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Non-erosive reflux disease compared with erosive esophagitis with regards to acid reflux and symptom patterns

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Background/aims: *Non-erosive reflux disease and erosive esophagitis are the most common phenotypic presentations of gastroesophageal reflux disease. Recent reports suggest that patients with non-erosive reflux disease treated with antireflux medications show lower symptom improvement rates than patients with erosive esophagitis treated with the same medications. The aim was to assess the acid reflux and symptom patterns of patients with non-erosive reflux disease in comparison with those with erosive esophagitis and to identify different non-erosive reflux disease subgroups.* ***Material and Methods:*** *One hundred and twenty consecutive patients (67 male, age: 37.6±12.9 years) seen for classic heartburn symptoms were evaluated for the study. The patients underwent upper endoscopy and 24-hour ambulatory pH monitoring.* ***Results:*** *Erosive esophagitis was identified in 51 patients and non-erosive reflux disease in 69 patients. According to pH metric findings (DeMeester Score >14.72 or Fraction Time >4%), 31.9% of the non-erosive reflux disease group and 47.1% of the erosive gastroesophageal reflux disease group had abnormal acid reflux (p=0.134). Erosive esophagitis patients showed a similar pattern of acid reflux to non-erosive reflux disease patients in the different positions (supine and upright). Non-erosive reflux disease-negative (normal pH test) patients demonstrated a significantly lower degree of esophageal acid exposure when compared with those with erosive esophagitis. About 10.6% of the non-erosive reflux disease-negative patients and 45.5% of the non-erosive reflux disease-positive (abnormal pH test) patients had a positive symptom index (≥50%) during the distal pH metry (p=0.003).* ***Conclusions:*** *Acid reflux characteristics and symptom patterns suggest that the non-erosive reflux disease group represents a heterogeneous group of patients.*

Key words: Acid reflux, gastroesophageal reflux disease, non-erosive reflux disease, erosive esophagitis

Eroziv olmayan reflü hastalığı ile eroziv özofajitin asit reflüsü ve semptom özellikleri açısından karşılaştırılmaları

Amaç: *Eroziv olmayan reflü hastalığı ve eroziv özofajit gastroözofageal reflü hastalığının en sık karşılaşılan fenotipleridir. Güncel yayınlara göre antireflü tedavi verilen eroziv olmayan reflü hastalarının semptomlarındaki iyileşme oranları aynı tedavi verilen eroziv özofajit hastalarınınkine göre daha düşük olmaktadır. Bu çalışmanın amacı eroziv olmayan reflü hastalığı ve eroziv özofajit hastalarının semptom ve asit reflüsü paternlerini karşılaştırarak farklı eroziv olmayan reflü hastalığı gruplarının tespit edilmesidir.* ***Yöntem:*** *Göğüste klasik yanma semptomları nedeni ile görülen 120 ardışık (67 erkek, yaş: 37.6±12.9) hasta çalışmaya dahil edildi. Hastalara üst endoskopi ve 24 saat pH monitorizasyonu uygulandı.* ***Bulgular:*** *Ellibir hastada eroziv özofajit ve 69 hastada eroziv olmayan reflü hastalığı tespit edildi. Hastaların pH-metri takiplerine göre (DeMeester Skoru>14,72 veya fraksiyone süresi >%4), eroziv olmayan reflü hastalığı hastalarının %31,9'unda ve eroziv özofajit grubunun %47,1'inde anormal asit reflüsü tespit edildi (p<0.134). Farklı pozisyonlarda (Supin ve ayakta) eroziv özofajit hastalarının reflü paterni eroziv olmayan reflü hastalığı hastalarınınkine benzer bulundu. Asit reflüsü olmayan eroziv olmayan reflü hastalığı hastalarının (Normal pH testi) asit maruziyetleri eroziv özofajit hastaları ile karşılaştırıldıklarında belirgin düşük bulundu. Asit reflüsü olmayan eroziv olmayan reflü hastalığı hastaların %10.6'sında ve asit reflüsü olan eroziv olmayan reflü hastalığı hastaların %45.5'inde distal pH-metride pozitif semptom indeksi (≥%50) tespit edildi (p=0.003).* ***Sonuç:*** *Asit reflüsü karakteristikleri ve semptom paternlerinin sonuçlarına göre eroziv olmayan reflü hastalığı hastaları heterojen bie hasta grubudur.*

