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Prevalence of oesophagitis in asthmatics

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Abstract

The exact relation between gastro-oesophageal reflux and asthma remains poorly understood. To determine whether gastro-oesophageal reflux in asthmatics results in oesophagitis, endoscopy and oesophageal biopsy were performed on 186 consecutive adult asthmatics. The presence or absence of reflux symptoms was not used as a selection criterion for asthmatics. Endoscopy was performed 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 oesophageal mucosa was graded as normal if no erosions or ulcerations were present in the tubular oesophagus; as oesophagitis if a mucosal break with exudate (erosions and/or ulcerations) was present; and as Barrett's if specialised (intestinal) columnar epithelium was present. A hiatal hernia was diagnosed if ≥2 cm of gastric mucosa appeared above the diaphragm during endoscopy. Thirty nine per cent of the patients with asthma had oesophagitis or Barrett's oesophagus, or both. There was no difference in the oesophageal mucosal status between asthmatics who required and those who did not require bronchodilators. Fifty eight per cent of asthmatics had a hiatal hernia. It is concluded that oesophagitis is common and independent of the use of bronchodilator therapy in asthmatics.

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Gastro-oesophageal reflux (GOR) and asthma often co-exist. Although their relationship remains poorly understood, one of cause and effect has been suggested by a number of authors.[1-12] Prolonged ambulatory pH monitoring has shown acid reflux in more than 80% of asthmatics.[13] This reflux does not seem to be a result of the use of bronchodilators. In addition, asthmatics with or without bronchodilators have been shown to have diminished but similar lower oesophageal sphincter (LOS) pressures.[13] The purpose of this study was to determine by endoscopic examination the prevalence of oesophageal mucosal injury in asthmatics.

Patients

As part of a clinical research protocol on the relationship between GOR and asthma, 330 patients from the 'drop-in' clinic, pulmonary clinic, and general outpatient clinics were screened for asthma. The presence or absence of GOR symptoms was not used as a selection criterion. Of the 330 patients, 144 were excluded from analysis for the following reasons: asthma present, but referred for endoscopy because of gastrointestinal symptoms (56); chronic obstructive airways disease present rather than asthma (18); no asthma present (58); and declined offer to have endoscopy (12). The remaining 186 asthmatics, whose primary diagnosis was asthma, represent a group of patients recruited from the outpatient, 'drop-in,' pulmonary, and non-gastrointestinal clinics. Thus, of the 198 asthmatics who qualified as 'consecutive and unselected,' 12 (6%) declined and 186 (94%) consented to have endoscopy.

We previously reported the oesophageal pH test results in 104 of the 186 asthmatics in this group.[14] This study reports the endoscopic findings in the 186 consecutive, unselected asthmatics.

GROUP I: ASTHMATICS WHO RECEIVED CHRONIC BRONCHODILATOR THERAPY

One hundred and forty asthmatics (134 men and six women; age range 21–76 years, mean (SEM) 54 (1·1) years) were studied while taking their usual combinations of theophylline, terbutaline, inhalants, and prednisone.

GROUP II: ASTHMATICS WHO DID NOT RECEIVE CHRONIC PULMONARY MEDICATION

Forty six asthmatics (44 men and two women; age range 27–70 years, mean (SEM) 49 (2·0) years) were studied while receiving no bronchodilator medication. Although these patients may have used bronchodilators intermittently in the past for control of asthma, none required them during the week before endoscopy.

Methods

DOCUMENTATION OF ASTHMA

Asthma was defined as discrete episodes of wheezing and either a previous diagnosis of asthma or documented reversible airway obstruction as determined by a 20% improvement in forced expiratory volume in one second (FEV_1) after bronchodilator administration[15] or a 20% decrease in FEV_1 after methacholine bronchoprovocation, performed in accordance with the American Thoracic Society guidelines.[16] A patient was considered to have a previous diagnosis of asthma if they were enrolled in the pulmonary clinic with the diagnosis of asthma, were receiving chronic bronchodilator therapy, and had a FEV_1 of not less than 1·5 litres.

ENDOSCOPY

All endoscopies were performed by either of two endoscopists using predefined criteria. Tissue

TABLE I *Endoscopic classification of oesophagitis**

Grade 1 – Normal, erythematous, or hyperaemic oesophageal mucosa with no macroscopic erosions or ulcerations
Grade 2 – Superficial ulceration or erosions involving <10% of the last 5 cm of the oesophageal squamous mucosal surface
Grade 3 – Superficial ulceration or erosions involving >10–50% of the last 5 cm of the oesophageal squamous mucosal surface
Grade 4 – Deep ulceration anywhere in the oesophagus or confluent erosion of more than 50% of the last 5 cm of the oesophageal squamous mucosal surface

*Taken from Hetzel *et al.*[16]

was obtained under direct vision from the squamocolumnar junction to establish the presence or absence of Barrett's oesophagus. The oesophageal mucosa was scored from grade 1 to 4 based on the endoscopic not histological appearance[17] (Table I).

