Prevalence of Gastroesophageal Reflux Symptoms in Asthma*

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Study objective: To determine the prevalences of symptomatic gastroesophageal reflux (GER), reflux-associated respiratory symptoms (RARS), and reflux-associated β-agonist inhaler use in asthmatics.

Design: Questionnaire-based, cross-sectional analytic survey.

Setting: Outpatient asthma and clinical research clinics attached to the University of Calgary tertiary care centre and two family practices.

Patients: Asthma group consisted of 109 patients referred to an outpatient asthma clinic. First control group consisted of 68 patients visiting their family physicians. Second control group consisted of 67 patients with thyroid disease, hypercholesterolemia, or diabetes participating in drug trials.

Results: Among the asthmatics, 77%, 55%, and 24% experienced heartburn, regurgitation, and swallowing difficulties, respectively. Symptoms were less prevalent in the control groups. At least one antireflux medication was required by 37% of asthmatics (p<0.001, vs controls). None of the asthma medications were associated with an increased likelihood of symptomatic GER. In the week prior to completing the questionnaire, 41% of the asthmatics noted RARS, including cough, dyspnea, and wheeze and 28% used their inhalers while experiencing GER symptoms. Inhaler use correlated with the severity of heartburn (r=0.28, p<0.05) and regurgitation (r=0.40, p<0.05)

Conclusions: The questionnaire demonstrated a greater prevalence of GER symptoms, RARS, and reflux-associated inhaler use in asthmatics. This excessive inhaler use may explain how GER indirectly causes asthma to worsen. (CHEST 1996;109:316-22)

BMI=body mass index; GER=gastroesophageal reflux; NS=not significant; PEFR=peak expiratory flow rate; RARS=reflux-associated respiratory symptoms

Key words: asthma morbidity and mortality; β-agonist; bronchial hyperreactivity; bronchodilator; cough; dyspnea; esophagitis; gastroesophageal reflux; heartburn; regurgitation

The association between gastroesophageal reflux (GER) and asthma has been reported repeatedly over the last 30 years.1,6 The reasons for the strong association are not fully understood. Studies from the 1960s and 1970s of patients referred for evaluation and treatment of hiatal hernia and GER indicated that respiratory symptoms, including asthma, were prevalent in this population and improved after successful esophageal surgery.1–4 At that time, the diagnosis of GER was confirmed by GI contrast radiographs and fluoroscopy. More recently, ambulatory pH monitoring has proved to be more sensitive and specific and has become the diagnostic standard for GER.7 It can demonstrate abnormal GER even in asymptomatic patients.8 A recent ambulatory pH monitoring study of asthma patients demonstrated that more than 80% have abnormal GER.9 However, the prevalence of symptomatic GER in asthma is unknown.

Ekstrom and coworkers10 reported the results of antireflux therapy in 50 patients with symptomatic reflux selected from 350 moderate to severe asthmatics. However, it is not clear whether these were the only patients with reflux symptoms. If so, it would suggest that approximately 15% of asthmatics experience symptomatic reflux. Approximately half of the 50 patients with symptomatic reflux had reflux-associated respiratory symptoms (RARS).

Recently, Sontag and coworkers11 reported that 40% of asthmatics have endoscopic evidence of erosive esophagitis; therefore, it would be expected that the prevalence of reflux symptoms would be greater than that reported by Ekstrom et al.10

The purpose of the present study was to estimate the prevalence and severity of GER symptoms in the population of asthma patients attending our clinic, determine the association of asthma medication use with symptomatic GER, the prevalence of RARS, and the association of GER symptoms with increased bronchodilator use.

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**ASTHMA AND GER QUESTIONNAIRE**

**LAST NAME: ___________________ FIRST NAME: ___________________ DATE: __/__/____
DOB: __/__/____ GENDER:  1. MALE  2. FEMALE
PHONE: HOME # ___________________ BUS # ___________________

MEDICATION: CHECK off all medications taken and put a check(✓) under yes, no. ?(tumor) as to whether or not medication improves asthma symptoms:

1. ASHMA
   1. NO 2. YES 3.7
   2. OTHOPHYMNE
   3. CROMOLYN/TILADE
   4. NHALED
   5. INHALED STEROID
   6. ORAL STEROID
   7. CONCERTA/PLAZA
   8. PENICILLAMINE

1. Have you been diagnosed as having asthma?  1. No  2. Yes
2. If yes, look at the BLUE CARD and check the number which best describes your asthma symptoms this past week:  0  1  2  3

Check the number that best describes your symptoms (use GREY CARD):

1. after drinking coffee?  0  1  2  3
2. after drinking alcohol?  0  1  2  3
3. after eating a large meal?  0  1  2  3
4. lying down < 2 hours after eating?  0  1  2  3