Anahtar kelimeler: Asit reflüsü, gastroözofageal reflü hastalığı, eroziv olmayan reflü hastalığı, eroziv özofajit

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Its prevalence has increased dramatically in recent decades, mostly in the Western world, where it affects about 10% to 30% of the population (1, 2). The prevalence of GERD varies from 2.6% to 20% in different areas around Iran, and it has shown an increasing trend (3-5).

Non-erosive reflux disease (NERD) and erosive esophagitis (EE) are the most common phenotypic presentations of GERD (6). NERD has been defined as the presence of typical symptoms of GERD in the absence of visible esophageal mucosal injury on endoscopy (7). For decades, investigators have presumed, based on physiological studies, that this group of GERD patients has a mild form of the disease (8). Patients with NERD tend to have a lower incidence of acid reflux events or a comparable esophageal acid exposure profile compared with patients with EE. Consequently, a much more conservative therapeutic approach has been suggested to be adequate for these patients. However, therapeutic trials in patients with NERD have consistently demonstrated lower efficacy in symptom control than what has been achieved in patients with EE (9). This unexpected response to therapy of NERD patients, which is also observed for proton pump inhibitors, is likely to be due to the diversity of patients who meet the broad definition of NERD.

Patients with acid exposure within the normal limits in the distal esophagus (37–60% of patients with NERD), described as suffering from functional heartburn, were the least likely to respond to anti-reflux treatment (10,11). These findings suggest that patients with functional heartburn are likely to be a heterogeneous group, with different characteristics on 24-hour (h) esophageal pH monitoring.

The aims of this study were to evaluate the different acid reflux and symptom patterns of patients with NERD compared with those with EE, and to determine whether there were identifiable potential subgroups of NERD patients suggesting a heterogeneous disorder.

MATERIALS AND METHODS

Consecutive patients who presented to the Gastroenterology Clinic, Taleghani Hospital, Shaheed Beheshti University, Tehran, Iran, who had typical heartburn symptoms (a burning feeling rising from the stomach or lower chest up towards the neck), were enrolled in the study. All subjects who agreed to participate signed an informed consent. Subsequently, subjects underwent an upper endoscopy to assess the presence of esophageal mucosal injury. Thereafter, ambulatory 24-h esophageal pH monitoring was carried out to quantify the extent of acid exposure in the distal and proximal esophagus. Based on the results of the upper endoscopy and pH testing, patients were divided into two major groups: EE and NERD. NERD was defined as proposed previously by the Genval Workshop (7). Further partition of the latter group was based on the results of 24-h esophageal pH testing. Those with an abnormal test were considered to be NERD-positive and those with values within the normal range were considered to be NERD-negative.

Patients who had Barrett's esophagus, gastric or duodenal ulcer, cancer in the upper gastrointestinal tract, history of operation of upper gastrointestinal tract, irritable bowel syndrome, severe cardiac or pulmonary diseases, diabetes, and rheumatic diseases were excluded. Patients were excluded if they were on non-steroidal anti-inflammatory drugs (NSAIDs) or had already been treated with a proton pump inhibitor (patients receiving H2-blockers were allowed to participate if treatment was discontinued 14 days prior to the initial evaluation). Patients were also excluded if they were unable to complete the 24-h esophageal pH monitoring, were unable or unwilling to fully complete all stages of the study, or were unable or unwilling to provide informed consent. The study was approved by the ethics committee of the hospital and was conducted in conformity with the Helsinki Declarations.

