Endoscopic prevalence of different grades of gastroesophageal reflux in adult asthmatics with or without reflux symptoms

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Background Gastroesophageal reflux and asthma often coexist in the same patient. Persons with asthma are particularly prone to asymptomatic gastroesophageal reflux disease (GERD). Esophageal pH-probe studies have documented that 32–84% of the asthmatics have abnormal acid reflux. The endoscopic assessment of esophageal mucosal changes in patients with reflux symptoms is important to diagnose patients with various degrees of severity.

Aim of the study The aim of the study was to detect the prevalence of different grades of GERD in adult asthmatics with or without GERD symptoms by using upper gastrointestinal endoscopy.

Patients and methods This study included 50 adult patients with different levels of asthma control according to the Asthma Control Test scoring system. Patients were classified into two groups (symptomatic and less symptomatic) according to the GERD questionnaire. All patients were blindly subjected to upper gastrointestinal endoscopy. Endoscopic grading was carried out using the Los Angeles grading system for GERD.

Results GERD was endoscopically detected in 36 patients out of 50 (72%); most of them presented with grade B gastroesophageal reflux (28%). No significant difference was observed in GERD prevalence related to the level of asthma control (P=0.98). No significant difference was observed in endoscopic GERD prevalence between symptomatic and less symptomatic groups (P=0.53).

Conclusion GERD with variable grades is prevalent endoscopically among adult asthmatics at all levels of asthma control with no difference between symptomatic and less symptomatic groups.

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Introduction

Asthma has been defined as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation [1].

Gastroesophageal reflux disease (GERD) is commonly seen at gastroenterology outpatient clinics as well as ear, nose and throat, and allergy and asthma clinics. The reflux of acid and pepsin may affect the respiratory tract and cause respiratory problems such as asthma, pneumonia, and interstitial fibrosis. Chronic cough, chronic laryngitis, and asthma are significantly associated with GERD [2].

Gastroesophageal reflux and asthma, both common conditions, often coexist in the same patient. Persons with asthma are particularly prone to asymptomatic GERD. Esophageal pH-probe studies have documented that 32–84% of the asthmatics have abnormal acid reflux [3–5].

It has been suggested that acid reflux has a negative impact on asthma control and asthma symptoms, and in particular on nocturnal symptoms [5]. Accordingly, evaluation and treatment of GERD in patients with difficult-to-control asthma is recommended regardless of the presence of GERD symptoms [6].

The extent to which GERD plays an important role in causing or maintaining asthma symptoms is not known. Symptoms of asthma – cough and chest discomfort – may overlap those of GERD, making it difficult to distinguish between the two conditions [7]. Moreover, the causal relationship between asthma and GERD is complex. Acid reflux causes bronchoconstriction by microaspiration into the airways as well as by reflex-mediated effects of acid on the esophagus or the upper airway [8,9]. Alternatively, asthmatic bronchoconstriction can induce acid reflux. Descent of the diaphragm with hyperinflation increases the pressure gradient between the abdomen and thorax and may cause the lower esophageal sphincter (LES) to herniate into the chest where its barrier function is diminished. This may be exacerbated by the accentuated negative inspiratory pleural pressure in acute asthma, which opposes the tone of the LES. Furthermore, β-agonists and

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methylxanthine bronchodilators may decrease LES tone, but it has been difficult to demonstrate that these agents actually worsen reflux [10].

Studies to interpret the effect of GERD on asthma control may be complicated by the reliance on self-report of GERD. Indeed, a significant portion of patients with asthma with symptoms of GERD do not have GERD documented by pH-probe measurements, whereas up to 60% of the patients with asthma with no symptoms of reflux have GERD measured by esophageal pH probe. Thus, important questions remain regarding the clinical diagnosis of distal and proximal GERD and the effect on patients with poorly controlled asthma [11].

The endoscopic assessment of esophageal mucosal changes in patients with reflux symptoms is important to diagnose patients with various degrees of severity. It is well known that the endoscopic severity of esophagitis correlates with the likelihood of responding to certain treatments and with the risk of developing complications – for example, peptic strictures [12].

Aim of the work

The aim of the study was to detect the prevalence of different grades of GERD in adult asthmatics with or without GERD symptoms by using upper gastrointestinal (GI) endoscopy.

