



Study of Esophageal Changes in Gastroesophageal Reflux Disease in young Adult Patients

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ABSTRACT

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Background: According to the Montreal definition, gastroesophageal reflux disease (GERD) is “a condition in which stomach contents reflux into the esophagus, causing unpleasant complications and symptoms.” The purpose of this research is to learn more about the esophageal alterations related with GERD in young adults.

Patients and Methods: In this study, 70 patients (36 males and 34 females) complaining of classic gastroesophageal reflux symptoms were included. In addition to 30 persons (16 males and 14 females) without esophageal symptoms and normal upper GI endoscopy results as controls, all were subjected to a clinical assessment followed by upper GI endoscopy with multiple esophageal biopsies obtained 2-3 cm above the squamocolumnar junction. All of them underwent 24-hour pH metry and esophageal motility studies.

Results: The occurrence of erosive esophagitis was shown to have a statistically significant positive connection with male gender, age group (greater in age >30), and hiatus hernia in the current study. Esophagitis has no statistically significant link to H. pylori infection, medicine intake, coffee use, or smoking. Age, female sex, coffee use, smoking, and Hiatus hernia are all linked to frequent reflux symptoms.



Conclusion: There is a strong link between the global severity score obtained for all biopsies and the time spent below pH 4.0 during the whole monitoring period. In addition, the global severity score and the 24-hour composite pH score have a clear connection (DeMeester Score). As a result, histology's diagnostic significance in GERD in young adult patients should be reassessed.

Keywords: Gastroesophageal reflux disease; gastrointestinal; erosive esophagitis; proton pump inhibitors

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Introduction:

GERD is described as symptoms or lesions produced by stomach contents flowing backwards into the esophagus, according to [1]. The frequency of reflux episodes, the proximal extent to which the refluxate migrates, the acidity of the refluxate, esophageal hypersensitivity, and cognitive hypervigilance are all variables that might induce GERD symptoms. As a result, depending on the clinical setting, pathology, physiology, or symptomatology might be used to define GERD [2]. Reflux disease is linked with many histologic alterations, many of which are the result of acid injury and mucosal repair [3]. Biopsy offers tissue to rule out other probable

Aim of the work: The study's objective is to learn more about esophageal changes in young adult patients with typical GERD symptoms using clinical, endoscopic, histological, manometric, and ambulatory monitoring of the pH for 24-hour.

SUBJECTS AND METHODS

Subjects:

This prospective non randomized controlled research included 70 patients who had the typical symptoms of GERD (36 male, 34 female). In addition to 30 persons (16 males and 14 females) without esophageal symptoms and normal upper GI endoscopy results as controls, patients were recruited from the endoscopy units of Al-Azhar University Hospitals and Mansoura University Hospitals during the period from March 2020 to August 2021. Eligible persons were offered a place in the study and both; informed and written consent were collected. Patients who have one of the following are excluded from the study: Previous history of upper abdominal surgery, Esophageal varices,

diagnoses such as malignancy, infection, drug damage, or bullous disease when macroscopic abnormalities, such as a stricture or ulceration, are present. The Rome IV agreement recommended esophageal biopsies during upper endoscopy (EGD) to rule out eosinophilic esophagitis.⁴An EGD is recommended when suspected GERD symptoms do not respond to empiric PPI therapy, to rule out other illnesses that may require therapeutic redirection. According to Roman et al. (2017), high-grade esophagitis (LA grades C or D), Barrett's esophagus, or a peptic structure are all strong indicators of GERD [5].

uncontrolled significant co morbidities: (scleroderma and other collagen disorders, psychiatric disorders, diabetes mellitus, decompensated hepatic disease, hematological diseases with bleeding tendency, advanced cardiopulmonary disease, decompensated heart failure, renal failure and malignancy), age less than 18 years or over 35 years, Patients were classified into (2) groups: Group (1): include 70 patients with the typical symptoms of GERD (36 male, 34 female). Group (2): include 30 subjects (16 males and 14 females) without esophageal symptoms and normal upper GI endoscopy results as controls.