Upper Endoscopy

After an overnight fast, patients were placed in the left lateral position. Gastroscopy was performed with use of a PQ-20 or GIF-Q165 upper-gastrointestinal endoscope (Olympus Europa, Hamburg, Germany). The distal portion of the esophagus was carefully evaluated to determine the presence of mucosal injury. The stomach and duodenum were also inspected to exclude possible ulcers. The extent of esophageal mucosal damage was assessed using the Los Angeles grading system: Grades 0–1 were considered to be diagnostic of NERD and grades 2–4 of EE (12). Patients with grade 5 were excluded from the study.

Ambulatory 24-h Esophageal pH Monitoring

After an overnight fast, two pH probes with lower esophageal sphincter identifier (Digitrapper MK III, Medtronics, Minneapolis, MN, USA) were inserted through the nostril and into the stomach. One probe was positioned 5 cm and the other 10 cm above the upper margin of the lower esophageal sphincter and both were connected to a digital portable recorder. A reference electrode was attached to the upper chest. Patients were instructed to keep a diary recording meal times, position changes and the time and type of their symptoms. Patients were encouraged to pursue their normal daily activities and maintain their usual diet. At the beginning and end of the study, the electrode and the system were calibrated in standard solutions of pH 1 and pH 7. Reflux was defined as pH <4, and the reflux time as the interval until pH >4. The 24-h pH test was considered to be positive when the percentage total time pH <4 was greater than 4% or the DeMeester score was more than 14.72 for distal refluxes (13). Analysis of the recorded data was performed using standard, commercially available computer software (Medtronics).

The 24-h esophageal pH strips were closely evaluated for symptoms and their relationship to acid reflux events. The period spent in supine position was noted in the diary. The symptom index (SI) was calculated as the percentage of heartburn symptoms that occurred during an acid reflux event (pH <4). The SI was defined as the number of symptoms associated with reflux divided by the total number of symptoms. A positive SI (SI(+)) was declared if ≥50% (14).

Statistical Analysis

The statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA; Version 16). For all the continuous variables, the mean and standard deviation were presented. Student's t test was used to compare parametric quantitative variables and chi-square test or Fisher's exact test was used to compare the proportions. All p-values were two-tailed with the level of significance defined at 0.05.

RESULTS

One hundred and twenty patients (67 male, age: 37.6±12.9 years) with typical symptoms of heartburn who met the inclusive criteria were enrolled: 69 were found to have NERD and 51 EE. The demographics of the patients in each group are presented in Table 1. There was no difference concerning the male to female ratio and mean age among these two groups, while significant difference was obtained in body mass index. In the EE group, 32 patients had grade A esophagitis, 17 patients grade B esophagitis, and 2 patients grade C esophagitis.

Parameters of pH metry were compared among the groups, including DeMeester score, acid reflux episodes in different body positions and percentage time of esophageal pH value <4 in different body positions; values were also compared according to supine and upright position changes (Table 2). In erosive GERD patients, while the mean level of all distal PH metry parameters, including frequency of acid reflux episodes, fraction of time for pH <4, SI, and DeMeester score, in both upright and supine positions, were higher than in NERD patients, these differences were not statistically significant. Also, proximal pH metric findings demonstrated no significant differences between the two groups. In both groups, pH metric findings in the upright position were higher than in the supine position, but this difference was not statistically significant (p>0.05 for all comparisons). In each group, frequency of acid refluxes episodes, fraction of time for pH <4, SI, and the DeMeester score at the distal level were significantly higher than at the proximal level (p<0.05 for all comparisons). Twenty-two NERD patients (31.9%) demonstrated an abnormal 24-h pH test (NERD-positive), in comparison with 24 (47.1%) with EE (p>0.05).

