

ASTHMA TREATMENT

Erosive Esophagitis Worsens Reflux Signs and Symptoms in Asthma Patients Without Affecting Pulmonary Function Tests

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Objectives. To determine whether erosive esophagitis (EO) worsens reflux signs and symptoms and affects pulmonary function test in asthma patients. **Methods.** Sixty asthma patients with gastroesophageal and laryngopharyngeal reflux symptoms were included. Spirometry, reversibility test, esophagogastroscore, laryngoscopy, and esophagogastroscore biopsies were conducted. **Results.** EO was diagnosed in 25% ($n = 15$) of the patients. The remaining 45 patients were placed into the non-erosive esophagitis (NEO) group. Of the 15 EO patients, grade 1 esophagitis was identified in 75% ($n = 9$), grade 2 in 12.5% ($n = 3$), and grade 3 in 12.5% ($n = 3$). Pulmonary function test results were not significantly different between the EO and NEO groups. Gastroesophageal and laryngopharyngeal reflux symptoms such as regurgitation, dysphagia, dyspnea, globus sensation, dysphonia, and sore throat were more frequent in EO patients than in the NEO group. The reflux finding score (RFS) was 7.33 and 4.55 in EO and NEO patients, respectively ($p < .001$). Posterior commissure hypertrophy was the most common laryngoscopic finding in both of the groups followed by diffuse laryngeal edema, erythema, and pseudosulcus. **Conclusions.** Gastroesophageal and laryngopharyngeal reflux symptoms were more frequent in EO patients than in the NEO group. The laryngoscopic findings of laryngopharyngeal reflux were more severe and the RFS was significantly higher in EO patients than in NEO patients. The presence of EO seems to be associated with an increase in reflux without affecting pulmonary function as EO did not cause a significant decrease in pulmonary function tests.

Keywords asthma, erosive esophagitis, gastroesophageal reflux, laryngopharyngeal reflux

INTRODUCTION

Gastroesophageal reflux is described as the backflow of gastric or duodenal contents into the esophagus. The most recognizable symptoms are heartburn and acid regurgitation. The prevalence of gastroesophageal reflux in the general population varies from 10% to 17% (1–3). In addition to esophageal complications, gastroesophageal reflux is believed to lead to extra-esophageal symptoms and complications. Laryngopharyngeal reflux is the retrograde movement of gastric contents (acid and enzymes such as pepsin) into the laryngopharynx leading to extra-esophageal symptoms occurring in the larynx/hypopharynx. Reflux of acid and pepsin may affect the respiratory tract and cause respiratory problems such as asthma and chronic cough. The association between gastroesophageal reflux and asthma has been known for many years. The prevalence of asthma in individuals with gastroesophageal reflux as well as the prevalence of gastroesophageal reflux in individuals with asthma is higher than that reported in the general population (4–8).

Using gastroesophageal endoscopy, gastroesophageal reflux has been classified into two categories: erosive esophagitis (EO) and non-erosive esophagitis (NEO) (9, 10). EO has been reported to occur in 20–40% of patients with gastroesophageal reflux and in 20–47% of patients with asthma (4, 6, 9, 11, 12). The presence of esophagitis

indicates severe gastroesophageal reflux and severe gastroesophageal reflux may worsen respiratory symptoms in asthma patients (4, 7, 8). The aim of this study is to compare the results of pulmonary function tests of asthma patients with EO to those with NEO.

MATERIAL AND METHODS

Sixty controlled asthma patients with gastroesophageal and laryngopharyngeal reflux symptoms participated in the study at the pulmonary specialty outpatient clinic at Taksim Training and Research Hospital in Istanbul, Turkey, between January 2006 and April 2007.

To be eligible for the study, several inclusion parameters were used. Eligible patients had been given the diagnosis of asthma according to the guidelines of the Global Strategy for Asthma Management (GINA) at least 6 months prior to entry into the study (13). A skin allergy test panel that included dust mites, molds, weeds, grass, wood pollens, feathers, and cockroach was given to all patients (ALK—ABELLO, Prick Test Diagnostic, Madrid, Spain). When the mean diameter of a wheal is 3 mm greater than or equal to a saline control in the presence of a positive histamine control, the test was deemed positive. All of the patients had reflux symptoms such as heartburn, regurgitation, chest pain, dysphagia, globus, hoarseness, and sore throat. All of the symptoms lasted for a period of longer than 6 months. Symptoms were occasionally provoked by a heavy meal and were severe enough to disturb sleep. Patients used inhaled steroids and beta-agonist therapy without antireflux drugs. None of the

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patients had been previously diagnosed with any other chronic illness, gastroenterological disease, or obstructive or restrictive pulmonary diseases. Patients who had pulmonary findings in chest radiographs were excluded. This study was approved by the Taksim Training and Research Hospital ethics committee and all patients were given written informed consent.

