Turk J Gastroenterol 2005; 16 (4): 199-202

Does acid reflux cause pulmonary disease?

Asid reflü akciğer hastalığına neden olur mu?

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Background/aims: *Gastroesophageal reflux is considered as a factor in pulmonary diseases. The aim of this study was to assess whether gastroesophageal reflux is associated with abnormalities in lung function in patients without respiratory disease.* ***Methods:*** *Forty- four patients with reflux symptoms were studied prospectively. Standardized methods of esophageal manometry and ambulatory 24-h esophageal pH testing were used throughout the study period, along with a standardized reflux and respiratory symptom questionnaire. Spirometric measurements were performed in all patients.* ***Results:*** *Reflux to distal esophagus was observed in 9 patients, to proximal esophagus in 4 and to both distal and proximal in 20 of the 44 patients. Eleven patients revealed reflux neither to distal nor proximal esophagus. Respiratory function tests of these groups showed no significant differences (p>0.05).* ***Conclusion:*** *There is no correlation between esophageal acid events and respiratory function tests. There are no data to answer the question of whether or not reflux precedes onset of cough/asthma. Better-designed prospective cohort studies may provide further insight.*

Key words: Esophageal pH testing, gastroesophageal reflux, airway function

Amaç: *Gastroesophageal reflu, akciğer hastalıklarının oluşumunda sorumlu faktörlerden biri olarak düşünülmektedir. Bu çalışmanın amacı; solunum yolu hastalığı olmayan olgularda gastroözofageal reflünün solunum fonksiyon bozukluğu ile ilişkisi olup olmadığını araştırmaktır.* ***Yöntem:*** *Reflü semptomları olan 44 olgu prospektif olarak çalışmaya alınmıştır. Olguların tümüne özofagus manometrisi, 24 saatlik pH monitorizasyonu ve spirometri yapılmıştır.* ***Bulgular:*** *Distal özofagusa patolojik reflü 9 olguda, proksimal özofagusa reflü 4 olguda, hem distal hem proksimale reflü 20 olguda tespit edilmiştir. On bir olguda ne distale ne proksimale patolojik reflü izlenmemiştir. Bu gruplar arasında solunum fonksiyon testleri açısından anlamlı farklılık gözlenmemiştir (p>0.05).* ***Sonuç:*** *Özofagusa asid reflüsü ile solunum fonksiyon testleri arasında anlamlı bir ilişki bulunmamıştır. Asit reflünün asthmayı başlatıp başlatmadığına dair yeterli veri yoktur. Bu konuda yapılacak daha ileri çalışmalara gereksinim vardır.*

Anahtar kelimeler: Özofageal pH testi, gastroözofageal reflü, solunum fonksiyon testleri

INTRODUCTION

It has been speculated that gastroesophageal reflux (GER) is a risk factor for extraesophageal pulmonary complications. The relation between GER disease (GERD) and asthma, cough and other pulmonary disease is unclear. It is frequently coexistent, and may be causative or may exacerbate preexisting lung disease (1).

The simultaneous occurrence of GER and asthma suggests a causal relationship. The aspiration of gastric contents or a vagally mediated bronchoconstriction has been suggested as an explanatory mechanism. Chronic inflammation in the lung parenchyma may progress to pulmonary fibrosis with airway obstruction and gas exchange impairment. In the airways, it may also cause airway hyperresponsiveness (2).

There are no data to answer the question of whether or not reflux precedes onset of cough/ asthma. The reported high prevalence of GER in a variety of respiratory diseases has led some investigators to argue that a causative relationship underlies the association.

The aim of this study was to assess whether GER is associated with abnormalities in lung function in patients without respiratory disease using 24-h esophageal pH testing.

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Manuscript received: 10.05.2005 **Accepted:** 16.08.2005

MATERIALS AND METHODS

Forty-four patients with reflux symptoms presenting to the Gastroenterology Outpatient Department of Yüksek İhtisas Hospital from February 2003 through January 2004 participated in the study. Nineteen of the patients (43.2%) were male and 25 (56.8%) female. The mean age was 47.1 years (range, 25 to 65). None of the patients smoked. Endoscopic findings were normal in all of the patients included in this study.

Exclusion criteria included the following: (1) respiratory disorders; (2) known esophageal disease such as cancer, achalasia, stricture; (3) active peptic ulcer disease; (4) history of esophageal or gastric surgery; (5) scleroderma.