NERD-positive patients had a higher fraction of time for pH <4 in all positions than NERD-negative patients at distal (upright, 9.7±6.1 vs. 1.6±1.2; supine, 1.6±3.7 vs. 0.4±0.4; p<0.0001, p=0.14, respectively) and proximal levels (upright, 6.2±11.1 vs. 1.1±1.1; supine, 4.2±5.4 vs. 0.5±0.5; p=0.05, p=0.005). Even though NERD-positive patients demonstrated more esophageal acid exposure and

Table 1. Demographics of the patients with gastroesophageal reflux disease

	NERD	EE	P value
n	69	51	
Gender (male/female)	37/32	30/21	0.321
Mean age (years)	37.6±12.8	37.6±12.9	0.986
Age range (years)	15-68	15-65	
Body mass index	23.4±3.5	24.7±3.2	0.031

NERD: Non-erosive reflux disease. EE: Erosive esophagitis.

Table 2. Comparison of acid reflux patterns and gastroesophageal reflux disease symptoms in patients with non-erosive reflux disease (NERD) and erosive esophagitis (EE) undergoing pH testing

24-h pH test	NERD	EE	P value
n	69	51	
Abnormal pH test	22 (31.9%)	24 (47.1%)	.134
No. of patients reporting heartburn at pH <4	32 (46.4%)	25 (49%)	.459
Distal			
Symptom index	19.75±26.44	25.87±32.24	.256
No. with symptom index ≥ 50% (% of those reporting symptoms)	15 (21.7%)	12 (23.5%)	.493
Mean no. of acid reflux events			
Upright	65.5±63.6	94.0±161.6	.185
Supine	14.3±31.9	21.9±34.9	.211
Fraction of time for pH <4			
Upright	4.21±5.19	6.06±8.86	.188
Supine	.75±2.11	.67±.96	.775
DeMeester score	17.93±29.15	23.45±34.15	.342
Proximal			
Symptom index	15.92±26.79	12.67±21.7	.483
No. with symptom index ≥ 50% (% of those reporting symptoms)	9 (13.0%)	6 (11.8%)	.532
Mean no. of acid reflux events			
Upright	40.64±42.23	39.09±36.97	.837
Supine	9.32±29.05	13.70±34.77	.458
Fraction of time for pH <4			
Upright	2.71±6.59	2.69±5.70	.986
Supine	1.70±3.47	1.82±2.64	.828
DeMeester score	11.09±28.07	11.61±21.91	.913

acid reflux events than EE patients, there was no statistical difference between them during the pH test (Table 3).

Patients with EE had a higher mean number of acid reflux events compared with NERD-negative patients. Moreover, patients with EE had higher fraction of time for pH <4 in both upright and supine positions (Table 4).

Patients with EE more commonly reported heartburn symptoms at pH <4 during pH testing (49%) than those with NERD (46%), although the difference was not statistically significant (p=0.459). Of the NERD patients, 19 (40.4%) NERD-negative subjects and 13 (59.1%) NERD-positive subjects had symptoms of heartburn at pH <4 during the pH test. Despite the fact that NERD-negative patients demonstrated less esophageal acid exposure than NERD-positive patients, there was no statistical difference in the mean number of reported heartburn symptoms among the subgroups during the pH test (p=0.197). Of these, 10.6% of the NERD-negative patients and 45.5% of the NERD-positive patients had a positive SI (≥50%) during the distal pH metry (p=0.003). Therefore, the majority of NERD-negative subjects had heartburn unrelated to acid reflux (SI <50%).

The mean number of distal acid reflux events in the upright position during 24-h pH testing was significantly higher in the NERD–SI(+) group than in the NERD–SI(–) group (p<0.001 for distal and p=0.01 for proximal). However, there was no statistically significant difference in the acid reflux events in the supine position and time for pH <4 between the two groups (p>0.05).