Patients and methods

This prospective study was performed from July 2014 to October 2015 in Kasr Al Aini Hospital, Cairo University. The study included 50 adult patients (≥18 years) who were randomly chosen with different levels of asthma control. The first three asthmatic patients presenting to the outpatient clinic each week were chosen in a consequent manner to avoid selection bias. Overall, 27 male patients (54%) and 23 female patients (46%) with an age range between 23 and 54 years were included in the present study. All patients had a clinical diagnosis of bronchial asthma according to the GINA guidelines [13]. Patients with acute severe asthma together with patients who are not fit for general anesthesia and patients with bleeding diathesis were all excluded from our study.

The Asthma Control Test (ACT) was carried out for all our patients. The ACT survey is a patient-completed questionnaire with five items assessing asthma symptoms (daytime and nocturnal), use of rescue medications, and the effect of asthma on daily functioning. Each item includes five response options corresponding to a five-point Likert-type rating scale. A validated Arabic version of the ACT was used in our study [14].

In scoring the ACT survey, responses for each of the five items are summed up to yield a score ranging from 5 (poor control of asthma) to 25 (complete control of asthma). According to the ACT score, patients were classified as controlled (>19), partially controlled (16–19), or uncontrolled (<16) [15].

All patients were assessed for GERD manifestations using the GERD Questionnaire (GerdQ) [16]. The questionnaire utilizes six main points as follows:

(1) Burning feeling behind the breastbone (heartburn)?
(2) Stomach contents moving up to the throat or mouth (regurgitation)?
(3) Pain in the middle of the upper stomach area?
(4) Nausea?
(5) Trouble getting a good night's sleep because of heartburn or regurgitation?
(6) Need for over-the-counter medicine for heartburn or regurgitation?

Scoring system depends upon how many times per week do each of the symptoms occur as follows:

(1) Score 0: occurs on 0 days.
(2) Score 1: occurs on 1 day.
(3) Score 2: occurs on 2–3 days.
(4) Score 3: occurs on 4–7 days.

The interpretation will be as follows:

(1) Total score of 0–2 points means 0% likelihood of GERD.
(2) Total score of 3–7 points means 50% likelihood of GERD.
(3) Total score of 8–10 points means 79% likelihood of GERD.
(4) Total score of 11–18 points means 89% likelihood of GERD.

The patients were then classified into two groups.

Group 1 [the symptomatic group (C and D)], comprising patients with high likelihood of GERD.

Group 2 [the less symptomatic group (A and B)], comprising patients with less likelihood of GERD.

All patients from both groups were blindly subjected to upper GI endoscopy; patients with acute severe asthma were excluded from our study. The included patients were properly prepared as regards their asthma condition; they were closely monitored before and during the procedure. The endoscopist was not informed about the results of our patient's questionnaire. A written informed consent was obtained from all patients before endoscopy.

Endoscopic grading was performed using the Los Angeles grading system, which is a diagnostic and grading system for GERD [12], as follows:

Grade A: one or more mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds.

Grade B: one or more mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds.

Grade C: one or more mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference.

Grade D: one or more mucosal break that involves at least 75% of the esophageal circumference.

Statistical analysis

Qualitative data were presented as frequencies (*n*) and percentages. The χ^2-test was used for comparisons between the two groups. Post-hoc analysis was carried out for multiple proportion comparisons. *P* values less than 0.05 were considered statistically significant. All statistical calculations were carried out using the computer program SPSS release 15 for Microsoft Windows, 2006 (SPSS Inc., Chicago, Illinois, USA).

Results

This study included 50 adult patients with an age range between 23 and 54 years. Patients were randomly selected and then classified into two groups according to the GerdQ. Group 1 included symptomatic patients and group 2 included less symptomatic patients. Patients were then classified according to the level of asthma control, as shown in Table 1.

In total, 17 patients (34%) were classified on the basis of the ACT score as having well-controlled asthma, 18 patients had partially controlled asthma (36%), and 15 patients had uncontrolled asthma (30%). There was no significant difference in the level of asthma control between the two groups (*P* values were 0.76, 1, and 0.75 for controlled, partially controlled, and uncontrolled asthma patients, respectively).