Normal (grade 1)
The absence of macroscopic oesophagitis or the presence of erythema only.

Oesophagitis (grades 2–4)
Any break in the mucosa (erosions and/or ulcerations) with or without exudate, as observed during endoscopy.

Barrett's oesophagus was defined as any columnar epithelium of the specialised (intestinal) type, with or without oesophagitis, obtained by biopsy from any level of the tubular oesophagus. The presence of columnar epithelium of the gastric type only was not considered to be Barrett's oesophagus.

Histological examination of the oesophageal mucosa was only used to establish the presence of Barrett's oesophagus and not the diagnosis of oesophagitis.

OESOPHAGEAL MANOMETRY
Oesophageal manometry was performed through the nose using a NARCO 'Bio-systems' (Houston, Texas) Motility Transducer catheter and Physiograph Recording System. The LOS was identified by a sustained resting pressure area that relaxed with swallowing; it was measured in centimeters from the nose. When resting pressure was not increased, the point of initial peristalsis, as determined on withdrawal of the catheter, was used to define the LOS area.

HIATAL HERNIA
A hiatal hernia was considered to be present if during endoscopy gastric folds were seen extending at least 2 cm above the diaphragmatic hiatus during quiet respirations. If during the procedure the two endoscopists present did not agree, a hiatal hernia was considered to be not present.

HABITS
Consumption of tobacco and alcohol was recorded as follows

Quit smoking; quit drinking
Abstinence for at least the previous 12 months.

Active smoking; active drinking
Presently consuming or consumed in the previous 12 months.

Pack years; ounce years
Number of cigarette packs daily×number of years; ounces of alcohol daily×number of years. One ounce was equivalent to (a) one 12 ounce can of beer, (b) one ounce (30 cc) of spirits, or (c) four ounces of wine. Since alcohol consumption may have varied with time, efforts were made to obtain estimates based on patient recall and chart review.

This study was approved by the Human Studies Subcommittee at the Veterans Administration Hospital, Hines, IL.

STATISTICAL ANALYSIS
χ^2 tests of significance were used for comparisons between study groups (bronchodilators *v* no bronchodilators; smoking *v* non-smoking; drinking alcohol *v* not drinking alcohol; hiatal hernia *v* no hiatal hernia) and categorical dependent variables (oesophagitis *v* no oesophagitis).

The Mann-Whitney U test was used to detect differences in continuous dependent variables (age, pack years, ounce years) between the two groups.

Logistic regression analysis was used to determine whether any of the reflux variables was predictive of oesophagitis. Three logistic regressions were conducted in which the oesophageal mucosal status was a dichotomous criterion variable. For each regression the severity of oesophageal mucosal disease was considered differently:

(1) [grade 1] *v* [grade 2 or 3 or 4]
(2) [grade 1 or 2] *v* [grade 3 or 4]
(3) [grade 1 or 2 or 3] *v* [grade 4]

Hiatal hernia, LOS pressure, pack years of smoking, current smoking status, ounce years of alcohol consumption, age, and the use of bronchodilators were used as predictor variables in the logistic regressions.

Odds ratios were used to determine the magnitude of the association between two dichotomous variables.

TABLE II *Criteria used to establish asthma*

	No	*(%)*
Discrete attacks of wheezing:	186	(100)
Evidence of hyper-reactivity	113	(61)
Positive methacholine test	92	(50)
20% improvement in FEV_1	21	(11)
Previous diagnosis of asthma	73	(39)

Results

Table II shows the criteria used to establish asthma. All 186 patients had discrete attacks of wheezing. Objective evidence of bronchial hyper-reactivity was obtained in 113 patients: 92 had a positive methacholine test and 21 had a 20% improvement in FEV_1 after bronchodilator

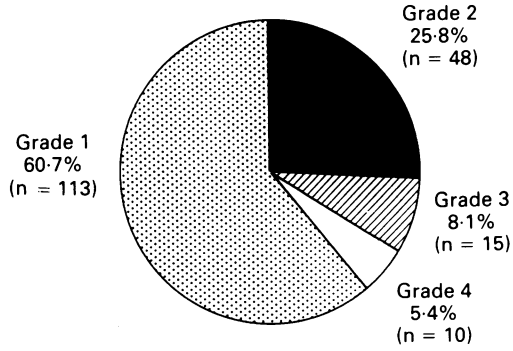

Figure 1: Oesophageal mucosal grades in 186 consecutive adult patients with asthma. Oesophagitis, manifest by macroscopic erosions or ulcers, or both, was present in 39·3% of asthmatics.