DISCUSSION

In this study, acid reflux patterns of patients with NERD and EE were compared using ambulatory 24-h esophageal pH monitoring. The percentage of EE patients with pathologic acid reflux in our study tended to be higher than in NERD patients, but this difference was not statistically significant. Martinez et al. (15) also reported a higher percentage of abnormal pH test in EE patients compared with NERD patients. Unlike patients with EE and Barrett's esophagus, NERD patients with normal

Table 3. Comparison of acid reflux patterns and gastroesophageal reflux disease symptoms in non-erosive reflux disease-positive (NERD+) and erosive esophagitis (EE) patients undergoing pH testing

24-h Ph test	NERD	EE	P value
n	22	51	
Abnormal pH test	22 (100%)	24 (47.1%)	
No. of patients reporting heartburn at pH <4	13 (59.1%)	25 (49%)	.456
Distal			
Symptom index	32.64±32.17	25.88±32.25	.413
No. with symptom index ≥ 50% (% of those reporting symptoms)	10 (45.5%)	12 (23.5%)	.094
Mean no. of acid reflux events			
Upright	131.04±69.96	94.04±161.63	.307
Supine	35.45±50.32	21.98±34.92	.262
Fraction of time for pH <4			
Upright	9.73±6.10	6.06±8.86	.082
Supine	1.59±3.66	.67±.96	.266
DeMeester score	42.93±41.83	23.46±34.15	.041
Proximal			
Symptom index	27.15±33.81	12.68±21.71	.081
No. with symptom index ≥ 50% (% of those reporting symptoms)	6 (27.3%)	6 (11.8%)	.165
Mean no. of acid reflux events			
Upright	40.64±42.43	39.09±36.98	.837
Supine	22.91±49.44	13.71±34.77	.266
Fraction of time for pH <4			
Upright	6.16±11.07	2.69±5.70	.185
Supine	4.17±33.81	1.82±2.64	.063
DeMeester score	25.30±47.49	11.61±21.91	.218

ambulatory 24-h esophageal pH monitoring may not represent a false-negative test. In our study, approximately 47% of NERD patients had a pH test within normal limits. Other investigators have reported similar results, suggesting that NERD patients include a large subgroup with pH values that fall within the normal range (16).

We found that EE patients showed a similar pattern of acid reflux to NERD patients in the different positions (supine and upright). In addition, as a group, NERD-negative patients demonstrated a significantly lower degree of esophageal acid exposure when compared with those with EE. However, when NERD-positive patients were compared with the other GERD groups, the degree of acid exposure in the different positions and the number of acid reflux events were similar to those of patients with EE. These results may suggest that the NERD group represents a mixture of two main types of patients: those with abnormal acid reflux and symptom patterns similar to those of patients with EE, who fit the more classic form of GERD, and those with acid reflux patterns that fall within the physiological range. NERD-negative patients (normal pH test) have been labeled by other authors as having "functional heartburn". The lack of esophageal mucosal breaks in NERD-positive patients is probably due to the preservation of local mucosal defensive mechanisms, as well as other factors that have been shown to play an important role in preventing mucosal damage (17). In the study by Martinez et al. (15), EE patients showed a higher incidence of acid reflux episodes compared with NERD patients However, when only NERD-positive patients (abnormal pH test) were taken into consideration, the degree of acid exposure and the number of acid reflux events were similar to those of patients with EE. Another possible explanation for the lack of differences in reflux patterns between EE and NERD patients in our study could be that most EE patients had low-grade esophagitis, because it has been demonstrated that patients with low-grade esophagitis and NERD patients have similar underlying reflux mechanisms (15). It can be argued that the similarities between EE and NERD patients found in

Table 4. Comparison of acid reflux patterns and gastroesophageal reflux disease symptoms in non-erosive reflux disease-negative (NERD-) and erosive esophagitis (EE) patients undergoing pH testing

