Gastroesophageal reflux in bronchial asthma patients

A clinical note

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ABSTRACT

Objective: The objective is to correlate the symptoms of gastroesophageal reflux with the results of esophageal reflux with the results of esophageal pH metry in asthmatic patients.

Methods: A prospective study was carried out in King Fahd Hospital of the University, Al-Khobar, Kingdom of Saudi Arabia (KSA), during the period January 2000 through to February 2001, whereby 50 patients (34 females and 16 females) with primary diagnosis of bronchial asthma were consecutively enrolled, their mean age + SD was 38.01 + 9.8 years. Twenty-two subjects who were not suffering from asthma or gastroesophageal reflux (GER) (13 females and 9 males) constituted the control group. A questionnaire was administered to all participants and demographic data; asthma and GER symptoms were obtained. Esophageal manometry was performed, whereby the location, length and resting pressure of the lower esophageal sphincter (LES) were determined, pH catheter was inserted nasogastrically, and ambulatory pH data over 24 hours were collected. Pulmonary function tests were also performed.

Results: Twenty-two (44%) patients with asthma had a Demeester score greater than 14.7 and were therefore diagnosed as having pathological GER. Accordingly, the asthma patients were divided into 2 groups, asthma patients with GER (n=22) and those without GER (n=28). Multiple logistic regression analysis revealed that age did not significantly influence occurrence of GER, but it indicated that hoarseness of voice and nocturnal symptoms were significant predictors for the presence of GER in asthmatic patients, hence, the probability of having GER in an asthma patient is nearly 8 times if he/she has nocturnal symptoms and about 7 times if they have hoarseness of voice. However 36.4% of asthmatic patients diagnosed by esophageal ph metry as having GER did not complain of heartburn and hoarseness of voice; such as the reflux was silent.

Conclusion: The frequency of GER among 50 patients with asthma reporting to KFHU, Al-Khobar, KSA is 44%. The presence of nocturnal symptoms and hoarseness of voice are significant clinical predictors of GER in asthmatic patients. Patients with difficult to treat asthma should be subjected to esophageal pH metry since a substantial proportion of them may have silent reflux.

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Gastroesophageal reflux (GER) is defined as the regurgitation of gastric contents into the esophagus. This material which contains acid, and pepsin has the ability to irritate or injure tissues not adapted to the presence of this potentially noxious material.[1] As reflux may proceed more proximal than

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the esophagus, other tissues may be affected which may lead to a number of remote manifestations through anatomic or neural connections to the esophagus. Both clinical and experimental data have demonstrated that such events may lead to a variety of esophageal, laryngeal and pulmonary complications, which may present with hoarseness of voice, cough, chest pain, aspiration pneumonia and bronchial asthma.[2] Pulmonary manifestations of GER, such as lung and airway involvement during reflux may take several forms including pneumonia, chronic cough, interstitial fibrosis and asthma. Indeed, pulmonary complications may be the presenting symptom in (GER). Recurrent lung injury and pneumonia in GER may result from direct contact with the caustic refluxed gastric contents (acid and pepsin) and possibly aspirated gastric, esophageal or pharyngeal bacteria.[3] Pulmonary manifestations of GER have been reported in the medical literature for the last 2 decades and in particular the association of GER and asthma has been well recognized. The latter was suggested first by Sir William Osler more than a century ago. Nowadays its presence is well known in terms of gastric asthma, but its importance is still a matter of debate.[4] The prevalence of GER among patients with asthma is generally reported to be higher than in the normal population but with a wide range from 30-90% in several reports.[5] Part of the variability may be due to differences in the definition of GER and the extent to which objective measures of reflux were used to confirm the diagnosis. In 199 asthmatic patients who were referred for 24 hour esophageal pH testing, reflux symptoms were present in 164 (82%) of whom 118 (72%) had abnormal esophageal acid contact times. Of the 35 asthmatics without reflux symptoms 10 (29%) had abnormal esophageal acid contact times consistent with the diagnosis of GER. Among asthmatics with GER, 119 of 151 (79%) reported respiratory symptoms associated with esophageal acid events. Seventy-six of 84 (91%) reported cough associated with esophageal acid events.[6] An important observation is that some asthmatics who were diagnosed as having GER through esophageal pH monitoring did not complain of typical GER symptoms. The potential frequency of this problem was assessed in a study of difficult to control asthmatics. Gastroesophageal was found to be a definite asthma causing factor in 64%; of clinically silent reflux was present in 24% of asthmatic patients diagnosed as having GER. Similar findings have been described in other reports. These observations underscore the importance of esophageal pH testing for identifying GER in asthmatics without esophageal symptoms. Hence, this study aimed at correlating the symptoms of GER with the results of esophageal pH metry in asthmatic patients, and to determine the possible clinical predictors of GER in asthmatics.

