The Prevalence of Gastroesophageal Reflux Disease in Adult Asthmatics

Toni O. Kiljander, MD, PhD; and Jukka O. Laitinen, MD, PhD

Background: Asthma and gastroesophageal reflux disease (GERD) often coexist. However, the results of the studies investigating the prevalence of GERD among patients with asthma vary greatly.

Study objective: To investigate the prevalence of GERD in adult patients with asthma.

Subjects and methods: The basic study population consisted of 2,225 asthmatic patients who were treated in six specialist-headed hospitals during 1 year. From the common computer-based discharge register, every 14th patient was randomly selected for the study. Ninety of the 149 contacted patients (60%) agreed to participate in the study. Twenty-four-hour esophageal pH monitoring was performed on all patients.

Results: GERD was found in 32 of the patients (36%). Eight of these patients (25%) were free from classical reflux symptoms. Forty-seven of the 90 patients (52%) presented with typical reflux symptoms. Twenty-four of these patients (51%) were found to have abnormal acidic reflux.

Conclusions: According to the current study, one third of adult patients with asthma have GERD. These patients often do not have typical reflux symptoms. However, the presence of typical reflux symptoms in an asthmatic patient does not seem to guarantee the presence of abnormal acidic reflux.

Key words: asthma; gastroesophageal reflux disease; prevalence

Abbreviations: ATS = American Thoracic Society; GERD = gastroesophageal reflux disease; LES = lower esophageal sphincter

Gastroesophageal reflux disease (GERD) is a common disorder, with almost 20% of the US population suffering from its classical symptoms at least weekly.1 Using daily heartburn and/or regurgitation as indicators, it has been estimated that up to 10% of Finns may have GERD.2 In adult patients with asthma, GERD appears to be even more common,3,4 and can be present without any classical reflux symptoms in these patients.5 GERD is a potential trigger for asthma.6 However, airway obstruction and some asthma medications may induce esophageal reflux.7–10 The results of the studies investigating the prevalence of GERD among asthmatics vary greatly. The studies11–14 using 24-h esophageal pH monitoring report GERD prevalences ranging from 32 to 82%, and sometimes even higher prevalences have been reported.15 The aim of this study was to investigate the prevalence of GERD among adult patients with asthma.

Materials and Methods

Patients

The basic study population consisted of all adult patients examined because of asthma in the following specialist-headed (respiratory or internal medicine) hospitals: Tampere University Hospital; Regional Hospitals of Mänttä, Valkeakoski, and Vammala; and the City Hospitals of Nokia and Tampere during 1990. The establishment of the study group was based on a common computer-based discharge register. Altogether, 2,225 patients with asthma attended the outpatient clinics or were treated on the wards of the study hospitals during that year. A random sample of 158 asthmatics was formed by arranging the patients in ascending order according to date of birth and social security number, and selecting every 14th patient for the sample. From further investigation were excluded two patients whose asthma diagnosis was not made according to American Thoracic Society (ATS) criteria, three patients because of an erroneous personal code in the register, and four patients because of death. Ninety of the remaining 149 patients (60%) agreed to participate. Demographic data of the patients are shown in Table 1.

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Table 1—Demographic Data of the 90 Patients Participating in the Study*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>54.3 ± 16.0</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.7 ± 5.2</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>41 (46)/49 (54)</td>
</tr>
<tr>
<td>Smokers</td>
<td>18 (20)</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>2.2 ± 1.1</td>
</tr>
<tr>
<td>FEV$_1$, % of predicted</td>
<td>66.7 ± 22.5</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.1 ± 1.3</td>
</tr>
<tr>
<td>Asthma medication</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroid</td>
<td>63 (70)</td>
</tr>
<tr>
<td>Oral corticosteroid</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Inhaled sympathomimetic</td>
<td>81 (90)</td>
</tr>
<tr>
<td>Oral sympathomimetic</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Inhaled anticholinergic</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Theophylline</td>
<td>21 (23)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) or mean ± SD.