24-h Ph test	NERD	EE	P value
n	47	51	
Abnormal pH test	0 (0%)	24 (47.1%)	
No. of patients reporting heartburn at pH <4	19 (40.4%)	25 (56.8%)	.422
Distal			
Symptom index	13.73±21.09	25.88±32.25	.029
No. with symptom index ≥ 50% (% of those reporting symptoms)	5 (10.6%)	12 (23.5%)	.114
Mean no. of acid reflux events			
Upright	34.83±26.94	161.63±22.63	.013
Supine	4.34±6.19	21.98±34.92	.001
Fraction of time for pH <4			
Upright	1.63±6.19	6.06±8.86	.001
Supine	.37±.36	.67±.96	.042
DeMeester score	6.24±4.37	23.46±32.25	.001
Proximal			
Symptom index	10.69±21.29	12.68±21.71	.651
No. with symptom index ≥ 50% (% of those reporting symptoms)	3 (6.4%)	6 (11.8%)	.286
Mean no. of acid reflux events			
Upright	.09±.35	.53±2.48	.025
Supine	3.13±5.11	13.71±34.77	.036
Fraction of time for pH <4			
Upright	1.14±1.12	2.69±5.70	.062
Supine	.54±.50	1.82±2.64494	.001
DeMeester score	4.61±3.97	11.61±21.91	.029

the current study could also be due to a type II statistical error because of the relatively small number of patients included in the study.

Frazzoni et al. (18) reported a greater esophageal acid exposure in EE patients compared with NERD patients only in the supine position. They concluded that nocturnal acid reflux occurring in the recumbent position has the highest probability of damaging the esophageal mucosa as the loss of gravity is coupled with the absence of primary peristalsis and salivation during sleep. In the study of Kuran et al. (19), reflux was observed especially in the upright position, and they explained that transient lower esophageal sphincter relaxation, which is an important factor in reflux pathogenesis, occurs especially in the upright position, which may account for this finding (20).

Laryngopharyngeal reflux is one of hot topics in GERD research these days. We showed that EE and NERD patients had equivalent proximal reflux events. The study by Conchillo et al. (21) also yielded similar findings. Meanwhile, EE patients were observed to have more proximal reflux than NERD patients in the study by Xiao et al. (22), which differed from the study by Cicala et al. (23), in which NERD patients had more proximal reflux instead. The difference might result from diverse inclusion criteria.

Some investigators have already shown that NERD-positive patients are more likely to report symptoms during pH testing than NERD-negative patients (24). We found that NERD-positive patients were more likely to have a high SI (50%) than were NERD-negative patients. The latter may suggest that some NERD-negative patients experience heartburn that is not related to acid reflux. When the NERD-negative group was further stratified on the basis of their calculated SIs, those with a negative SI reported having heartburn at pH <4 only 40.4% of the time, compared with 59.1% of the time in those with a positive SI. These data further support the concept that NERD patients with a negative SI are likely to include a group with heartburn that is not due to acid reflux, and NERD-negative patients with a positive SI may represent a potential group with altered

pain perception by increased chemoreceptor sensitivity to acid. There is a growing body of literature demonstrating non-acid-related stimuli that cause classic heartburn. On the other hand, non-acid-related stimuli such as duodenogastroesophageal reflux, mechanosensitivity, motor events, and reflux content (intraduodenal fat content) may result in heartburn in normal subjects and patients with GERD (25,26).

It should be noted that the setting of our study was a large hospital with both secondary care (general gastroenterology clinic, referrals from general practitioners) and tertiary care (specialized motility clinic, referrals from specialists) functions. The findings are not necessarily relevant to primary care dyspeptic patients, and this limitation that should be taken into account when generalizing our findings.

In summary, this study evaluated the acid reflux characteristics and symptom patterns of patients with NERD compared with those of patients with EE. We found that EE patients showed a similar pattern of acid reflux to NERD patients, but NERD-negative patients demonstrated a significantly lower degree of esophageal acid exposure when compared with those with EE. The majority of NERD-negative subjects had heartburn unrelated to acid reflux (SI <50%). It is needed to further define the different subgroups of patients who meet the broad definition of NERD. Such information may force us to rethink our current definitions of NERD and improve our understanding of the pathophysiology and therapy of this disorder.

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