Standardized methods of esophageal manometry and ambulatory 24-h esophageal pH testing were used throughout the study period, along with a standardized reflux and respiratory symptom questionnaire. After an overnight fast, esophageal manometry (8 channel, dent-sleeve catheter, water perfusion) was performed in all patients to localize the lower esophageal sphincter (LES).

pH Recordings were made using single-use antimony pH catheters (Zinectics Medical, Salt Lake City , USA) that have two channels for pH monitoring. pH electrodes, 15 cm apart, were calibrated before each procedure. A pH probe was passed transnasally into the stomach and then slowly withdrawn, and a distal pH electrode was positioned 5 cm above the LES. pH was monitored 5 and 20 cm above the LES, and was stored at 4 s intervals using a portable recorder (Digitrapper Mk III; Synectics Medical). All patients were asked to stop possible antacid, H2-blocker, prokinetic, or proton pump inhibitor medications at least three days before pH monitoring, and they were also told to avoid these drugs during the monitoring. During pH monitoring, the patients carried on their normal daily routines. During the 24-hour measurement, patients indicated on the records their meals, sleep periods and beginning of the complaints as heartburn. No dietary restriction was used.

After ambulatory recording, the data was downloaded into an IBM-compatible computer using appropriate analysis software. DeMeester score (3) was used for the distal esophagus. In this software program, pH falls less than 4 above the LES, % duration of pH falls in upright and supine position, reflux rates, number of the pH falls lasting more than 5 minutes, and longest reflux episodes were taken into consideration and scored. pH monitoring was considered to be abnormal if total time pH < 4 was > 4.5% or if the > 14.7 (3). For the proximal esophagus, pH less than 4 lasting more than 1% of the total time was accepted as pathologic. Any proximal pH falls did not accompany the falls in the distal esophagus were not taken into consideration (4).

Spirometry was measured using Vmax 229 (Sensormedics, USA). Values for forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and FEV_1% are reported as percent predicted values. Spirometric measurements were performed three consecutive times and the highest value was recorded. A respiratory scientist who was blinded to the presence or severity of GER performed these measures.

For the statistical analysis between the groups, Student's t, X^2 and Mann-Whitney U tests were used.

RESULTS

Thirty-three of 44 patients (75%) were found to have pathologic GER in the ambulatory esophageal pH recording. A comparison of the patients with and without GER is shown in Table 1.

Reflux to distal esophagus was observed in nine patients, to proximal esophagus in four and to both distal and proximal in 20 of the 44 patients. Eleven patients revealed reflux neither to distal nor proximal esophagus. Respiratory function tests (RFT) of these groups revealed no significant differences ($p>0.05$) in FEV_1, FVC, PEF, FEV_1%, VC and forced expiratory flow (FEF) (25-75) (Table 1).

Table 1. The association between reflux and respiratory functional tests

	FEV_1 Mean ±SD	FVC Mean ±SD	PEF Mean ±SD	FEV_1/FVC Mean ±SD	VC Mean ±SD	FEF 25-75 Mean ±SD
Proximal & distal GER 20 (45.5%)	89.4±35.4	92.3±40.1	75.5±29.8	105.1±31.9	96.6±61.4	80.8±41.1
GER (-) 11 (25%)	96.9±26.8	91.8±22.4	73.2±27.3	107.7±11.9	92.3±24	86.9±26.4
Proximal GER (+) 4 (9.1%)	86.7±27	81.5±20.4	77.5±37.1	107.5±13.5	93.5±12.9	85.5±49.2
Distal GER (+) 9 (20.5 %)	91.2±30	87±18.2	82.5±28.2	108.1±19.5	86.3±15.8	88.8±35.2

Table 2. A comparison of type of reflux and respiratory function test (RFT) (FEV_1)

Patients	Impaired RFT n	Normal RFT n	Total
Proximal & distal GER	11	9	20
GER (-)	8	3	11
Proximal GER (+)	2	2	4
Distal GER (+)	6	3	9
Total	27	17	44

Of the 44 patients participating in the study, 27 (61.4%) patients had normal RFT, 10 (22.7%) had mild restriction, 4 (9.1%) had mild obstruction, 1 (2.3 %) had mixed type, 1 had moderate restriction, and 1 had moderate obstruction. When these groups were compared in terms of reflux incidence, no significant difference was observed (p: 0.209) (Table 2).

Table 3 shows esophageal parameters in the two groups. There were no differences in esophageal manometry and esophageal pH tests in those with impaired versus normal RFT.