2. Have you ever experienced any symptoms of heartburn ("burning sensation, pain and discomfort in the chest after meals or when lying down")?
   1. No (SKIP TO QUEST#3)  2. Yes (IF yes, last episode __/__/____)
   Answer the following questions only if you experienced heartburn symptoms in this past week:
   - Based on the RED CARD, choose the number that best describes your symptoms:
   - Total number of episodes of heartburn: daytime ______ nightime ______
   - Duration of worst episode: daytime ______ mins. nightime ______ mins.
   - Severity of worst episode: (SEE BLUE CARD)

Check the number that best describes your symptoms (GREY CARD):

1. How much alcohol consumed ______ per day, week, month (circle one)
2. Have you any difficulties swallowing?  1. No  2. Yes

**FIGURE 1. Asthma and GER questionnaire.**

**MATERIALS AND METHODS**

**Patient Selection**

Asthma Patients: Consecutive patients, both newly referred and follow-up, attending the Calgary Asthma Clinic over a 10-week period were surveyed. All patients who fulfilled the following criteria for the definition of asthma were included in the study. Patients had at least one of the following: an increase in FEV1 of at least 15% after bronchodilator, spontaneous variability of peak expiratory flow rates (PEFR) or FEV1 of 20% or more, or a positive histamine challenge test and a clinical picture consistent with the diagnosis of asthma.

Control Groups: Two control groups were also surveyed. The first included patients attending a family practice and the people accompanying them. The second included subjects with diabetes mellitus or hypercholesterolemia involved in clinical drug trials and patients with thyroid disease.

Control subjects were between the ages of 15 and 75 years, not pregnant, and not asthmatic. Prior to being surveyed, they were asked whether they would be willing to participate in a research study but were not told of its purpose. They were surveyed by a research nurse with the same questionnaire and response categories as were the asthma patients.

**Protocol**

Prior to seeing a physician, the patients were questioned by one of the asthma clinic nurses. Their medication use and inhaler technique were assessed and the patients were questioned to allow the nurse to assess their understanding of asthma. Spirometry and maximal expiratory flow volume loops were then performed before and after bronchodilator. Predicted values for FVC, FEV1, and PEFR were derived from the data of Crapo et al. Predicted values for PEFR were taken from the data of Knudson et al. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

The patients were surveyed about their reflux symptoms. A nurse clinician administered a questionnaire in which specific questions and response categories were provided. The use of the questionnaire was approved by the institutional ethics committee.

**Questionnaire**

The questionnaire (Fig 1) was designed to assess the severity of asthma symptoms, the severity of GER symptoms, both heartburn and regurgitation, and determine whether asthma symptoms worsened or whether patients required their β-agonist inhaled during periods of symptomatic reflux. They were also surveyed about asthma and reflux medication use, and whether their asthma worsened in situations that would favor reflux such as eating a large meal, lying down after eating, or drinking alcohol or coffee.

The asthma patients were asked to estimate the severity of their asthma symptoms. Asthma severity was graded using the blue response card (Table 1).

All subjects were questioned to determine whether they suffered from heartburn. Heartburn was described to them as a burning sensation, pain and discomfort in the chest after meals or when lying down.
sensation or pain and discomfort in the chest after meals or when lying down. If present, patients were asked to grade its severity, both during the day and night. Severity was graded using the green response card (Table 1).

They were asked whether their cough worsened or whether their shortness of breath, wheeze, or inhaler use increased during periods of heartburn, either during the day or night. They were also asked how often they had heartburn-associated respiratory symptoms. The response choices were never, occasionally, usually, or always.

Questions regarding regurgitation were then posed. It was described as return of stomach contents or acid to the mouth or choking. Patients were questioned about its severity both during the day and night grading it with the red response card (Table 1). They were also asked whether they experienced an increase or worsening of their cough, shortness of breath, wheeze, or inhaler use either during the day or night with regurgitation. The scoring options were never, occasionally, usually, or always.

Current asthma medication use was recorded. Patients were specifically asked whether they were taking a theophylline preparation, B-agonists, ipratropium bromide, inhaled or oral corticosteroids, Cromolyn, nedocromil, or ketotifen. Antireflux medications specifically asked about included antacids, Histamine-H2-receptor antagonists, omeprazole, prokinetic agents, and cytoprotective agents.

They were asked whether their asthma worsened after consuming coffee, alcohol, a large meal, or with recumbency within 2 h after eating. The response choices were never, occasionally, usually, or always.

Subjects were surveyed about their smoking and alcohol habits. Alcohol consumption was measured in ounces of alcohol. One ounce of spirits, 4 oz of wine, or 10 oz of beer (5% alcohol) were assumed to be equivalent to 1 oz of alcohol. Subjects were also asked whether they had any difficulty swallowing.