The symptomatic group presented with a variable array of symptoms. Table 2 shows the most common symptoms encountered in our patients.

Heartburn was the most reported symptom (48%) in the patients of group 1 with symptomatic GERD; this was followed by regurgitation (40%) and dyspepsia (36%).

In our study, upper GI endoscopy was performed for all our patients for the detection of different endoscopic grades of GERD. Table 3 shows the prevalence of different grades of GERD in symptomatic and less symptomatic groups.

Gastroesophageal reflux was endoscopically detected in 36 patients out of 50 (72%); most of them presented with grade B gastroesophageal reflux with a prevalence of 14 out of 50 studied patients (28%).

On applying the χ^2-test, no statistical difference was observed in the grades of GERD between groups 1 and 2 patients (P=0.83).

The χ^2 statistical value was 1.5079.

Table 1 Patients classification in both groups according to level of asthma control

Control level	Group 1: symptomatic	Group 2: less symptomatic	Total [*n* (%)]
Controlled	8	9	17 (34)
Partially controlled	9	9	18 (36)
Uncontrolled	8	7	15 (30)
Total	25	25	50 (100)

Table 2 Most prevalent symptoms in group 1 (symptomatic group)

Symptoms	Number of patients (%)
Heartburn	12/25 (48)
Regurgitation	10/25 (40)
Dyspepsia	9/25 (36)
Dysphagia	7/25 (28)
Epigastric pain	6/25 (24)
Nausea and vomiting	3/25 (12)
Trouble getting a good night's sleep	2/25 (8)

In the present study, we aimed at the detection of GERD at different levels of asthma control. Table 4 reveals the endoscopic evidence of GERD in controlled, partially controlled, and uncontrolled asthmatic patients in our study.

The total number of endoscopically detected GERD changes was 36 patients out of the 50 patients included in the whole study (72%).

GERD was endoscopically detected in 19 out of 25 patients of group 1 (76%). In group 2, however, 17 cases of GERD were detected among the 25 studied patients (68%), with no significant difference between the two groups (P=0.53).

The endoscopic detection of GERD in controlled, partly controlled, and uncontrolled asthmatics was 70.6, 72.2, and 73.3%, respectively, with no significant difference in GERD prevalence related to the level of asthma control (P=0.98).

Post hoc test for multiple comparisons.

Discussion

Asthma is a serious global health problem affecting all age groups, with a global prevalence ranging from 1 to 21% in adults [1].

Gastroesophageal reflux is common in patients with asthma, particularly in those with difficult-to-control asthma, with a reported prevalence of 32–84% [17]. About half of the asthma patients who have reflux have no symptoms [18].

The actual effect of gastroesophageal reflux on asthma severity and symptoms has not been reported systematically in a large series of patients. The mechanism by which acid reflux might affect asthma control is controversial. It may also be important to know whether proximal reflux into the upper esophagus affects patients differently from distal acid reflux [9].

Subsequently, well over 30 different sets of criteria describing the endoscopic assessment of GERD have been published over the years, but they all lacked formal development, validation, or peer review [19].

The Los Angeles classification system was published in its final form back in 1999 [12]. It was developed by the International Working Group for the Classification of Oesophagitis, supported by the World Organization of Gastroenterology, and was first proposed in 1994 [20]. It was first presented at the Los Angeles World Congress of Gastroenterology, and hence the name of the classification.

It is the most validated classification system yet. Furthermore, it has been consistent at predicting the outcome of an acid reflux therapy, correlates well with other tests of acid reflux such as 24 h pH monitoring studies, and when compared with other grading systems, is the most reproducible and practical [20].

This study included 50 adult patients with different levels of asthma control. All patients had a clinical diagnosis of bronchial asthma confirmed by using spirometry and reversibility tests. The study included 27 male patients (54%) and 23 female patients (46%).