Gastroesophageal Reflux Evaluation

The severity and frequency of gastroesophageal reflux symptoms were evaluated according to a validated Mayo Clinic questionnaire, previously translated into Turkish and culturally adapted. This questionnaire identifies gastroesophageal reflux symptoms and excludes other digestive system disorders such as peptic ulcer, gastritis, etc. (14). We selected only patients who had reflux symptoms at least weekly. We excluded known esophageal diseases such as cancer, achalasia, mastocytosis, stricture, active peptic ulcer disease, Zollinger Ellison syndrome, and scleroderma. None of the patients had alcohol and/or coffee addiction. They drank at most one cup of tea daily at breakfast.

Esophago-gastroduodenoscopic assessment (Olympus GIF 130 instruments) was done by gastroenterologists for all patients. The severity of EO was determined endoscopically by the presence and extent of reflux-related "mucosal breaks" (erosions or ulcers) as defined by the Los Angeles classification (grade A: one or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds; grade B: one or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds; grade C: mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of esophageal circumference; grade D: mucosal breaks which involve at least 75% of the esophageal circumference) (15). Endoscopy is an objective method to identify esophagitis, but does not detect microscopic changes in the esophageal mucosa. To document microscopic changes, esophago-gastric biopsies were taken. The biopsy specimens were embedded in paraffin wax and 3 μ m sections were obtained. Three or four sections were stained with hematoxylin-eosin. Intestinal metaplasia was detected using PAS-ab. Standard histological sections were stained with Giemsa for *Helicobacter pylori*. The presence and severity of gastritis were graded according to the revised Sydney classification by a pathologist (16).

Laryngopharyngeal Reflux Evaluation

Patients were screened for the presence of laryngopharyngeal reflux symptoms such as globus, hoarseness, and sore throat. Fiberoptic laryngoscopic (Xion Nasopharyngoscope, Endostrop DX Berlin, Germany) examination was conducted by an otorhinolaryngologist in all patients. Pseudosulcus, ventricular obliteration, erythema/hyperemia, vocal cord edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma,

and thick mucus were assessed according to the reflux finding score (RFS) (17).

Pulmonary Functions Evaluation

Spirometry [forced expiratory volume in the first second (FEV1), forced expiratory vital capacity (FVC), FEV1/FVC, peak expiratory flow (PEF), forced expiratory flow 25–75% (FEF 25–75%)] and early reversibility tests were performed. Spirometry was evaluated according to European Respiratory Society standards. During evaluation of symptoms, asthma patients who were stable under treatment were re-examined with spirometry (PC using Ocean Winspiro Program, Spirolab, MIR—Medical International Research, Rome, Italy).

Statistical Analysis

Descriptive statistics were determined for symptom scores (frequency, mean, and standard deviation), demographic data, pulmonary function test results, and endoscopic and laryngoscopic data. Chi-square tests, Fisher's exact test, independent sample *t*-tests, and the Mann–Whitney *U*-test were used to measure frequency distributions. Logistic regression analysis was used in the evaluation of the EO and NEO patients. Parameters determining the severity of regurgitation and heartburn symptoms (based on the validated Mayo Clinic questionnaire) were assessed with one-way analysis of variance (ANOVA). A statistical significance level of $p = .05$ was used. All statistics were performed with UNISTAT 5.1.