Study Design

After establishment of the study population, the medical records of the patients were reviewed in order to ensure that the diagnosis of asthma was made according to the ATS guidelines. The patients were first informed about the study by mail, and were then contacted by telephone and asked to participate in the study. A 24-h esophageal pH monitoring was performed on all patients participating in the study. During the pH monitoring, patients filled in a demographic questionnaire including questions about their pulmonary and gastric symptoms. Among the other questions, patients were asked: “do you have heartburn at least once a week” and “do you have regurgitation at least once a week?” Patients were considered to be free of typical GERD symptoms if they reported heartburn and/or regurgitation less than weekly. Pulmonary function tests were done during the same visit when the pH monitoring was completed. All study-related interventions were done during the years 1992 and 1993.

The definition for GERD is not unambiguous. For the current study, GERD was defined as abnormally high acid exposure time in the distal esophagus during 24-h esophageal pH monitoring. The study was approved by the Ethics Committee of the Tampere University Hospital, and every patient gave written informed consent.

Twenty-Four-Hour Esophageal pH Monitoring

After an overnight fast, the lower esophageal sphincter (LES) was located by manometry using a solid-state pressure transducer (Sentron 92–3001; Sentron Europe BV; Roden, Netherlands) connected to the LES identifier (Synectics Medical; Stockholm, Sweden). Esophageal pH recordings were made using dual monocrystalline antimony pH catheters with 15 cm spacing the two pH electrodes (Synectics Medical), which were calibrated in buffer solutions of pH 1.0 and 7.0 before and at completion of each procedure. The pH catheter was passed transnasally into the esophagus, and the distal pH electrode was positioned 5 cm above the previously manometrically determined LES. An external reference electrode was attached to the skin of the chest wall. Esophageal pH was monitored 5 cm and 20 cm above the LES, and stored at 4-s intervals in a portable recorder (Digitrapper Mk II Gold; Synectics Medical). After the recording, the data were downloaded into a computer using appropriate analysis software (Esophagram 5.90; Gastrosoft; Irving, TX). Esophageal pH monitoring results were considered to be abnormal if total time pH < 4 in the distal esophagus was > 5.4%. During the pH monitoring, patients carried out their daily routines. All of the patients had been asked to stop possible histamine type-2 blocker or proton-pump inhibitor therapy for at least 1 week, and possible antacid therapy for at least 3 days before the pH monitoring.

Pulmonary Function Tests

Flow-volume spirometry (Medikro 101; Medikro; Kuopio, Finland) was performed on all patients, and at least two repeatable flow-volume curves were recorded. Finnish reference values were utilized. A methacholine bronchial challenge was then performed on all patients whose FEV$_1$ was > 45% of predicted. During the challenge, methacholine chloride was nebulized in five cumulative doses of 18, 72, 270, 810, and 2,600 µg, and spirometry was repeated after each dose. The challenge was stopped when FEV$_1$ fell ≥ 20% compared to baseline, or when 2,600 µg of methacholine had been administered. A patient was considered to have bronchial hyperresponsiveness if his/her FEV$_1$ decreased ≥ 20% during the challenge. Prior to the pulmonary function tests, the patients were not allowed to use inhaled sympathomimetics for at least 8 h. Oral sympathomimetics and inhaled anticholinergics were withheld for at least 12 h, and theophylline was withheld for 48 h before pulmonary function tests.

Statistical Analysis

Descriptive analysis was used unless otherwise noted; p < 0.05 was interpreted as statistically significant.

Results

Fifty-nine subjects (40%) in the original sample refused to participate in the study. The only difference between the study group and those refusing was that the nonparticipants were younger than study subjects (p = 0.01 with χ² test). Of the 90 patients participating in the study, 75 patients had FEV$_1$ > 45% of predicted and were thus challenged with methacholine. Bronchial hyperresponsiveness was found in 52 of these patients (69%).