Eighteen patients (36%) were classified on the basis of the ACT score as having well-controlled asthma, 17 patients had partially controlled asthma (34%), and 15 patients had uncontrolled asthma (30%). There was no

Table 3 Severity of GERD as detected by upper GI endoscopy in both groups

	n/*N* (%) No GERD	Grade A	Grade B	Grade C	Grade D	Total
Group 1: symptomatic	6/25 (24)	4/25 (16)	7/25 (28)	5/25 (20)	3/25 (12)	19/25 (76)
Group 2: less symptomatic	8/25 (32)	5/25 (20)	7/25 (28)	4/25 (16)	1/25 (4)	17/25 (68)
Total	14/50 (28)	9/50 (18)	14/50 (28)	9/50 (18)	4/50 (8)	36/50 (72)

Table 4 Endoscopic evidence of GERD in both groups

Asthma control level	*n*/*N* (%) Controlled	Partially controlled	Uncontrolled	Total
Number and percentage of GERD in group 1 (symptomatic patients)	5/8 (62.5)	7/9 (77.8)	6/8 (75)	19/25 (76)
Number and percentage of GERD in group 2 (less symptomatic patients)	7/9 (77.8)	6/9 (66.7)	5/7 (71.4)	17/25 (68)
Total	12/17 (70.6)	13/18 (72.2)	11/15 (73.3)	36/50 (72)

significant difference in the level of asthma control between the two groups in the study (Table 1).

Heartburn was the most reported symptom (48%) in group 1 patients with symptomatic GERD; this was followed by regurgitation (40%) and dyspepsia (36%) (Table 2).

Heartburn and regurgitation are the most characteristic symptoms of GERD. These symptoms are sufficiently descriptive to be diagnostic. Esophageal and extraesophageal symptoms and syndromes that form part of the framework of GERD also include chest pain, sleep disturbances, cough, hoarseness, asthma, and dental erosions [2].

Chest pain may be a symptom of GERD, even the presenting symptom [21]. Atypical symptoms including dyspepsia, epigastric pain, nausea, bloating, and belching may be indicative of GERD but overlap with other conditions. A systematic review found that nearly 38% of the general population complained of dyspepsia. Dyspepsia was more frequent in GERD patients than in those without epigastric pain, early satiety, belching, and bloating were more likely to respond to a proton-pump inhibitors therapy compared with nausea. The balance of evidence suggests that symptom frequency does not change with age; however, the intensity of symptoms may decrease after the age of 50 [22]. Aging increases the prevalence of erosive esophagitis, Los Angeles grades C and D [23].

Most of our patients presented with grade B gastroesophageal reflux with a prevalence of 14 out of 50 studied patients (28%). No statistical difference was observed in the grades of GERD between groups 1 and 2 patients (Table 3).

According to the Los Angeles classification system, Nakase and colleagues observed a higher prevalence of endoscopic mucosal changes, grades A or B rather than grades C or D, in their study among 72 adult asthmatic patients. This is in agreement with our results, as most of our patients had grade B gastroesophageal reflux. The authors assessed their patients as regards asthma severity rather than the level of control. They correlated grades C and D with patients with severe asthma but they found conflicting results in the form of decreased number of eosinophils and serum immunoglobulin E levels in patients with severe asthma [24].

Furthermore, consistent with our findings, Shimizu and colleagues found high prevalence of GERD in asthmatic patients (69.2%) on the basis of the Los Angeles classification with minimum change (grades A and B). Their results indicated a high frequency of GERD in asthmatic patients. The study recommended that physicians should carefully observe asthmatic patients with minimal change on endoscopy [25].

The total number of endoscopically detected GERD changes was 36 patients out of the 50 patients included in the whole study (72%) (Table 4). GERD was endoscopically detected in 19 out of 25 patients in group 1 (76%). In group 2, however, 17 cases of GERD were detected among the 25 studied patients (68%), with no significant difference between the two groups.

In their study for GERD detection using upper GI endoscopy, Sontag and colleagues found esophageal erosions or ulcerations as seen on endoscopy in 39% of consecutive asthmatics and 13% had Barrett's esophagus. The presence or absence of reflux symptoms was not used as a selection criterion for asthmatics. Endoscopy was carried out by two endoscopists using predefined criteria. All asthmatics had discrete wheezing and either a previous diagnosis of asthma or documented reversible airways obstruction of at least 20%. The esophageal mucosa was graded as normal if no erosions or ulcerations were present in the tubular esophagus; as esophagitis if a mucosal break with exudate (erosions and/or ulcerations) was present; and as Barrett's if specialized (intestinal) columnar epithelium was present. The authors eliminated from their study any patients who were referred for workup because of GI symptoms and who were not part of the consecutive asthmatic protocol. Thus, this study appears to be one of the few that report the prevalence of GERD as it relates to esophageal mucosal disease in consecutive asthmatics [26].