Methods. Fifty patients with primary diagnosis of asthma were enrolled consecutively as they reported or were referred to the pulmonary clinic at King Fahd Hospital of the University (KFHU), Al Khobar, Kingdom of Saudi Arabia (KSA). The presence or absence of symptoms related to GER was not employed as a selection criterion. Diagnosis of bronchial asthma was reviewed and confirmed by a pulmonologist. The diagnosis was based on the guideline of American Thoracic Society; such as either a 20% increase in forced expiratory volume in one second (FEV_1) after administration of bronchodilator or a 20% decrease in FEV_1 after administration of methacholine. All medications were thoroughly reviewed. If the patient was receiving other medications that are known to affect gastroesophageal motility or gastric acid secretion, they were discontinued for a minimum of 48 hours in case of prokinetic agents, antacids and H_2 –receptor blockers, and for one week in case of proton pump inhibitors before the procedure. Twenty-two patients who were not suffering from asthma or GER were recruited as control subjects. Gastroesophageal was excluded on the basis of absence of symptoms. Control subjects were excluded if they had history of esophageal or gastric surgery, diabetes mellitus, alcoholism, smoking, collagen vascular diseases or neurological disorders. Each subject (patient or control) was interviewed and was given a full description of the procedures (esophageal manometry and ambulatory 24 hour pH monitoring). Informed consent was obtained and the subject was instructed to fast from the middle of the night before the test.

Questionnaire. A questionnaire was administered to all participants before being subjected to the test procedures. It included demographic data namely age, sex, occupation, smoking and history of alcohol consumption. Symptoms of asthma were reviewed with patients. These included duration of the disease, family history, precipitating factors, presence of night symptoms, seasonal variation and the medications. Symptoms of GER were reviewed as well, and they included heartburn, regurgitation, dysphagia, odynophagia, and hoarseness of voice, chest pain and sore throat.

Esophageal manometry. Esophageal manometry was performed using polyvinylchloride catheter (PVC) with 4 channels 5cm apart numbered sequentially, starting with the most proximal channel, connected to 4 transducers which converted the measured pressure into voltage (Synectic Medical AB, Sweden). Xylocaine spray and gel were used to anesthetize the pharynx and the nares. The catheter was passed horizontally through the nose. As it entered the pharynx the subject was instructed to swallow water to allow the catheter to progress easily. The catheter was then inserted further (60-65 cm) until the 4 ports were inside the stomach. This could easily be ascertained by

Table 1 - Demographic features of the 3 groups.

Variables	Control (N=22)	Asthmatic without GER (N=28)	Asthmatic with GER (N=22)
Male	9 (40.9)	6 (21.4)	10 (45.5)
Female	13 (59.1)	22 (78.6)	12 (54.5)
Saudi	15 (68.2)	21 (75)	15 (68.2)
Non-Saudi	7 (31.8)	7 (25)	7 (31.8)
Age	29.36 ± 8.59	37.50 ± 9.89*	38.59 ± 10.02**
Body mass index	26.63 ± 5.52	28.73 ± 5.57	30.10 ± 7.28
Age of onset of asthma	-	29.64 ± 12.04	29.60 ± 14.31

* for p=0.015 and ** for p=0.008 versus the control group using analysis of variance
GER - gastroesophageal

Table 2 - Frequency of symptoms of gastroesophageal in the 2 patient groups.