RESULTS

Sixty asthma patients were included in the study, and the male to female ratio was 42:18. The mean age was 39.94 ± 11.55 and the mean body mass index was 26.93 ± 11.55 . None of the patients were current smokers, however, 20.8% had a history of smoking. None of the patients consumed alcohol. According to the GINA classification, 27 of 60 had intermittent asthma (FEV1 and PEF $\geq 80\%$, predicted and variability $<20\%$ – step 1), 4 had mild persistent (nocturnal symptoms, variability 20–30% – step 2), 22 had moderate persistent (daily symptoms, FEV1 and PEF 60–80%, variability $\geq 30\%$ – step 3), and 7 had severe persistent asthma (daily symptoms, FEV1 and PEF $\leq 60\%$, variability $>30\%$ – step 4). The daily PEF variability was around 20%. All of the patients had received asthma medications for longer than 6 months (step 1 patients: short-acting inhaler beta-mimetics; step 2: low-dose inhaler steroids; step 3: average-dose inhaler steroids and long-acting beta-mimetics; step 4: high-dose inhaler steroids, long-acting beta-mimetics, short-acting inhaler beta-mimetics, if needed, and leukotriene antagonists). In addition to clinical data, airway obstruction and reversibility after bronchodilator administration (salbutamol) were measured. Allergies were diagnosed in 60% ($n = 36$) of patients by means of skin-prick testing and the main

allergens were dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) (60%). Non-allergic asthma was found in 40% ($n = 24$).

Pulmonary function test results are summarized in Table 1. There was no significant difference between EO and NEO patients with regards to pulmonary function test parameters ($p > .05$) (Table 1).

Using gastroesophageal endoscopy, EO was found in 25% ($n = 15$) of patients (Figure 1). Endoscopic grading was used to classify esophagitis, with 53.3% being ($n = 8$) grade A, 26.7% ($n = 4$) grade B, and 20% ($n = 3$) grade C. EO could not be identified in 75% ($n = 45$) of the patients and these patients constituted the NEO group.

Histopathological assessment was used to classify the severity of EO with 75% of patients ($n = 9$) having grade 1 EO, 12.5% ($n = 3$) having grade 2, and 12.5% ($n = 3$) having grade 3. Of the 15 patients with EO, 83.3% had mild activated gastritis and 16.7% had moderate activated gastritis according to the Sydney classification (16). All EO patients had concurrent gastritis ($n = 15$, 100%), including 60% ($n = 9$) with pangastritis, 20% ($n = 3$) with antral gastritis, and 20% ($n = 3$) with gastroduodenitis. Forty-three of the NEO patients had concurrent gastritis (95%). About 92.3% ($n = 14$) of EO patients and 91.4% ($n = 42$) of NEO patients were positive for *H. pylori*.

Table 2 summarizes the distribution of symptoms regularly present (daily or several times per week) in EO and NEO patients (Table 2). Patients with EO had significantly higher rates of frequent severe regurgitation (pyrosis) than NEO patients ($p < .05$). Dysphagia, dyspnea frequency, and dyspnea severity were also high in the EO group. The most common laryngopharyngeal reflux symptoms were globus sensation (73.3%), followed by dysphonia (80%) and sore throat (26.7%) in EO patients (Table 2). Similarly, the most common symptoms in NEO patients were globus sensation (51%), dysphonia (59%), and sore throat (8.5%), though these symptoms occurred with less frequency than the EO group. Except for cough, none of the laryngopharyngeal reflux symptoms were higher in NEO patients than EO patients ($p < .001$).

On the basis of RFS, laryngoscopic evaluation revealed posterior commissure hypertrophy to be the most common finding in EO patients, with a prevalence of 66.6% ($n = 9$) (Table 3). Other common findings were erythema and hyperemia 52.3% ($n = 8$), pseudosulcus 14.3% ($n = 2$), vocal cord edema 14.3% ($n = 2$), granuloma 7.1% ($n = 1$), and thick mucus 7.1% ($n = 1$). The most common

finding in NEO patients was also posterior commissure hypertrophy (73.6%, $n = 25$), followed by diffuse laryngeal edema (52.9%, $n = 31$), erythema (44.1%, $n = 31$), and pseudosulcus (32.4%, $n = 12$). The total RFS was 7.27 ± 1.39 in EO patients and 4.51 ± 1.36 in NEO patients ($p < .05$).

DISCUSSION

Although the precise mechanism remains uncertain, there is a strong association between EO and asthma. The potential mechanisms for reflux to affect the respiratory system are aspiration of gastric contents (acid and enzymes such as pepsin) into the airways and aspiration into the lung parenchyma or alveolar tissue causing chronic inflammation. A novel rat model of esophagitis and asthma has demonstrated significant interactions between the two diseases (18–21).