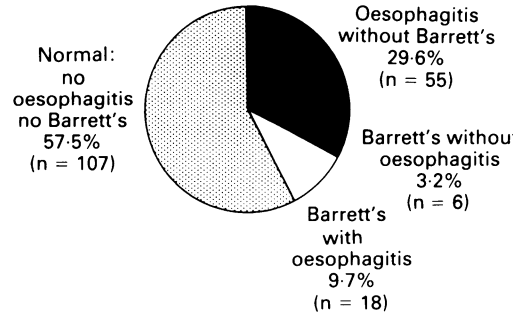

Figure 2: Oesophageal mucosal status in 186 consecutive adult patients with asthma. Oesophagitis or Barrett's oesophagus, or both, was present in 42·5% of asthmatics.

administration. The remaining 73 patients were enrolled in the pulmonary or medical clinics and had a previous diagnosis of asthma.

The prevalence of oesophageal mucosal disease is shown in Figure 1. Macroscopic oesophageal erosions or ulcerations, or both, were present in 39·3% of asthmatics – grade 2, 25·8%; grade 3, 8·1%; and grade 4, 5·4%. Figure 2 shows the detailed distribution of oesophageal mucosal abnormalities in the 186 asthmatics. Twenty four asthmatics (12·9%) had Barrett's oesophagus, 18 with oesophagitis and six without oesophagitis. Overall, 42·5% of the asthmatics had oesophagitis or Barrett's oesophagus, or both.

Table III shows the characteristics of the 186 asthmatics according to need for bronchodilators. Asthmatics who required bronchodilators were significantly older than those who did not ($p<0·05$). There were no differences between the two groups with regard to cigarette or alcohol consumption.

The logistic regression analysis showed that of the seven reflux variables only hiatal hernia predicted oesophageal mucosal status. The LOS pressure, current smoking status, pack years, alcohol ounce years, age, and the use of bronchodilators did not seem to affect the oesophageal mucosa. The percentage of patients with oesophagitis was similar in those taking and those not taking bronchodilators (Fig 3; p=NS).

Hiatal hernia was the only statistically significant predictor of oesophageal mucosal status. Individuals with a hiatal hernia were more likely to have oesophagitis. The relation between hiatal hernia and oesophageal status was stronger when the oesophageal mucosal status was categorised as either normal (grade 1) or oesophagitis (grades 2–4). Hiatal hernia occurred in asthmatics with oesophagitis seven times more frequently than it occurred in asthmatics without oesophagitis (odds ratio=7·0; confidence interval=3·5–14·2; $\chi^2=33·2$; $p<0·0001$). Figure 4 shows the percentage of patients with oesophagitis in relation to the presence of a hiatal hernia. Oesophagitis was present in 57·7% of asthmatics with a hiatal hernia compared with only 16·3% of those without hiatal hernia. Figure 5 shows a stepwise increase in the percentage of asthmatics with hiatal hernia as the oesophageal mucosal status worsens ($\chi^2=36·6$; $p<0·0001$). These results clearly show that hiatal hernia is associated with more severe oesophageal mucosal disease in asthmatics.

Discussion

This study is the first to report the prevalence of oesophageal mucosal disease in unselected asthmatics. The results clearly show a high preval-

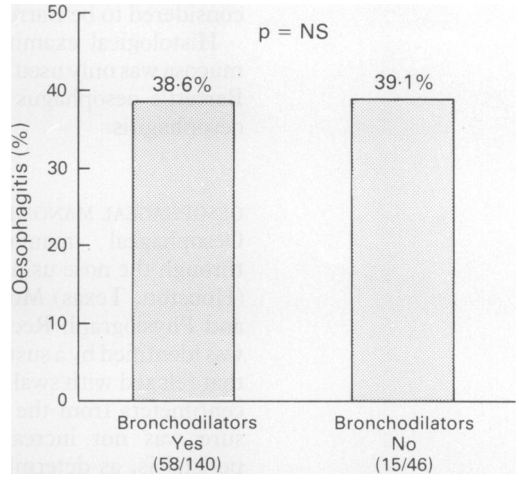

Figure 3: Percentage of patients with oesophagitis according to need for bronchodilators. The percentage of patients with oesophagitis was similar in patients receiving and not receiving bronchodilators (p=NS).