Symptoms	Asthmatic without GER N=28 (%)	Asthmatic with GER N=22 (%)
Heartburn	14 (50)	14 (63.6)
Regurgitation	8 (28.6)	9 (40.9)
Dysphagia	2 (7.1)	2 (9.1)
Odynophagia	3 (10.7)	3 (13.6)
Hoarseness of voice	10 (35.7)	14 (63.6)
Chest pain	9 (32.1)	9 (40.9)
Sore throat	5 (17.9)	9 (40.9)

Difference were assessed by Chi-square test
GER - gastroesophageal

Table 3 - Symptoms significantly predicting the presence of gastroesophageal in patients with asthma.

Symptoms	Coefficient (beta)	SE of beta	*p* value	Odds ratio	95% CI of *p* value
Night symptoms	2.04	0.74	0.006	7.71	1.81-32.72
Hoarseness of voice	1.89	0.66	0.004	6.64	1.84-24.06

The result emerged after multiple logistic regression involving 8 factors, family history, precipitating factors, nocturnal symptoms, heartburn, regurgitation, hoarseness of voice, chest pain and sore throat
CI - confidence interval

the presence of well defined respiratory increase in pressure on inspiration. The station pull through technique was performed at one cm station; then, as the channels passed through the lower esophageal sphincter (LES) its location, length and resting pressure were determined.

Ambulatory 24 hour monitoring. The pH catheter consists of proximal and distal sensors 15 cm apart; the catheter fed the pH information into a digit trapper (MKIII, Synectic, Medical, AB, Sweden). The catheter was inserted nasogastrically and the distal electrode positioned at 5 cm above the manometrically determined upper border of LES. The patient was sent home and asked to perform his/her daily activities. They were asked to indicate time of eating, sleeping, and symptoms whether related to asthma or GER by pressing the appropriate buttons on the digit trapper. The patients were also provided with a diary to record their symptoms. The patient reported to the lab in the next morning after 20-24 hour of recording and the data was downloaded and analyzed by a software program. DeMeester Score was calculated.

Pulmonary function tests. Spirometric measurements FVC, FEV_1, FEV_1/FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, in addition to residual volume and total lung capacity were determined.

Statistical analysis. Student's T-test and analysis of variance were used for assessing differences in age, body mass index (BMI), and variables from manometry and pulmonary function tests. Chi-square test was used to compare data of demographic features and factors in the history of asthma and GER symptoms. In order to find a predictor in the history of asthma for the presence or absence of GER, multiple logistic regression was employed.

Table 4 - Indices as compared between asthmatic patients with and without gastroesophageal.

Index	Asthmatic without GER N=28	Asthmatic with GER N=22
Distal electrode pH <4		
Respiratory symptom index ≥ 50%	7 (38.9)	9 (69.2)
Gastrointestinal symptom index ≥50%	4 (36.4)	8 (80)
Proximal electrode pH <4		
Respiratory symptom index 50%	2 (11.1)	6 (46.2)
Gastrointestinal symptom index ≥50%	2 (18.2)	3 (27.3)

Differences between frequencies were assessed by Chi-square test
* for p=0.044, ** for p=0.028
GER - gastroesophageal

Table 5 - Results of pulmonary function tests (mean ± SD).