EO was found in 25% of our patients. The average prevalence of EO has been reported to be between 20% and 47% in patients with asthma (4, 6, 9). These rates are higher than healthy control subjects where the prevalence has been found to be 8.5% (18). Gastroesophageal reflux symptoms are observed in 34–89% of asthmatics (4, 6, 20, 21).

Increasingly severe reflux symptoms are related to worsening esophagitis. One of the aims of this study was to determine whether gastroesophageal reflux is severe enough to induce EO and would aggravate laryngopharyngeal reflux symptoms and findings, as determined by laryngoscopy. Although our patients with EO had higher rates of reflux symptoms than NEO patients, only severe regurgitation was significantly different. Therefore, when asthma patients with reflux symptoms specifically present with acid regurgitation, they should be evaluated by means of esophagoscopy to determine the presence or absence of esophagitis.

Another purpose of this study was to determine if there is any difference between asthma patients with EO and NEO with regards to pulmonary function tests. The effects of gastroesophageal reflux on pulmonary function tests have been previously investigated, and no influence was found on spirometry or on bronchial hyperactivity indexes (22, 23). As an extension of the previous data, our results indicate that EO, in which severe gastroesophageal reflux is present, does not influence spirometry because no significant difference was seen in the pulmonary function

TABLE 1.—Spirometry parameters in asthma patients with erosive esophagitis and non-erosive esophagitis (mean $\pm$ SD, %).

Spirometry parameters	EO ($n = 15$)	NEO ($n = 45$)	P
FVC	3.93 ± 1.17 (105.40% $\pm$ 21.91)	3.36 ± 0.79 (98.24% $\pm$ 14.51)	NS
FEV1	3.16 ± 1.15 (99.13% $\pm$ 23.54)	2.79 ± 0.64 (93.99 $\pm$ 17.55)	NS
FEV1/FVC	$79.41\% \pm 10.31$	$82.22\% \pm 11.90$	NS
PEF	6.19 ± 2.06 (79.67% $\pm$ 16.38)	5.22 ± 1.69 (74.85% $\pm$ 18.59)	NS
FEF 25–75%	2.99 ± 1.39 (74.80% $\pm$ 27.76)	2.88 ± 0.91 (79.47% $\pm$ 22.64)	NS

FVC, forced expiratory vital capacity; FEV1, forced expiratory volume in the first second; PEF, peak expiratory flow; FEF 25–75%, forced expiratory flow 25–75%; EO, erosive esophagitis; NEO, non-erosive esophagitis; NS, non-significant ($p > .05$).

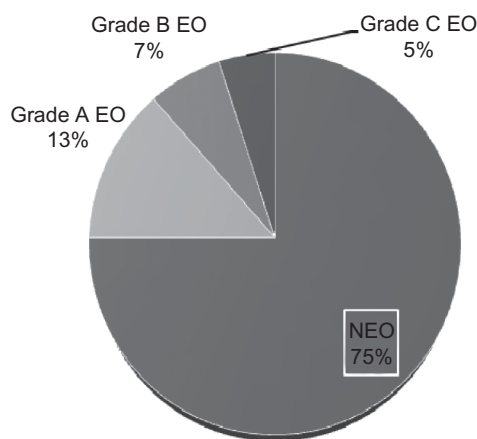


FIGURE 1.—Rates of erosive esophagitis (EO) and non-erosive esophagitis (NEO) in asthma patients as determined by gastroesophageal endoscopy.

tests of EO and NEO patients. Most of our asthma patients were clinically stable when the study was conducted, and this may be a partial explanation for the similarity in pulmonary function test parameters. In contrast to several previous reports and our data, a 12% decrease in PEF has been shown in esophagitis patients via experimental acid perfusion (24).

The established LA classification divides esophagitis into four grades indicating increasing severity; A, B, C, and D. By means of the LA classification, Shimizu et al. have found that grade A esophagitis is present in 28% of asthma patients, followed by grade B in 14%, and grades C and D in 2.6% (9). However, it is widely accepted that

there are a large number of patients who are below grade A and these patients are classified as Grade N and M (9). According to this classification, 25% of our asthmatic patients had EO and the remaining 75% had NEO. We found that 12% of all asthmatics and 53% of asthmatics with EO had grade A esophagitis. Grades B and C were observed in 26.7% and 20% of the patients, respectively. The histopathological assessment was consistent with the endoscopic evaluation, as 75% of the patients with EO had grade 1, 12.5% had grade 2, and the remaining 12.5% had grade 3 histopathologically confirmed esophagitis.