Evaluating 104 consecutive asthma patients, Sontag *et al.* [27] observed that 82% of the asthma patients had abnormal amounts of acid reflux on 24 h esophageal pH testing. Ambulatory 24 h esophageal pH testing plays a key diagnostic role in asthma patients without reflux symptoms. Using this test, Irwin *et al.* [28] studied a group of difficult-to-control asthma patients and found that gastroesophageal reflux was 'clinically silent' in 24% of them. In their earlier study, Perrin-Fayolle *et al.* [29] found evidence of reflux symptoms in 65% of 150 consecutive asthmatics. Sontag *et al.* [30] reported that 72% of 189 consecutive asthmatics had heartburn. Almost half of the 189 had supine nocturnal heartburn and 18% had nocturnal burning in the throat. Field and colleagues

studied 109 asthmatics and 135 controls in a questionnaire-based, cross-sectional analytic study; 77% of the asthmatics had heartburn, 55% had regurgitation, 24% had difficulty with swallowing, whereas 37% of the group required at least one antireflux medication and 41% had reflux-associated respiratory symptoms during the prior week. Pulmonary symptoms occurred significantly more frequently in the asthmatics than in controls [3].

Using a GerdQ, Kiljander and Laitinen randomly selected every 14th patient from a multicenter group of 2225 asthmatics. Of the 90 asthmatics who joined, 51% had GERD, which was defined by the presence of GERD symptoms [18]. However, a different GerdQ used in this study was carried out before validation of the GerdQ, which was used in our current study.

In our study, the endoscopic detection of GERD in controlled, partly controlled, and uncontrolled asthmatics was 70.6, 72.2, and 73.3%, respectively, with no significant difference in GERD prevalence related to the level of asthma control (Table 4).

In agreement with our study, DiMango and colleagues studied GERD among 304 asthmatic patients. They studied patients with poorly controlled asthma to determine whether proximal or distal esophageal reflux is associated with asthma severity, symptoms, physiology, or functional status. They concluded that asymptomatic GERD is not associated with distinguishing asthma symptoms or lower lung function in individuals with suboptimal asthma control. Their patients with asymptomatic GERD did not manifest with lower lung function, worse asthma control, or increased airway responsiveness, but they had significantly worse asthma quality of life [31]. The researchers also concluded that asymptomatic GERD frequently accompanies poorly controlled asthma. Unlike our study, the authors did not study patients with other levels of asthma control including well-controlled and partially controlled asthma.

In their study, Jaimchariyatam and colleagues, on the other hand, observed a higher prevalence of GERD among those with uncontrolled asthma than in those without GERD (57.17 and 25.72%, respectively). The ACT score of less than 20 (poor controlled asthma) was higher in the asthmatic patients with GERD than those without GERD (80.95 and 48.57%, respectively). GERD was detected using 24 h esophageal pH monitoring [32]. These results are rather different from that of our study where no significant difference in GERD prevalence was detected in relation to the level of asthma control. The study included different population of patients and was not confined to adult asthmatics. In addition, the authors in this study used 24 h esophageal pH monitoring rather than upper endoscopy to detect GERD in asthmatics, which may explain the different results compared with our study.

Conclusion

According to our study, GERD with its different grades is a common association in adult asthmatics at all levels of asthma control. The condition is still common even in asymptomatic patients and this raises the concept of proper investigation for associated GERD in asthmatics even in the absence of classic GERD symptoms. The study was limited by the number of patients; a wider scale of patients needs to be studied for associated GERD in the future. In addition, the study was confined to adult asthmatic patients and did not include pediatric asthmatics who may also need further studies for associated GERD. We also recommend further studies evaluating the effect of GERD treatment as an adjunctive therapy for proper asthma control in adult asthmatics with suspected GERD.

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Conflicts of interest

There are no conflicts of interest.

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