Methodology: The following was done to all of the patients:

1-Complete medical history: All participants were asked about the frequency and severity of clinically relevant gastrointestinal symptoms during the previous 12 months. Symptoms of heartburn and acid regurgitation were classified into two groups: often (at least 2 days per week) and seldom (fewer than 2 d/w) (symptoms for less than 2 d/w).

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2-Thorough clinical examination including: General examination and anthropometric measurements were taken, which included body weight, height, waist circumference (WC), and hip circumference. By dividing the weight in kilos by the square of the height in meters, the BMI was calculated. The breadth of the chest was measured at the midway between the lowest rib and the iliac crest.

3-Investigations: A full blood count (CBC) The hemoglobin level was determined using an automated blood cell counter (ADVIA 120, Bayer, NY, USA), the lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and S. creatinine and blood urea levels were determined using an automated chemistry analyzer for the enzymatic reactions (Toshiba TBA-120 FR, Toshiba Medical Systems, Tokyo, Japan), and fasting blood glucose levels were determined using an (FBG).

4-Upper GI endoscopy: Upper GI endoscopy was done for all subjects in the study using Olympus type endoscopy PQ20 and pantax endoscopy. **A)-** Multiple esophageal biopsies was obtained from each subjects using esophageal biopsy forceps (ACMI Martin biopsy forceps), 2-3 cm above the squamocolumnar junction (the Z line). Also, an antral biopsy was taken for detection of *H. pylori*. **B)-** Gross endoscopic symptoms of gastroesophageal reflux are present or absent: The Los Angeles Classification of Esophagitis is used to assess the severity of gastroesophageal reflux [26]. **C)-** Other esophageal disorders (ulcer, stricture, etc.), a hiatal hernia's presence or absence, as well as its size.

5-Esophageal Manometry: Patient should be fasting for the last 6-8 hours before the time of the study. The subjects did not receive any pre-medications or sedatives during the procedure.

Procedure: Eight lumen pressure catheters with an outside diameter of 4.5mm, side holes at 5,5,5,2,1,1 and 1 cm apart, radially oriented by 360, and were continuously perfused with distilled water from a "Mui-scientific" perfusion pump at a rate of 0.5ml/min were used to measure the pressure characteristics of the gastro-esophageal junction. Each channel had a

pressure transducer attached to it, which provided data to a computer (PC Pol-ygraf ID Motility System, Medtronic-Synectics, Sweden). The probe was withdrawn 0.5 cm at a time using a station pull-through approach, and each level was held for at least 30 seconds or until the recording became steady. The catheter assembly was inserted into stomach through the nose.

Interpretation of results: Results were classified as hypertension if the distal body amplitude was greater than 180 mmHg, and hypotensive if the distal body amplitude was less than 35 mmHg.

6-Ambulatory 24-Hour pH Monitoring: The subject should be fasting for the last 6-8 hours before the beginning of this research. Proton pump inhibitors were stopped 7 days prior to the study. Any other drugs known to interfere with gastric motility and/or secretion were discontinued at least 48 hours prior to the study. The equipment is initially calibrated by inserting the catheter in buffer solutions of pH 4 and 7. A disposable antimony or glass pH electrode was inserted via the nose and attached with one electrode which positioned 5cm above the LES as indicated by manometric evaluation and have a connection with portable Digtrapper MKIII pH electrode (Synectics medical Sweden). Patients were hospitalized for a period of 24 hours. The DeMeester and Johnson scoring method was then used to assess esophageal acid exposure.

7-Histologic Examination: Our pathologist examined subserial slices of each biopsy block at three or more levels until perpendicular cuts were achieved. All of the portions were scanned to see which one would be the best aligned, and measurements were taken from this one. The histopathological report will include: basal cell hyperplasia (BH), papillae elongation (PE), and dilatation of intercellular spaces (DIS). Each slide was stained using hematoxylineosin with the grading system as follows: 0 (missing), 1 (moderate), and 2 (marked). Eosinophil infiltration (IE) was also measured (score: 0=absent, 1=1 eosinophil, 2=>1 eosinophil per HPF 40), as



well as neutrophils (0=absent, 2=present) and necrosis/erosions (0=absent, 2=present).