Gastritis was found in 83.3% and 95% of our asthma patients with EO and NEO, respectively, and *H. pylori* was identified in 92.3% of EO asthmatics and 91.4% of NEO asthmatics. Some studies have suggested that colonization with *H. pylori*, particularly CagA strains, may be protective against the more severe forms of GERD, and that the incidence of new GERD-type symptoms or endoscopically confirmed esophagitis was greater in cases where *H. pylori* was eradicated. However, the relationship between GERD and *H. pylori* is complex and remains poorly defined (25–27). *H. pylori* was not negatively associated with esophagitis in other studies. Additionally, the prevalence of *H. pylori* was reported to be more frequent in developing countries than in industrialized countries (28–30).

Posterior commissure hypertrophy has been demonstrated to be the most common finding in laryngopharyngeal reflux disease, rather than the relatively non-specific findings of laryngeal erythema and hyperemia (31, 32).

TABLE 2.—Frequencies of reflux symptoms in asthma patients with erosive and non-erosive esophagitis.

Symptoms	EO (n = 15)	NEO (n = 45)	P
Dyspnea	86.7% (n = 13)	82.2% (n = 37)	NS
Acid regurgitation	86.7% (n = 13)	40% (n = 18)	.02
Dysphonia	80.0% (n = 12)	62.2% (n = 28)	NS
Globus	73.3% (n = 11)	53.3% (n = 24)	NS
Heartburn	46.6% (n = 7)	46.6% (n = 21)	NS
Wheezing	40% (n = 6)	31.1% (n = 14)	NS
Dysphagia	26.7% (n = 4)	6.6% (n = 3)	NS
Sore throat	26.7% (n = 4)	8.8% (n = 4)	NS
Cough	6.7% (n = 2)	20% (n = 9)	<.001

EO, erosive esophagitis; NEO, non-erosive esophagitis; NS, non-significant ($p > .05$).

TABLE 3.—Laryngoscopy findings and reflux finding score (RFS) in asthma patients with erosive esophagitis and non-erosive esophagitis.

Laryngoscopic findings	EO (n = 15)	NEO (n = 45)	P
Posterior commissure hypertrophy	66.6% (n = 9)	73.6% (n = 25)	NS
Diffuse laryngeal edema	52.3% (n = 8)	52.9% (n = 31)	NS
Erythema	52.3% (n = 8)	44.1% (n = 31)	NS
Pseudosulcus	14.3% (n = 2)	32.4% (n = 12)	NS
Thick mucus	7.1% (n = 1)	—	—
Vocal cord edema	14.3% (n = 2)	—	—
Granuloma/granulation	7.1% (n = 1)	—	—
Means of RFS	7.27 ± 1.39	4.51 ± 1.36	<.001

EO, erosive esophagitis; NEO, non-erosive esophagitis; RFS, reflux finding score; NS, non-significant ($p > .05$).

Similarly, posterior commissure hypertrophy was also the most common finding in our patients. RFS is designed to classify the severity of laryngoscopic findings. In laryngopharyngeal reflux patients, RFS is reported to be higher than 7, whereas it is approximately 5.2 in 40 years old healthy individuals (17). In this study, the mean RFS was over 7.27 in EO patients and 4.51 in NEO patients. A diagnosis of laryngopharyngeal reflux in asthma patients using RFS alone may not be objective, as asthma patients routinely use inhaler steroid drugs. These drugs decrease inflammation and may influence laryngoscopic findings. Large-scale studies specifically evaluating the laryngoscopic findings in asthma patients are necessary to further clarify the issue.

In conclusion, we investigated the differences between EO and NEO patients with regards to pulmonary function tests, reflux symptoms, laryngoscopic findings, esophago-gastroduodenoscopic examinations, and histopathologic assessments. The rate of EO was 25% and diagnosis of EO was confirmed histopathologically in all of the cases. The presence of EO seems to be associated with an increase in reflux without affecting pulmonary functions as we found that EO did not cause a significant decrease in pulmonary function test results. Gastroesophageal and laryngopharyngeal reflux symptoms were more frequent in EO patients than NEO patients. The laryngoscopic findings in patients with laryngopharyngeal reflux were more severe and the RFS was significantly higher in EO patients than NEO patients.

DECLARATION OF INTEREST

None of the authors have any conflicts of interest.

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