Pulmonary function tests	Control	Asthmatic without GER	Asthmatic with GER
FVC%	93.45 ± 13.00	88.70 ± 14.71	91.72 ± 17.80
FEV_1%	94.10 ± 12.52	79.20 ± 19.63	81.28 ± 24.65
FEV/FVC%	86.60 ± 6.00	75.48 ± 11.81**	73.83 ± 13.10**
$FEF_{25-75\%}$	104.45 ± 24.45	66.85 ± 30.82**	66.50 ± 40.10**
$FEF_{25\%}$	89.10 ± 20.42	70.75 ± 23.76*	75.76 ± 25.45**
$FEF_{50\%}$	106.80 ± 23.68	74.37 ± 28.82**	70.93± 40.30**
$FEF_{75\%}$	97.05 ± 29.18	60.80 ± 25.53**	62.00 ± 43.80**
$FEF_{75-85\%}$	100.65 ± 39.40	51.26 ± 21.96**	58.13 ± 44.80**
Total lung capacity%	92.70 ± 12.74	105.33 ± 20.38	100.63 ± 17.89
Residual volume%	82.90 ± 33.0	121.00 ± 50.22	109.00 ± 35.00

* for p<0.05 and ** p<0.01 versus the control group using analysis of variance
GER - gastroesophageal

Results. Fifty patients with asthma, 36 Saudis and 14 non-Saudis, were investigated. There were 34 females and 16 males. Their mean age ± SD was 38.0 ± 9.8 years and their mean body mass index (BMI) was 29.4 ± 6.3. The control group consisted of 22 healthy volunteers without asthma or GER. They were 15 Saudis and 7 non-Saudis, 13 females and 9 males. Their mean age was 29.4 ± 8.6 years. Although the controls were significantly younger than the patients (non-paired student's test, p=0.001), there were no significant differences between the patients and controls regarding nationality, sex distribution and BMI. Using the esophageal pH data obtained from the distal electrode at a threshold pH <4, and the 95th percentile value for the DeMeester score of 14.72 incorporated into the Synectics Esophagram software program, 22 patients with asthma had a DeMeester score greater than 14.72 and were therefore diagnosed as having pathological GER. The proportion of asthma patients having GERD was 22 out of 50 (44%). Accordingly the asthma patients were divided into 2 groups: those without GER (n=28) and those with GER (n=22). All data will subsequently be presented in relation to these 2 patient groups and compared with the control group.

When the analysis of the demographic data was repeated for the 3 groups there were no significant differences in the sex distribution, nationality, BMI or age of onset of asthma but both patient groups remained significantly older than the controls (**Table 1**). There were no significant differences between the 2 patients groups regarding family history of asthma, presence of precipitating factors or night symptoms of asthma. **Table 2** shows the proportion of asthmatic patients in each group who had symptoms of GER. There were no significant differences between asthma patients with and without GER using Chi-square test, but it is noteworthy that 50% of the patients not diagnosed as having GER still complained of heartburn and to a lesser extent of other symptoms, while a considerable proportion of patients diagnosed by esophageal pH metery as having GER did not complain of symptoms. The proportions ranged from 63.6% for heartburn and hoarseness of voice to 9.1% for dysphagia. Reflux in these patients was thus silent. To find out whether the presence of any of the demographic variables, age of onset of asthma, presence of family history of asthma, precipitating factors, nocturnal symptoms or the symptoms of GER could significantly assess the odds of developing GER in patient with asthma, each factor was assessed separately by logistic regression. There were no significant relation to the variables mentioned above.

However multiple logistic regressions of these factors showed that the presence of GER in patients with asthma was influenced significantly by the presence of nocturnal symptoms and hoarseness of voice **(Table 3).** Thus the probability of having GER in a patient with asthma is nearly 8 times if he/she has nocturnal symptoms and about 7 times if they have hoarseness of voice, as compared to an asthmatic patient without these symptoms. The symptom index (SI) such as the proportion of reflux episodes that correspond to an indicated symptom events was calculated for the respiratory and gastrointestinal symptoms in asthmatic patients with and without GER. The symptom index is generally clinically significant when ≥50%. The proportions of patients in each group with the respiratory or gastrointestinal symptom index ≥50%, were compared by Chi-square test for the distal electrode at threshold pH <4 and the proximal electrode at threshold pH <4 **(Table 4)**. At the distal electrode, significantly more patients with GER had a gastrointestinal symptoms index ≥50% (p=0.044). At the proximal electrode significantly more patients with GER had a respiratory symptom index ≥50% when the threshold pH was <4 (p=0.028).