TABLE III *Characteristics of 186 asthmatic according to need for bronchodilators*

	No	Age* (Mean (SEM))	Alcohol users (%)	Quit or never drank (%)	Smoker† (%)	Quit or never smoked† (%)	Ounce years‡ (Mean (SEM))	Pack years‡ (Mean (SEM))
On bronchodilators	140	54·1 (1·1)	53	37	31	65	114 (18) (n=122)	40 (4) (n=127)
No bronchodilators	46	48·9 (2·0)	57	28	48	43	92 (28) (n=34)	29 (5) (n=40)
Total	186	52·8 (1·0)	54	35	35	60	109 (15) (n=156)	38 (3) (n=167)

*p<0·05; age of asthmatics requiring bronchodilators *v* age of those not requiring bronchodilators.
†p=0·066; percentage of smokers requiring bronchodilators *v* percentage of smokers not requiring bronchodilators.
‡The quantity of cigarettes smoked and alcohol consumed was not known with certainty in 30 patients.
Asthmatics on bronchodilators were similar to asthmatics not on bronchodilators in all variables tested except for age, which was significantly greater by five years in the bronchodilator group.

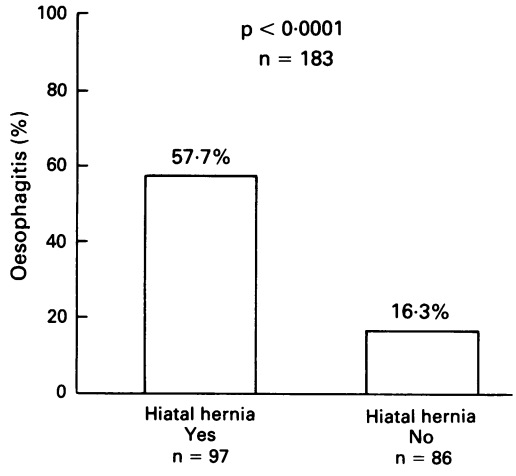

Figure 4: Percentage of patients with oesophagitis according to the presence of hiatal hernia. Oesophagitis was present in a significantly greater percentage of asthmatics with hiatal hernia (57·7%) than without hiatal hernia (16·3%) (χ^2=33·2; p<0·0001; odds ratio=7·0; confidence interval= 3·5–14·2).

ence of oesophagitis in the adult asthmatic population. The design of the study was based on firm methodology: (1) the asthma was well defined and well documented; (2) the selection pattern included only asthmatics whose primary complaint was asthma; (3) all consenting asthmatics were studied; and (4) all endoscopies were performed by two endoscopists using the same predefined criteria. The definition of 'consecutive' or 'non-selected' asthmatics was strictly adhered to by excluding from the study all those referred for investigation because of gastrointestinal signs or symptoms. Because most of our patients were men (96%), our observations may apply only to the male population.

Numerous investigators have studied the relation between GOR and asthma.[1-12] Reported mechanisms by which GOR and asthma may be related include (1) activation by GOR of a vagal reflex arc from the oesophagus to the lung resulting in bronchoconstriction[10 18-24]; and (2) microaspiration of gastric contents into the lung resulting in an exudative mucosal reaction.[8 18 25 26] Indeed, reports showing a reduction, or even disappearance of the asthma with surgical repair or medical management of the reflux have further strengthened support for a GOR-asthma association.[27-30]

Our results do not clarify the nature of the GOR-asthma relation or the mechanisms of reflux induced asthma. The high frequency with which oesophageal mucosal disease occurs in asthmatics is consistent with both the vagal reflex theory and the microaspiration theory, and does not support one more than the other.

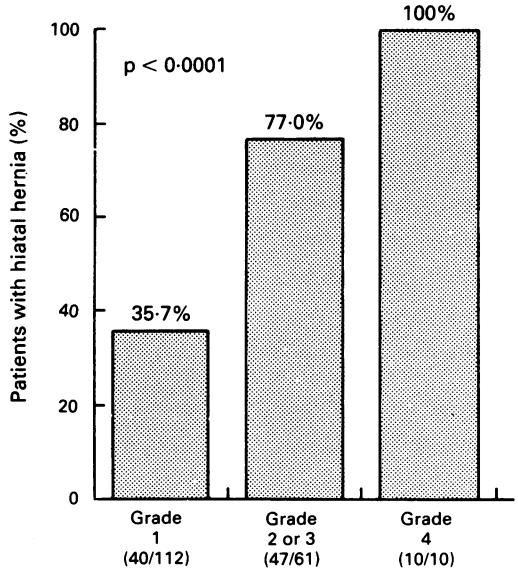

Figure 5: Hiatal hernia and grade of oesophageal mucosa in patients with asthma. There was a stepwise increase in the percentage of asthmatics with hiatal hernia as the oesophageal mucosal status worsened (χ^2=36·6; p<0·0001). N=183; the status of hiatal hernia was uncertain in 3 subjects.