Mean duration of the pH monitoring was 22.1 h (range, 19.5 to 23.5 h). Abnormal acidic reflux into the distal esophagus was documented in 32 of the patients (36%). Eight of these patients (25%) were free from typical GERD symptoms. As to demographic data, the patients with abnormal acidic reflux (n = 32) did not differ from those without (n = 58). Due to the small number of patients, the symptomatic (n = 24) and nonsymptomatic (n = 8) patients with GERD were not compared statistically. Detailed results of the pH monitoring are shown in Table 2. Forty-seven of the patients (52%) presented with typical GERD symptoms. Twenty-four of these patients (51%) were found to have GERD in the pH monitoring.

The association between FEV$_1$ (percentage of predicted) and pH parameters was assessed with the
GERD in patients with asthma appears not to be as high as reported by some previous studies.\textsuperscript{12,14,15} However, the prevalence of GERD was reported in patients with asthma. However, the prevalence of GERD in patients with asthma appears not to be as high as reported by some previous studies. In a previous study\textsuperscript{14} by our group, 24-h esophageal pH monitoring was performed on 107 patients with asthma, and GERD was found in 53% of the patients investigated. However, since we were not able to investigate consecutive patients, it is possible that the result is biased. After excluding patients who were referred because of typical GERD symptoms, Sontag et al\textsuperscript{12} performed 24-h esophageal pH monitoring on 104 consecutive asthmatic patients. GERD was found in 82% of the patients. Unfortunately, they did not report how many patients refused and how many patients had to be excluded. Although selection bias was attempted to be avoided in that study,\textsuperscript{12} it is highly possible that the result may be upwardly biased. In addition to possible selection bias, the high GERD prevalence found in that study might also partly be due to the fact that Sontag et al\textsuperscript{12} defined abnormal reflux separately for upright and supine positions, not for total esophageal acid exposure time as the other studies\textsuperscript{11,13,14} did. More recently, Avidan et al\textsuperscript{20} performed ambulatory esophageal pH monitoring on 128 consecutive asthmatic patients. Unfortunately, that study\textsuperscript{20} was focused only on the temporal association between reflux episodes and pulmonary symptoms, and no GERD prevalence was reported.

Nagel et al\textsuperscript{11} performed esophageal pH monitoring on 44 patients with asthma, of whom 15 patients (34%) were found to have GERD. Vincent et al\textsuperscript{13} investigated 105 consecutive asthmatic patients with ambulatory esophageal pH monitoring. In their study,\textsuperscript{13} the prevalence of GERD was found to be 32%. In accordance with these two studies\textsuperscript{11,13} the current study, using a random sample of asthmatics, found GERD in one third of the patients. It is of interest that a great number of the patients who were found to have GERD were free from typical reflux symptoms. This is substantiated by other studies.\textsuperscript{5,13,14} For example, Harding et al\textsuperscript{5} performed 24-h esophageal pH monitoring on 26 patients with stable asthma without typical reflux symptoms. In that study,\textsuperscript{5} abnormal esophageal acid reflux was found in 62% of the patients. In the present study, or in the study by Harding et al,\textsuperscript{5} no endoscopies were performed, and one could therefore speculate that perhaps the presence of esophagitis might be important for the presence of classical reflux symptoms. However, there appears to be only a poor correlation between esophagitis and classical reflux symptoms.\textsuperscript{21}

The authors accept that there are some limitations. Pearson correlation coefficient. No significant correlation between FEV\textsubscript{1} and pH parameters in the distal esophagus could be detected. Neither was there a significant association between FEV\textsubscript{1} and pH parameters in the proximal esophagus, except a weak association between FEV\textsubscript{1} and the number of reflux episodes \((r = 0.29, p < 0.05)\), and time pH < 4 in upright position \((r = 0.27, p < 0.05)\).

\textbf{Discussion}

This study revealed two important findings. Firstly, there is a high prevalence of GERD among patients with asthma. However, the prevalence of GERD in patients with asthma appears not to be as high as reported by some previous studies.\textsuperscript{12,14,15} Secondly, substantial acidic reflux can be present in patients with asthma without typical reflux symptoms. However, the presence of classical reflux symptoms in an asthmatic patient does not seem to guarantee the presence of pathologic acidic esophageal reflux.