Pulmonary function tests. The results of pulmonary function tests for the patients with asthma with and without GER and the control subjects are shown in **Table 5**. Patients with asthma, whether they had reflux or not, had uniformly and significantly lower spirometric values than the controls; there were no significant differences between the 2 groups of asthma patients. There were no significant differences regarding total lung capacity and residual volume.

Discussion. During the last 2 decades, there has been an increasing awareness of the association between gastroesophageal reflux disease (GERD) and bronchial asthma. Two mechanisms have been proposed to explain how GER may trigger asthma: the reflux mechanism whereby acid refluxed into the distal esophagus may cause bronchoconstriction through a vagally-mediated reflex, and the reflux mechanism whereby proximal esophageal reflux may lead to microaspiration of acid and bronchoconstriction. The present study aimed at determining the correlation between gastroesophageal symptoms of asthmatic patient with esophageal pH-metry.

Although our control group was significantly younger than the patients with asthma, the difference in age was probably of little or no consequence. This is supported by the finding that logistic regression revealed no significant influence of age on the occurrence of GER in patients with asthma. Richter et al[7] also did not find an independent effect of age on pH parameters. The critical level that indicates the presence of pathological GER is when the pH is less than 4 for more that 6% of the total recording time.[8] On that basis the frequency of GER in our 50 patients with asthma is 44%. This is well within the range of 34-89% reported by other investigators and is the same as that reported by Gastal et al[9] in 27 patients with asthma. The wide variation in the frequency of GER among asthmatic patients reported from several locations may reflect variation in the severity of asthma in the population studied as well as variation in racial and environmental factors. Multiple logistic regression analysis revealed that the presence of nocturnal symptoms and hoarseness of voice indicated a high probability for reflux in asthma patients. The presence of these symptoms should therefore alert the clinician to the presence of GER, which should be confirmed by esophageal pH monitoring, pulmonary function tests are not helpful in this regard. While 50% of asthma patients with no objective evidence of GER complained of heartburn, 36.4% of those diagnosed as having GER did not complain of heartburn and hoarseness of voice. Gastroesophageal in the latter group of patients was thus silent. Several studies have noted that asthma patients may have asymptomatic GER.[10-13] Larrain and co-workers prospectively examined adult onset non-allergic asthma patients and found that 21 of 81 (26%) subjects had GER without ever experiencing heartburn. Our study differs from that of Larrain and co-workers in the technique by which GER was diagnosed (an esophagram after a 300-ml barium meal which had an 8% false positive rate and 56% false negative rate in their patient population). Our study also differs from that of Harding and co-workers who reviewed

retrospectively 24 hour esophageal pH metry in 35 asthma patients without reflux symptoms, of whom 10 (29%) had abnormal esophageal acid contact times. These patients were referred to the esophageal pH laboratory; thus there was selection bias.[6] Other studies have shown that 35-50% of patients with asthma have no symptoms of GER despite presence of pathological esophageal acid exposure time.[14] Gastroesophageal is the most common cause of difficult to treat asthma, and 24% of such asthmatic patients diagnosed as having GER had silent reflux. It has been observed that vigorous treatment of GER was helpful in converting difficult to control asthma patients into ones who were no longer difficult to control.[15] It was suggested that identifying and treating GER, regardless of presence of reflux symptoms improves asthma control. Therefore, it is recommended that all patients with difficult to treat asthma should be subjected to esophageal pH metry.

Our results also highlighted the problem of silent reflux in patients with asthma.

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