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Helicobacter Pylori Infections in Chronic Obstructive Pulmonary Disease

Kronik Obstrüktif Akciğer Hastalığında Helicobacter Pylori *Enfeksiyonu*

Ali Tabaru[1], Metin Gorguner[1], Metin Akgun[1], Mehmet Meral[1], Ali Sahin[2]

[1]Department of Chest Diseases, Aziziye Hospital, Suleyman Demirel Medical Centre, Ataturk University, Erzurum, Turkey
[2]Department of Nuclear Medicine, Yakutiye Hospital, Suleyman Demirel Medical Centre, Ataturk University, Erzurum, Turkey

Abstract

Objective: We aimed to investigate the prevalence of *Helicobacter pylori* (*H. pylori*) in patients with chronic obstructive pulmonary disease (COPD) using the C-14 urea-breath test (C14UBT) and to determine whether there is an association between *H. pylori* infection and the severity of COPD. This is the first report in the literature of the use of C14UBT to investigate the prevalence of *H. pylori* in patients with COPD.

Materials and Methods: Fifty subjects with COPD (38 males and 12 females, aged 61±10 years) and 20 control subjects (10 males and 10 females, aged 55±11 years) were evaluated. C14UBT was used to determine *H. pylori* infection.

Results: The prevalences of *H. pylori* infection in subjects with COPD and in controls were 72% and 65%, respectively (p=0.56). Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) values were significantly higher in the *H. pylori*-infected subjects with COPD than in the uninfected subjects (p=0.008 and p=0.006, respectively).

Conclusion: The presence of *H. pylori* infection in COPD patients affects pulmonary functions, but the effects of *H. pylori* infection on the respiratory system and COPD are not clear.

Key Words: COPD, *Helicobacter pylori*, Infection, Lung

Özet

Amaç: Bu çalışmada kronik obstrüktif akciğer hastalığı (KOAH) bulunan hastalarda C-14 üre-nefes testi (C14ÜNT) kullanarak *Helicobacter pylori (H. pylori)* prevalansını ve *H. pylori* enfeksiyonu ile KOAH şiddeti arasında bir ilişki olup olmadığını araştırmayı hedefledik. Bu, KOAH hastalarında *H. pylori* prevalansını araştırmak için C14ÜNT'nin kullanıldığı literatürdeki ilk çalışmadır.

Gereç ve Yöntem: KOAH'lı 50 olgu (38 erkek ve 12 kadın, ortalama yaş: 61±10 yıl) ve 20 sağlıklı kontrol (10 erkek ve 10 kadın, ortalama yaş: 55±11 yıl) incelendi. *H. pylori* enfeksiyonunu saptamak için C14ÜBT kullanıldı.

Bulgular: KOAH olguları ve kontroller için *H. pylori* enfeksiyonu prevalansı sırasıyla, %72 ve %65 olarak belirlendi (p=0.56). *H. pylori* enfeksiyonu bulunan KOAH olgularında, birinci saniyedeki zorlu ekspiratuvar volüm (FEV_1) ve zorlu vital kapasite (FVC) değerleri, enfeksiyon bulunmayanlardan anlamlı olarak daha yüksek bulundu (sırasıyla, p=0.008 ve p=0.006).

Sonuç: KOAH hastalarında *H. pylori* enfeksiyonu varlığı solunum fonksiyonlarını etkilemektedir, fakat *H. pylori* enfeksiyonunun solunum sistemi ve KOAH üzerine etkileri tam olarak aydınlatılmamıştır.

Anahtar Kelimeler: KOAH, *Helicobacter pylori*, Enfeksiyon, Akciğer

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease systematically characterized by an abnormal inflammatory response affecting the airways, interstitium and vessel beds through reaction to gas and particles, especially smoke from cigarettes [1].

In recent studies, a seroepidemiological relationship between the *Helicobacter pylori* (*H. pylori)* infection and many inflammatory conditions has been observed. FEV_1 values *of H. pylori* in IgG-seropositive COPD patients have been found to be lower than those of seronegative patients [2-7].