Global severity score: To describe total severity of those lesions, a global score was utilized (GS). The score will be determined by multiplying the total number of assessable lesions by the sum of the BH, PE, ISD, IE, and intraepithelial neutrophils (IN) values (range 0–2). The GS was a scale with a range of 0 to 2 points. The provided score will be 2 in the presence of intraepithelial neutrophils or necrosis/ erosion (almost exclusively found in erosive illness), since these lesions represent the most severe end of the spectrum.

Statistical Considerations: Analytical Statistics The data was collected, edited, coded, and entered into IBM SPSS version 23 (Statistical Pack-

The results of this work showed the following:

1- Demographic and Clinical Data: The study include 100 subjects,52 males (52%) and 48 females (48%),with age ranging between 18 and 35 years with the mean age 28.06 ± 5.12 .Thirty

age for Social Science). When the data was parametric, it was provided as mean, standard deviations, and ranges; when the data was non-parametric, it was presented as median, inter quartile range (IQR). To compare the qualitative data, we used Chi-square test. The independent t-test was used to compare two groups with quantitative data and a parametric distribution. To distinguish between patents and controls, the Receiver Operating Characteristic Curve (ROC) was employed in a quantitative form to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve (AUC) for examined parameters. P value greater than 0.05 indicates that the difference is significant. Highly significant if the P value is less than 0.01.

RESULTS

healthy patientswere enrooled in the control group with 16 males and 14 females and age range 18- 35 with the mean 28.06 ± 5.12 .The Patients group included 70 patients:36 males and 34 females with age range 18- 35 with the mean age 28.06 ± 5.12 (**Table 1**).

Table (1) :Comparison between different results in the studied groups .

			Control group	Patients group	Test value	P-value
			No. = 30	No. = 70		
Demographic data	Age group	(18-25)	12 (40.0%)	22 (31.4%)	0.690*	0.708
		(26-30)	8 (26.7%)	21 (30.0%)		
		>30	10 (33.3%)	27 (38.6%)		
	Gender	Female	14 (46.7%)	34 (48.6%)	0.031*	0.861
		Male	16 (53.3%)	36 (51.4%)		
	Druge intake	No	26(86.7%)	53(75.7%)	1.518	0.218
Yes		4(13.3%)	17(24.3%)			
Smoking	Non-smoker	24(80.0%)	51(72.9%)	0.571	0.450	
	Smoker	6(20.0%)	19(27.1%)			
Coffee	No	24(80.0%)	51(72.9%)	0.571	0.450	
	Yes	6(20.0%)	19(27.1%)			
BMI	BMI<20	16(53.3%)	8(11.4%)	22.139	0.001	
	BMI 20-25	5(16.7%)	32(45.7%)			
	BMI 25-29	8(26.7%)	21(30.0%)			
	BMI >30	1(3.3%)	9(12.9%)			
Frequency of reflux episodes	Less than twice per week	30 (100.0%)	27 (38.6%)	32.331*	0.001	
	At least twice per week	0 (0.0%)	43 (61.4%)			