Few data are available on either the prevalence of oesophageal mucosal disease in asthmatics or the effect of bronchodilator therapy on the oesophageal mucosa. Several investigators have concluded that bronchodilator therapy may adversely affect GOR by decreasing the LOS pressure.[31-37] However, two recent placebo controlled studies using prolonged oesophageal pH monitoring failed to show any effect of theophylline[38 39] or β agonists[38] on the severity of GOR parameters. Furthermore, we previously showed that asthmatics, when compared with normal subjects, had diminished LOS pressures and significantly greater acid reflux that was not a result of the bronchodilator therapy.[13] Thus, this study, which shows that asthmatics dependent on chronic bronchodilator therapy have a prevalence of oesophagitis similar to asthmatics who are not dependent on this, supports the conclusion that long standing use of bronchodilators does not adversely affect the oesophageal mucosa in asthmatics.

We also showed that hiatal hernia was present in 58% of asthmatics. In asthmatics with oesophagitis, a hiatal hernia occurred seven times more frequently than in asthmatics without oesophagitis. Thus, hiatal hernia in asthmatics is associated with more severe oesophageal mucosal disease. It remains to be determined whether the presence of hiatal hernia, oesophagitis, or both, is a useful indicator of reflux induced or reflux exacerbated asthma.

We recognise the inherent limitations of our study. These limitations, which have the potential to bias the results, are concerned with the techniques used to select patients for study, the methods used to ensure a representative sample of oesophageal mucosal diseases, and the technique employed for diagnosing the presence or absence of hiatal hernia. Such limitations are referred to as patient selection bias, spectrum bias, and observer (signal detection) bias, respectively.

Firstly, patient selection bias would have affected the results if we 'picked and chose' (either consciously or unconsciously) which patients were to receive endoscopic examination.[40-43] If asthmatics with reflux were somehow more readily influenced to have endoscopy than asthmatics without reflux, our results would apply only to a selected group of asthmatics, and selection bias would be present. We attempted to avoid this bias by offering endoscopy to every asthmatic patient regardless of the presence or absence of reflux symptoms. In addition, we eliminated from the study all patients who were referred because of reflux symptoms even though they had asthma. We suggest that since 94% of the asthmatics consented to endoscopy, selection bias was unlikely to be a major factor in biasing our results.

Secondly, spectrum bias, which could occur if more asthmatics with severe asthma than without severe asthma were included in the study. This appears to be a common problem in clinical samples.[40-43] Spectrum bias is unlikely to have

influenced our results for two reasons: (1) almost all the asthmatics agreed to be studied (only 6% refused endoscopy) and (2) one quarter of the asthmatics did not require chronic bronchodilator therapy, indicating that not all the patients had severe asthma.

Thirdly, observer (signal detection) bias, which may occur when a particular sign or symptom signals the observer to look more intensely for another sign or symptom. For instance, observer bias would have occurred in our study if the endoscopist had looked more intensely for a hiatal hernia after noting that oesophagitis was present. In such circumstances, the presence of observer bias would increase the magnitude of the association between oesophagitis and hiatal hernia. Indeed, when compared with asthmatics without oesophagitis, asthmatics with oesophagitis had a sevenfold increase in the frequency of hiatal hernia. Although all the endoscopic examinations were performed by two endoscopists using the same criteria, there is still the possibility that observer bias was present. Unfortunately, we did not anticipate the importance of observer bias, and we did not arrange for third party blinded observation.

Nevertheless, regardless of hiatal hernia, the high prevalence of oesophagitis in asthmatics and the apparent lack of effect of bronchodilators on the oesophageal mucosa are important clinical observations that provide additional evidence for a close relation between GOR and asthma.

In summary, oesophageal mucosal disease as manifest by the presence of endoscopic oesophagitis or Barrett's oesophagus, or both, is present as a result of GOR in 39% of unselected asthmatics. The chronic use of bronchodilator therapy does not seem to influence adversely the oesophageal mucosal disease.

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