The collective report of the Maastricht meeting organized by the European *H. pylori* Study Group notes that infection diagnosis should be performed via the C-14 urea-breath test (C14UBT) or the stool antigen test [8].

In our study, we aimed to investigate the presence of *H. pylori* infection in COPD patients and the relationship between the severity of COPD and *H. pylori* infection in such patients.

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Correspondence to: Ali Tabaru, Department of Chest Diseases, Aziziye Hospital, Suleyman Demirel Medical Centre, Ataturk University, 25240 Erzurum, Turkey
Phone: +90 442 316 63 33 Fax: +90 442 316 63 40 e-mail: tabaruali@yahoo.com

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Materials and Methods

The research protocol was approved by the Ataturk University Ethics Committee, the institution in which the work was undertaken.

Patient selection

Fifty COPD patients (38 male and 12 female, median age: 61±10) and twenty smoking, healthy control subjects (10 male and 10 female, median age: 55±11) were included in the study. These subjects were admitted to the Ataturk University Faculty of Medicine Polyclinic of Chest Diseases between August 2007 and October 2009 after meeting the inclusion criteria.

Inclusion criteria

The study was performed with stage 1 and stage 2 COPD patients according to the GOLD 2009 guidelines; smoking, healthy subjects were selected as the control group. For patients with airway obstruction according to the ATS/ERS guidelines (FEV_1/FVC <70%), detection of COPD severity was performed according to the following criteria [9]:

Stage 1: FEV_1 ≥80% predicted

Stage 2: 50% ≤FEV_1 <80% predicted

Stage 3: 30% ≤FEV_1 <50% predicted

Stage 4: FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure.

Exclusion criteria

Subjects were not be considered for this study if they exhibited any of the following:

- Asthma
- Known peptic ulcers
- Presence of gastroesophageal reflux symptoms
- Active infection
- Cardiovascular disease

Individuals with one of the following conditions that may affect the diagnostic value of the non-invasive *H. pylori* infection diagnostic method C14UBT were excluded from the study:

- Having used antibiotics within the last month
- Having used a proton pump inhibitor within the last mon
- Having used histamine-2-receptor antagonists within the last week
- Having used an antacid within the last 24 hours
- Having *H. pylori* eradication treatment within the last 6 months

Pulmonary function tests

After the subjects were informed about the study, their consent for participation in the study was obtained. Pulmonary function tests were performed in our clinic's pulmonary function test unit using the V Max 22 (Sensor Medix, Solna, California) device. For the FEV_1% determination, the "European Community for Steel and Coal" prediction chart has been used.

During spirometric evaluation, the subjects were asked to inhale and exhale normally three times each, and they were then asked to inhale as deeply as possible and to exhale as rapidly as possible a few seconds later, which completed the test. The test was performed with technically accepted maneuvers, and an FEV_1/FVC ratio was calculated using the highest FEV_1 and FVC values of three separate curves [10]. Afterwards, patients with an FEV_1/FVC <75% inhaled 400 µg salbutamol (Ventolin inhaler®-Glaxo Smith Kline): pulmonary function tests were repeated 15-20 minutes later, and the bronchodilator response was checked. A basal value increase >12% in FEV_1 or an absolute value increase >200 has been considered positive for early reversibility [11].

C-14 urea-breath test

All subjects received C14UBT in the Ataturk University Faculty of Medicine Nuclear Medicine Department.

The subjects drank urea solutions containing C-14-labeled urea isotopes following a fast of 4-6 hours; exhaled air was collected after 20-25 minutes, and marked CO_2 was measured (in the presence of *H. pylori* in the stomach, the bacterial urease enzyme breaks down the urea and creates ammonia and marked CO_2, the latter of which is detected in the breath). Radioactive CO_2 measurement was performed using a mass spectrophotometer (Isotopes Co. Ltd. institute, Noster Sys. AB, HELIPROBE).

Statistical analysis

All data recorded in the study were analyzed using SPSS Windows 15.0 (SPSS, Chicago, IL). Average values and standard deviations for the ages of all subjects were collected.