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in the current study. Firstly, GERD was defined as pH < 4 in the distal esophagus > 5.4% of the total registration time. Most of the studies mentioned above used the reference values described by Johnson and DeMeester,\textsuperscript{22} using a 4.2% cutoff point to determine abnormal esophageal acid exposure time. However, other reference values use a 5.8% cutoff point to determine abnormal esophageal acid exposure,\textsuperscript{23} and for example the study by Harding et al\textsuperscript{5} used these reference values. In general, there are several different reference values for 24-h esophageal pH monitoring, and these differ only slightly.\textsuperscript{22–24} Thus, using our definition for GERD is not believed to be a major source of error in the present study. Secondly, 40% of the original study population refused to participate in the study. Thus, although using a random sample of asthmatic patients, the possibility of selection bias is present also in the current study. However, 60% of the patients participated, which can be interpreted as an excellent result when such a semi-invasive technique as 24-h esophageal pH monitoring is used. Moreover, those participating in the study and those refusing were not found to differ, except for the age. Thirdly, prior to the pulmonary function tests, and at the same time prior to the pH monitoring, a washout period in certain antiasthmatic drugs was held, and this prevented us to investigate the possible effects of these drugs on esophageal acid contact times. Finally, almost one third of the patients challenged with methacholine did not present with bronchial hyperresponsiveness. This might get one to question whether these patients actually had asthma. However, it must be kept in mind that 70% of the patients were receiving inhaled, and 6% were using oral corticosteroids, which are known to reduce bronchial responsiveness.\textsuperscript{25} Moreover, the medical records of the patients were reviewed in order to ensure that the diagnosis of asthma was made according to the ATS criteria.\textsuperscript{16} It has been suggested that airway obstruction may increase the negative pleural pressure, thereby increasing the pressure gradient across the diaphragm favoring gastroesophageal reflux, and that air trapping leads to flattening of the diaphragm and possibly weakens the antireflux barrier.\textsuperscript{26} Therefore, one could have expected to see a negative correlation between the severity of GERD and pulmonary function in the current study. We found no such correlation. On the contrary, there was a weak positive association between FEV\textsubscript{1} and two pH variables in the proximal esophagus. However, because these associations were very weak, and no other correlations could be found, they are concluded to be due to coincidence. The lack of correlation between asthma severity and the severity of GERD in our study may be due to the fact that the pathophysiology of GERD is very complex, and several other factors than transdiaphragmatic pressure influence the esophageal reflux. Nevertheless, on the basis of the previous studies, it is apparent that increased airway obstruction increases gastroesophageal reflux in asthmatics.\textsuperscript{7} The role of nonacidic reflux in the pathogenesis of reflux-associated respiratory conditions is yet to be solved. Combined multichannel intraluminal impedance and pH measurement is a promising new technique that hopefully will clarify this issue in the future.\textsuperscript{27} However, possible nonacidic reflux might, at least partly, explain why in the current study only 51% of the patients who presented with classical reflux symptoms were found to have GERD in the esophageal pH monitoring. Other explanations might include possible alterations in normal eating and activity patterns during the pH monitoring, and possible day-to-day variation of reflux.

It is well documented that airway obstruction and some medicines commonly used for asthma treatment can induce esophageal reflux.\textsuperscript{7–10} There is also evidence that in asthmatic patients with GERD, more severe reflux disease predicts favorable asthma outcome after acid suppressive therapy.\textsuperscript{25,29} This tempts one to speculate that mild GERD often found in asthmatic patients could be caused by asthma medication or by asthma itself, whereas only more severe GERD is capable of aggravating asthma. The above hypothesis explains the high prevalence of GERD found in asthmatic patients, but could also explain the inconsistent results of the intervention studies.\textsuperscript{4,26,30,31} Namely, patients with relatively mild GERD (which could be caused by asthma rather than be a trigger for asthma) have also been included in most of the treatment studies.\textsuperscript{14,28,32–35}

To conclude, according to the current data, one third of adult asthmatic patients have GERD. These patients do not often have typical reflux symptoms such as heartburn or regurgitation. However, the presence of typical reflux symptoms in an asthmatic patient does not seem to guarantee the presence of pathologic acidic esophageal reflux.

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