Statistical Analysis

Descriptive measures for quantitative variables are reported as mean±SD. Associations between binary variables were tested using Fisher's Exact Test. Spearman's rank correlation was used to assess association between ordinal variables. Symptom prevalence between asthma and control groups was compared using Pearson's χ2 test.

RESULTS

One hundred nine of 163 consecutive patients seen in the asthma clinic satisfied the criteria for the diagnosis of asthma (see Materials and Methods section) and comprise the asthma group. Their clinical data and those of the two control groups are presented in Table 2. The mean age, BMI, and gender ratios of the asthma group were similar to those of the control groups. Among the subjects in each group, the mean age, BMI, and gender proportions were similar in the subjects with and without symptomatic GER. Spirometric values of the asthma patients with and without GER were similar; (FEV1/FVC [%]: GER, 64.8±11.3 vs non-GER, 67±13.6, not significant [NS]). The proportions of smokers and former smokers and alcohol consumption were similar in the asthma and control groups (Table 2).

Prevalence of GER Symptoms

The prevalences of heartburn, regurgitation, and swallowing difficulties are shown in Figure 2. The prevalences of heartburn in the previous week, 3 weeks, 6 weeks, and ever were greater in the asthma patients.
patients than in the control groups. The prevalences of regurgitation in the previous week, 3 weeks, and 6 weeks were greater in the asthma patients than in the controls. Asthma patients had a greater prevalence of swallowing difficulties than the control subjects.

**Severity of Symptomatic GER**

The severity of heartburn and regurgitation experienced over the week prior to answering the questionnaire by the asthma patients and control subjects are shown in Figure 3.

A total of 41 asthma patients required at least one medication for their GER symptoms. Thirty-four (32.1%) took antacids with or without other medications. Only 8.2% of the control subjects used antacids (p<0.001). Antireflux medication use is shown in Figure 4.

**Asthma Severity**

Mild, moderate, and severe were each chosen by approximately one third of the patients to best describe their asthma symptoms in the previous week. Asthma symptom severity did not correlate with severity of either heartburn or regurgitation.

**Effect of Eating, Recumbency, Alcohol, and Coffee Consumption**

The percentages of asthma patients reporting breathing discomfort after eating (asthma 39.3% vs control 6.7%; p<0.001), regurgency (asthma 21.2% vs control 2.2%; p<0.001), and alcohol consumption (asthma 41.3% vs control 3.7%; p<0.001) were greater than controls. The prevalence of respiratory symptoms with coffee consumption was similar in the asthma patients and control subjects (asthma 7.6% vs control 2.5%; NS).

**Reflux-Associated Respiratory Symptoms**

A total of 45 asthma patients complained of RARS. Among the 49 asthma patients with at least one episode of heartburn in the previous week, 20, 22, and 18 complained of cough, dysnea, and/or wheeze, respectively. Cough, dysnea, and/or wheeze were noted by 18, 20, and 17 of the 23 asthma patients with regurgitation in the previous week.

**GER-Associated Inhaler Use**

Thirty-one asthmatics used their β-agonist inhalers when they experienced reflux symptoms. There were weak, although statistically significant, correlations between the frequency of additional β-agonist use and the severity of both heartburn (r=0.28, p<0.05) and regurgitation (r=0.40, p<0.05). None of the controls used asthma medication.

**Routine Asthma Medication Use**

Most of the asthma patients used β-agonists (93%)
and inhaled corticosteroids (84%). Oral corticosteroids and theophylline were each taken by approximately one third of the asthmatics. None of the asthma medications were associated with an increased likelihood of having heartburn or regurgitation.

**Discussion**

The most important findings of this study are that symptomatic GER is common and that it is associated with respiratory symptoms and β-agonist inhaler use in asthmatics. The questionnaire determined a greater prevalence of reflux symptoms in asthmatics than in two control groups of similar age, gender ratio, BMI, alcohol habits, and tobacco habits.

A recent ambulatory pH monitoring study done in an American Veteran's Administration hospital dem-

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21727/ on 06/26/2017)
demonstrated abnormal GER in more than 80% of asthmatics. Their population was virtually all male with an average age of 53 years. Most of our patients were female and were 10 years younger, yet as a group had a similar prevalence of GER symptoms. Moreover, only a minority of our subjects smoked cigarettes or drank alcohol on a regular basis.

Does Asthma Cause GER?