Pearson Chi-Square tests were used to compare urea-breath test positivity between COPD and the control group, COPD stage 1 and stage 2, the control group and COPD stage 1, and the control group and COPD stage 2, as well as between genders.

Mann-Whitney U tests were used for the C14UBT and pulmonary function test values comparison for all subjects, as well as for the C14UBT and pulmonary function test values comparison for COPD patients.

Values with a p value less than 0.05 were accepted as statistically significant.

Results

A total of 70 (mean age 59±10) subjects were included in the study, including 22 female and 48 male subjects. Among

these subjects, 50 (12 male and 38 female with a mean age of 61±10) were COPD patients, and 20 (10 male and 10 female with a mean age of 55±1) composed the smoking, healthy control group.

In 49 of the 70 subjects (70%), C14UBT, which reflects positive *H. pylori* infection, was detected. Although C14UBT positivity was more prevalent in the COPD subjects (72%) compared to the control group (65%), there was not a statistically significant difference between the two groups (p value=0.56).

When we compared the stage 1 and stage 2 COPD patients in terms of C14UBT positivity, no significant difference was observed between the two groups (p value=0.06). When we compared the control group with both stage 1 and stage 2 COPD patients in terms of C14UBT positivity, there was no statistically significant difference between the groups (p=0.12 and p=0.83, respectively). The C14UBT results of the subjects are given in Table 1.

When we compared the C14UBT-positive subjects and C14UBT-negative subjects in terms of FVC, FEV_1, FEV_1/FVC, FVC% predicted and FEV_1% predicted, including pulmonary function test parameters, the FVC, FEV_1, FVC% predicted and FEV_1% predicted values of the C14UBT-positive subjects were found to be greater than those of the negative subjects. However, the difference was not statistically significant (p=0.06, p=0.10, p=0.21, p=0.22, respectively). When the subjects were compared in terms of the FEV_1/FVC ratio used in airway obstruction detection, the FEV_1/FVC ratio was lower in C14UBT-positive subjects compared to negative subjects; however, the difference was not statistically significant (p=0.90). C14UBT results based pulmonary function test values of all the subjects are given in Table 2.

In the COPD patients with positive C14UBT results, the FVC, FEV_1, FEV_1/FVC, FVC% predicted and FEV_1% predicted values were greater compared to those of the negative test result subjects. The differences in the FVC, FEV_1, FVC% predicted and FEV_1% predicted values between the C14UBT-positive and negative COPD patients were statistically significant (p=0.006, p=0.008, p=0.01 and p=0.02, respectively). However, when the C14UBT-positive and C14UBT-negative COPD patients were compared in terms of FEV_1/FVC ratio, no statistically significant difference was found (p=0.50). C14UBT results-based pulmonary function tests values of the COPD patients are given in Table 3.

When the C14UBT positivity was compared in the male and female COPD patients, the positivity ratio was higher in males; however, this difference was not statistically significant (p=0.23). The C14UBT results of the COPD patients based on patient gender are given in Table 4.

Table 1. C-14 urea-breath test (C14UBT) results of the subjects

	C14UBT Negative (n=21)	C14UBT Positive (n=49)
All COPD (n=50)	14 (28%)	36 (72%)
Stage 1 COPD (n=21)	3 (14%)	18 (86%)
Stage 2 COPD (n=29)	11 (38%)	18 (62%)
Control (n=20)	7 (35%)	13 (65%)
All subjects (n=70)	21 (30%)	49 (70%)

Discussion

Recently, many effects of COPD other than typical pulmonary pathology have been defined [12]. Accompanying

Table 2. C-14 Urea-breath (C14UBT) test results based on pulmonary function test values

	C14UBT Negative (n=21)	C14UBT Positive (n=49)	All cases (n=70)	p value
FVC	3.11±0.97	3.48±0.91	3.37±0.94	0.06
FEV_1	2.12±0.86	2.33±0.68	2.26±0.74	0.10
FEV_1/FVC	67.19±9.78	66.61±10.48	66.79±10.21	0.90
FVC% predicted	90.9±24.64	99.80±20.46	97.13±22	0.21
FEV_1% predicted	79.19±25.01	83.24±19.90	82.03±21.46	0.22