Table 3. Esophageal manometry and 24-h esophageal pH results in impaired and normal respiratory function test (RFT) patients

	Impaired RFT (17)	Normal RFT (27)	P
Esophageal manometry			
LES pressure, mmHg (nl>10 mm Hg)	11.07 ± 6.5	10.6 ± 8.4	.836
Mean amplitude contractions, mm Hg	70 ± 3.8	77 ± 12	.800
Esophageal pH			
Distal probe			
Total (nl< 5.5%)	8.6 ± 7.0	7.1 ± 6.3	.458
Upright (nl<8.1%)	9.7 ± 8.7	7.9 ± 7.6	.475
Supine (nl<3 %)	8.9 ± 6.9	18.0 ± 10.8	.639
No of episodes >5 min (nl<4)	4.6 ± 3.7	26.6 ± 32	.832
Longest episodes, min (nl<18)	28.3 ± 31.7	26.6 ± 32	.862
Proximal probe			
Total (nl<1.1%)	1.5 ± 3.1	0.9 ± 4.0	.650
Upright (nl<1.7%)	1.3 ± 2.3	1.3 ± 4.6	.948
Supine (nl<0.6%)	3.2 ± 9.2	1.6 ± 8.1	.559
No of episodes >5 min (nl<0)	0.8 ±1.7	0.7 ±1.9	.839
Longest episode, min (nl<3)	6.8 ± 10.6	11.2 ± 39	.653

LES: Lower esophagal sphincter

DISCUSSION

It has been speculated that GERD is a risk factor for extraesophageal pulmonary complications. Suspected reflux-related supraesophageal symptoms and disorders such as choking, sore throat, hoarseness, asthma, nocturnal cough, and nocturnal dyspnea may result from reflux of gastric contents into the distal and proximal esophagus and into the pharynx and airways (5, 6). Therefore, measuring proximal acid reflux may be useful in the evaluation of patients with suspected reflux-related supraesophageal symptoms. However, the relation between GERD and pulmonary diseases is unclear.

In this study RFTs were evaluated in acid reflux-positive and -negative patients diagnosed with 24 h pH monitorization. RFTs of reflux-positive patients were not significantly different from those of reflux-negative patients. Both lung disease and GER have a high prevalence worldwide, and these conditions are frequently coexistent.

The studies performed to date are mostly based on reflux incidence in patients with pulmonary diseases. Epidemiologic studies show a moderate association between GERD and a range of pulmonary symptoms. A cross-sectional study of heartburn prevalence in 2,200 participants showed that incidence of pulmonary symptoms was slightly elevated among those with frequent GERD compared to those without GERD (7). A case-control study including over 100,000 cases compared rates of pulmonary disease among patients with erosive esophagitis and/or esophageal stricture (8). Increased risk for several extraesophageal conditions was significantly associated with esophagitis, including asthma, chronic obstructive pulmonary disease, bronchiectasis and pneumonia (8). An international cross-sectional study in 2,661 individuals found that, compared with those without GERD, individuals with GERD had increased risk of pulmonary conditions like wheezing, nocturnal cough, and chest tightness (9). In this study, association of GERD with physician-diagnosed asthma was marginally significant (OR=2.2; 95% CI, 1.04-4.70).

Other studies have demonstrated that GERD is highly prevalent in patients with asthma and that asthma symptoms correlate with severity of GERD (10, 11). While these studies show consistent association, they do not reveal a temporal relation of GERD and pulmonary symptoms. Furthermore, these studies show that pulmonary symptoms are frequent in the absence of GERD; therefore, GERD may be sufficient but not necessary to cause (or exacerbate) pulmonary symptoms.

On the other hand, the clinical usefulness of proximal ph monitoring remains unproven. It is unclear

which factors will determine the proximal extent of gastroesophageal reflux. Theoretically, several elements may be important: frequency of reflux in the distal esophagus, volume of the refluxate, esophageal body resistance, and esophageal clearance function. pH testing has the advantage of measuring the exposure time of the esophagus to excessive gastric acid and correlating these acid reflux episodes to patient symptoms. However, pH electrodes are able to measure exclusively hydrogen ion concentration at the sensor site; one of their greatest limitations is that non-acid refluxes are ignored. In recent years, multichannel intraluminal electrical impedance (MII) has been validated as a new technique for pH-independent detection of GER (12, 13). It provides a qualitative analysis of the various types of refluxate in that they are characterized by different conductivity. Its major advantages are to provide qualitative information on the different types of refluxate (gas, acid and non-acid liquid, mixed) and to know immediately the proximal extent of each single reflux event (13).

In conclusion, there are no data to answer the question of whether or not reflux precedes onset of cough/asthma. More work is required to identify the most useful esophageal tests and parameters that can best guide therapy. The addition of simultaneous impedance recording to detect nonacid reflux would be beneficial. Better-designed prospective cohort studies may provide further insight.

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