Endoscopic results	Non erosive reflux disease (NERD)	30 (100.0%)	45 (64.3%)	14.286*	0.001
	Erosive reflux disease (ERD)	0 (0.0%)	25 (35.7%)		
ERD Grade	Non erosive reflux disease (NERD)	30 (100.0%)	45 (64.3%)	14.286*	0.006
	Grade A	0 (0.0%)	7 (10.0%)		
	Grade B	0 (0.0%)	5 (7.1%)		
	Grade C	0 (0.0%)	10 (14.3%)		
	Grade D	0 (0.0%)	3 (4.3%)		
DeMeester score	Median (IQR) Range	5 (5 - 6) 4- 9	35.5 (9 - 48) 4- 85	-6.665‡	0.001
Acid Exposure Time	Mean ± SD Range	1.71 ± 0.73 1- 3.4	4.44 ± 1.72 1- 7	-8.369•	0.001
pH-metry	Negative Positive	30 (100.0%) 0 (0.0%)	19 (27.1%) 51 (72.9%)	44.606*	0.001
Endoscopic results with PH	NERD pH negative NERD pH positive ERD pH positive	30 (100.0%) 0 (0.0%) 0 (0.0%)	19 (27.1%) 26 (37.1%) 25 (35.7%)	44.606*	0.001

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P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS),
 *:Chi-square test; •: Independent t-test.

2- Frequency of Reflux Symptoms: (Table 2)

Table (2): Correlation between the frequency of reflux episodes and demographic and other factors in patient group.

		Frequency of reflux episodes		Test value	P-value
		Less than twice per week Frequency of reflux episode	At least twice per week		
		No. = 27	No. = 43		
Age	Mean ± SD Range	24.89 ± 4.04 18 – 32	30.05 ± 4.74 18 – 35	-4.682•	0.0001
Age group	Age (18-25) Age (26-30) Age >30	15 (55.6%) 10 (37.0%) 2 (7.4%)	7 (16.3%) 11 (25.6%) 25 (58.1%)	19.934*	0.0001
Gender	Female Male	8 (29.6%) 19 (70.4%)	26 (60.5%) 17 (39.5%)	6.313*	0.012
Drugs intake	No Yes	23 (85.2%) 4 (14.8%)	30 (69.8%) 13 (30.2%)	2.144*	0.143
Smoking	Non-smoker Smoker	14 (51.9%) 13 (48.1%)	37 (86.0%) 6 (14.0%)	9.807*	0.002
Coffee	No Yes	14 (51.9%) 13 (48.1%)	37 (86.0%) 6 (14.0%)	9.807*	0.002
H.pylori	No Yes	13 (48.1%) 14 (51.9%)	16 (37.2%) 27 (62.8%)	0.818*	0.366
Hiatus hernia	No Yes	25(92.6%) 2(7.4%)	22(51.2%) 21(48.8%)	7.328*	0.0371



BMI	BMI<20	4 (14.8%)	4 (9.3%)	1.459*	0.692
	BMI 20-25	10 (37.0%)	22 (51.2%)		
	BMI 25-29	9 (33.3%)	12 (27.9%)		
	BMI >30	4 (14.8%)	5 (11.6%)		

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS),

*:Chi-square test; •: Independent t-test

3- Endoscopic Results:

Erosive reflux disease was detected in 25 patients whereas the remaining 45 patients were labeled as non-erosive reflux disease. Of the 25 patients who had erosive reflux disease, 7 patients belonged to grade A, 5 patients belonged to grade B, 10 patients belonged to grade C and 3 patients belonged to grade D. Endoscopic hiatus hernia was detected in 23 patients out of 70. Individuals of the control group show no gross endoscopic abnormalities. In the current study, a statistically significant direct correlation is found between erosive esophagitis presence and male gender, age group (higher in age >30) and hiatus hernia. The

4- Intra esophageal pH checking results : In this paper, 51 patients are positive pH metry and 19 are negative, statistically significant difference is present between groups, with a direct link between PH positive patients and age, male gender, smoking, and coffee consumption, but