Table 3. C-14 Urea-breath test (C14UBT) results and pulmonary function tests values of the COPD patients

	FVC	FEV_1	FEV_1 /FVC	FVC% predicted	FEV_1% predicted
C14UBT Negative (n=14)	2.82± 0.68	1.72± 0.39	61.43± 5.36	82.86± 21.77	66.57± 13.34
C14UBT Positive (n=36)	3.53± 0.86	2.22± 0.60	61.97± 6.44	99.58± 21.29	78.44± 19.03
All COPD (n=50)	3.33± 0.87	2.08± 0.59	61.826± 6.11	94.90± 22.52	75.12± 18.30
p value	0.006*	0.008*	0.50	0.01*	0.02*

* Statistically significant

Table 4. C-14 Urea-breath test (C14UBT) results of the COPD patients based on gender

	C14UBT Negative	C14UBT Positive	Total
Male	9 (23.7%)	29 (76.3%)	38
Female	5 (41.7%)	7 (58.3%)	12

extrapulmonary diseases contribute to COPD severity and mortality [13].

Three epidemiological studies published between 1968 and 1986 revealed that the COPD prevalence in peptic ulcer (PU) patients is 2 to 3 times greater compared with controls without PU [14-16]. Additionally, a wide population study revealed that chronic bronchitis is a significant cause of death in PU patients [17]. Smoking was considered to be a significant factor underlying the relationship between these conditions. However, new studies revealed that tobacco consumption had a small role in PU development and that *H. pylori* infection was the main reason for PU disease [18, 19].

In 1998, Caselli et al. [20] performed a prospective pilot study on 60 chronic bronchitis patients and discovered an increased *H. pylori* seroprevalence (81.6% and 57.9% control). Two years later, a large epidemiological study on Danish adult population showed that COPD was much more widespread in *H. pylori* IgG-seropositive women than in uninfected women [21]. In the first of two case-control studies performed in Greece investigating this relationship, following cohort analysis of 144 bronchitis patients and 120 control cases, *H. pylori* seropositivity was found to be statistically significantly higher in bronchitis patients compared with the control group [22]. Gencer et al. [23] also showed that *H. pylori* IgG levels may be correlated with COPD severity.

In our study, the *H. pylori* frequency was found to be higher in COPD patients (72%) than the control group (65%). However, the difference was not statistically significant.

H. pylori may be detected indirectly both serologically and via C14UBT. C14UBT gives more correct results than serology, with a sensitivity and specificity over 95%; furthermore, C14UBT shows active infection, whereas serology has a low specificity and cannot be reliably used for active infection diagnosis. Therefore, the test for efficient detection where prevalence is low should be C14UBT. In our study, gastric biopsy for the histological identification of H. pylori has not been used because it is a more invasive method compared to C14UBT.

It has been determined that *H. pylori*-infected COPD patients had higher spirometric values compared with uninfected patients. We think that this finding arises from the fact that in our study, C14UBT was used for the first time for *H. pylori* diagnosis; stage 1 and stage 2 COPD patients were included in the study, and the number of patients was low. If we consider the COPD patients separately- specifically, chronic bronchitis patients and emphysema patients- we believe that the possible etiopathogenic factors that may explain the relationship of *H. pylori* infection may be put forth more easily, and questions regarding effects of *H. pylori* infection on COPD severity may be answered more easily. In our study, the separation of COPD cases into two groups (chronic bronchitis and emphysema) and their subsequent separate evaluations may be among the reasons explaining why the relationship between COPD severity and *H. pylori* infection was found to be opposite of other studies.

Possible effects of smoking on both COPD development and *H. pylori* may be considered a limiting factor.

In conclusion, the main evidence regarding *H. pylori* infection and COPD is based on serological case-control studies. Future studies should focus on the risk of COPD development among *H. pylori*-infected patients. The effect of *H. pylori* eradication on the natural progress of the disease is another matter of curiosity. As a result, the underlying mechanisms regarding the pathogenesis and the relevant connections between *H. pylori* infection and COPD still need to be revealed.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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