Ethnic Study of Atherosclerosis (MESA) study (Hankinson *et al*., 2010).

The studies that investigated the relationship between *H. pylori* infection and COPD is often difficult to compare because of differences in the study design, as well as in the study population and study protocol. In the present study we assessed the relationship between *H. pylori* infection and COPD and its impact on lung function investigating a group of never-smoking COPD patients and a group of never-smoking males without chronic respiratory disease. The examined groups included subjects with similar demographic characteristics. In either group there was a large proportion of passive smokers that is similar to its prevalence in R. Macedonia documented in our previous studies (Minov *et al*., 2006; 2008).

We found significantly higher prevalence of seropositive subjects in the group of COPD patients than in the control group with no significant difference in the *H. py*lori seropsotivity between the subjects with mild, moderate and severe COPD. Significantly higher seropositivity to *H. pylori* was detected in several studies which investigated the relationship between COPD and *H. pylori* infection. In the study including COPD patients and healthy controls matched by sex and age, Gencer *et al*. (2007) reported significantly higher prevalence of *H. pylori* seropositive subjects among COPD patients with no significant difference in gender, age and smoking status between seropositive and seronegative COPD patients. Similarly, in the study including COPD patients and age- and sex- matched controls, Roussos *et al*. (2005) reported significantly higher prevalence of *H. pylori* infection, as well as significantly higher prevalence of CagA-positive *H. pylori* infection in COPD patients. In the study including patients with CB and controls matched by sex and social status, Caselli *et al*. (1999) reported significantly higher prevalence of *H. pylori* seropositive subjects in the group of subjects with CB. On the contrary, Hashemi *et al*. (2011) reported similar prevalence of *H. pylori* seropositivity in a case-control study including COPD patients and age and sex-matched controls with pulmonary diseases other than COPD (asthma, lung cancer and sarcoidosis) with no significant difference in *H. pylori* seropositivity between the patients with mild, moderate and severe COPD. The absence of significant difference in the prevalence of *H. pylori* seropositivity between COPD and non-COPD patients may be due to the increased prevalence of *H. pylori* seropositivity in controls with chronic inflammatory or malignant respiratory disorders (e.g., asthma or lung cancer).

With exception of borderline significant difference in the mean values of baseline and post-bronchodilator FEV_1, we did not register significant difference in the mean values of the other measured spirometric parameters between seropositive and seronegative COPD patients. There was non-significant FEV_1 reversibility between *H. pylori* seropositive and seronegative COPD patients. In our previous study in which we investigated the impact of *H. pylori* infection on lung function and severity of bronchial hyperresponsiveness in subjects with allergic asthma, we did not register significant difference in the mean values of measured spirometric parameters between seropositive and seronegative allergic asthma patients (Minov *et al*., 2011). In the study conducted by Gencer *et al*. (2007) mentioned above, they reported significantly lower FEV_1 values in seropositive as compared to seronegative COPD patients. The difference between these groups regarding FVC and FEV_1/FVC was statistically non-significant (Gencer *et al*., 2007). On the other side, Roussos *et al*. (2005) reported no statistically significant difference regarding the spirometric values between *H. pylori* seropositive and seronegative COPD patients. In addition, in a population-based study in adults which investigated the relationship between *H. pylori* infection and lung function, asthma, atopy and allergic disease mentioned above, Fullerton *et al*. (2009) reported significantly lower FEV_1 and FVC values in *H. pylori* seropositive men in a cross-sectional analysis, but after adjustment for either height or social class the size of these associations were reduced. Furthermore, in a longitudinal analysis they did not register significant association between *H. pylori* serological status and decline in the lung function over 9 years (Fullerton *et al*., 2009). On the contrary, in the study of Nottinghamshire miners, Siva *et al*. (2004) reported that a past history of peptic ulceration was present in more than 50% miners with severe COPD but only in 3% of miners with no respiratory symptoms and normal spirometric values.

The present study has some limitations. First, relatively small number of the subjects in the study groups could have certain implications on the data obtained and its interpretation. Second, the study design, i.e., cross-sectional analysis, could also have implications on the data obtained and its interpretation. Third, the serological data for exposure to *H. pylori* is unable to distinguish current from prior infection which limits interpretation of the associations observed. The strength of the study is the assessment of the impact of *H. pylori* infection on COPD in never-smoking males that, to our knowledge, so far has not been reported in published literature, as well as extensive lung function measurements performed in the study subjects.

5. CONCLUSION

In conclusion, in a cross-sectional study including never-smoking male COPD patients and non-COPD matched controls we found significantly higher prevalence of *H. pylori* seropositivity in COPD patients with no significant difference between patients with mild, moderate and severe COPD. Borderline significance was registered for the difference of the FEV_1 mean value between seropositive and seronegative COPD patients, while the mean values of other measured spirometric parameters, as well as the mean degree of FEV_1 reversibility did not differ significantly. Our findings support the need of further larger prospective studies in order to assess the complex relationship between *H. pylori* infection and COPD.

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