There is little controversy about the association between GER and asthma, but the exact nature of the relationship is unclear. Moote and coworkers demonstrated an increase in GER during methacholine-induced bronchospasm in patients with mild asthma. Cough and the greater respiratory muscle effort that accompany asthma increase abdominal pressure, facilitating the movement of gastric secretions past the lower esophageal sphincter. Moreover, diaphragmatic contractions contribute to the development of lower esophageal sphincter pressure. Hyperinflation develops with bronchoconstriction changing the relationship between the diaphragm and lower esophageal sphincter, possibly decreasing the diaphragm’s contribution to sphincter tone. In the present study, asthma patients had a higher prevalence of GER symptoms and greater need for antireflux medication than two otherwise similar control groups.

Both β-agonists and theophylline reduce lower esophageal sphincter pressure in animals and humans. However, studies to determine whether they increase GER have not shown a clinically significant effect. The proportions of asthmatics, with and without GER symptoms, taking β-agonists, theophylline, ipratropium, and oral and inhaled corticosteroids, were similar suggesting that asthma medication is not an important determinant of GER symptoms.

Does GER Make Asthma Worse?

The high asthma prevalence in patients with GER and the beneficial effect of successful esophageal surgery on asthma has been reported repeatedly. However, the results of controlled studies designed to demonstrate that GER triggers asthma have been conflicting. Acid perfusion of the esophagus caused small but statistically significant increases in airway resistance in dogs and cats. Conservative therapy improved asthma symptoms and reduced bronchodilator requirements but did not improve results of spirometry. In asthmatics with GER, cimetidine improved both GER and asthma symptoms and was associated with a slight but statistically significant increase in PEFR. Ranitidine improved respiratory symptoms and decreased bronchodilator use in asthmatics with RARS. However, other studies have not been able to demonstrate a deterioration in lung function during episodes of GER or with acid perfusion of the esophagus.

The reasons for the conflicting findings in the literature are unclear, but there are a number of possible explanations. The most obvious is that only a minority of asthmatics are sensitive to GER. Asthmatics are a heterogeneous group with respect to their responses to different triggers. Asthma patients have different sensitivities to a variety of stimuli such as allergens, exercise, cold air, respiratory tract infections, air pollution, and cigarette smoke. It is not surprising that some patients with GER note an association between their GER and respiratory symptoms whereas others do not.

Inadequate acid suppression may also explain the lack of response of asthma to antireflux therapy in some patients. Harding et al reported that 30% of their patients did not obtain sufficient acid suppression with the standard dose of 20 mg of omeprazole per day. Previous studies of the effects of antacids and H₂-receptor blockers on patients with asthma and GER have not included ambulatory pH monitoring to ensure that acid production had been adequately suppressed. The apparent lack of response may have been due to persistent acid reflux despite therapy.

While GER might increase asthma symptoms, studies that have monitored esophageal pH and PEFR found no association between them. The design of these studies did not allow for the possibility that GER might serve as a trigger in only a minority of patients. Rauscher and coworkers reported that 40% of asthmatics experienced declines in PEFR during periods of reflux, but no association was apparent when the whole group was included in the analysis.

Patients were asked whether their asthma worsened in a number of situations that have been reported to worsen GER. Alcohol ingestion, large meals, and recumbency caused asthma to worsen in 41%, 39%, and 21% of asthmatics, respectively. Only 7.6% experienced a worsening of asthma with coffee consumption. This may be due to its bronchodilating effect antagonizing any adverse effect due to a worsening of GER.

Adverse Effect of GER-Related Inhaler Use

Forty-five (41%) asthmatics noted an association between reflux and respiratory symptoms. Thirty-one (28%) reported the need to use inhalers during symptomatic reflux. Ekstrom et al showed that ranitidine caused a modest improvement in asthma symptoms and a reduction in inhaler use but did not change PEFR in asthmatics with RARS. This suggests that some of the inhaler use in patients with GER and asthma may be related to RARS occurring in the absence of bronchospasm. This pattern of inhaler use does not help asthma control, and could worsen reflux which in turn could lead to further inhaler use. This increased β-agonist use could in turn adversely affect
long-term asthma control.\(^{31}\)

Several studies over the last 5 years have suggested that increased \(\beta\)-agonist use may have a detrimental effect on asthma. Regular use of inhaled \(\beta\)-agonists contributes to bronchial hyperreactivity\(^{32,33}\) and may cause a worsening of asthma control and increased mortality.\(^{34-36}\) Despite a lack of clear evidence that GER causes asthma worsening in the short term, some asthmatics may experience a deterioration in lung function related to their excessive use of \(\beta\)-agonist during periods of GER.\(^{36}\) Even in the absence of a direct effect of GER on bronchial reactivity, effective control of GER symptoms may be important for optimal asthma management.

In summary, the questionnaire demonstrated a greater prevalence of GER symptoms in asthma patients than in two control groups. GER and reflux-associated respiratory symptoms are common in asthma. Moreover, GER symptoms are associated with increased \(\beta\)-agonist inhaler use in asthmatics.

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