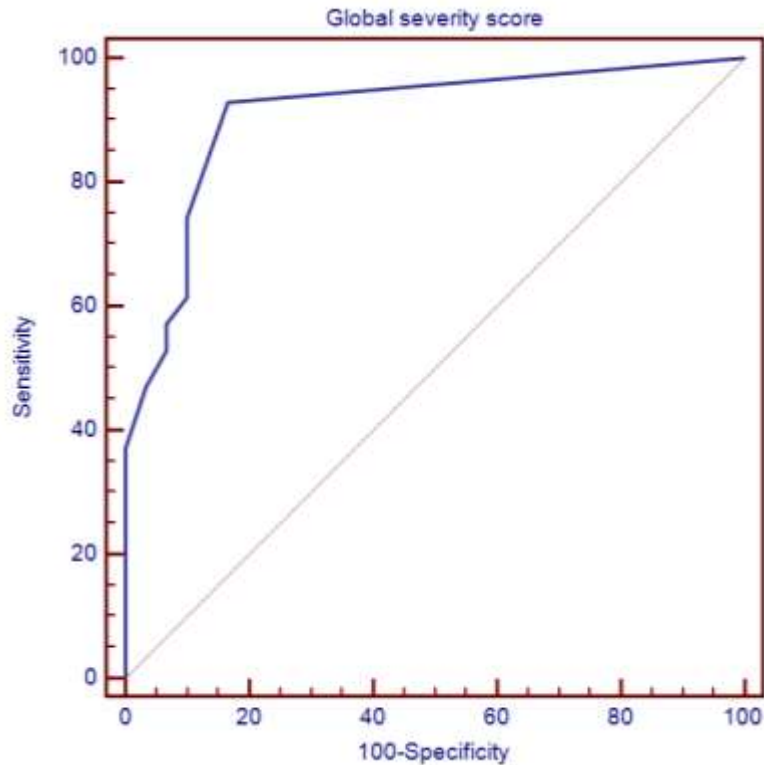
5- Histopathological results: In the present research, there is a statistically significant difference in the percentage of basal cell hyperplasia, papillary elongation, necrosis/or erosion, and intraepithelial neutrophil infiltration between the two analysed groups. In addition, GSS and the 24-hour composite pH score (DeMeester Score) has a direct link. For all biopsies, a global severity score is determined. In controls, it has a mean value of 0 whereas in patients it has a mean value of 0.5. (1 in ERD and 0.4 in NERD,

presence of erosive esophagitis is directly correlated with marked higher frequency of reflux symptoms. Esophagitis has a higher prevalence and severity (based on Los Angeles Classification) among the participants with more frequent reflux symptoms. No significant correlation is present between higher risk of esophagitis and H. pylori infection, drug intake, coffee consumption and smoking. Based on patients' symptoms, they were divided into three groups, endoscopy, and pH testing: 25 with erosive esophagitis (ERD), 26 with non-erosive reflux disease (NERD) and positive pH-metry, and 19 with non-erosive reflux disease (NERD) and negative pH-metry (functional heartburn).

no relation between PH positive patients and H.pylori, medication intake, or BMI in the current study. Positive PH patients have a positive connection with reflux episodes, duration of acid exposure, and DeMeester score (Table 1).

respectively). Receiver Operator Characteristic (ROC) curve analysis of values found among participants and healthy controls reveal that >0 is the most effective cut-off for separating patients (either GERD or NERD) from controls, whereas at 92.86 percent sensitivity and 83.33 percent specificity, the 0 cut-off distinguished GERD patients from controls (Figure 1).





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Parameter	AUC	Cut Point of	Sensitivity	Specificity	PPV	NPV
Global severity score	0.910	>0	92.86	83.33	92.9	83.3

Figure (1):ROC curve of global severity score as a predictor of patient .

DISCUSSION:

GERD is a condition in which stomach contents reflux into the esophagus, oral cavity, and/or lungs, causing symptoms and/or complications[6].Based on the results of an endoscopic examination, GERD can be categorized as either erosive reflux disease (ERD) or nonerosive reflux disease (NERD). Unlike NERD, ERD is thought to have the potential to develop to Barrett's esophagus (BE) and potentially esophage-

Our research discovered the prevalence of GERD in young adults. Obesity does not enhance the incidence of erosive esophagitis in Japanese young people, according to a prior study, but hiatal hernia and metabolic and lifestyle characteristics such as hypertension, dia-

al cancer (EAC). In the ERD spectrum, there is a male majority, but in the NERD spectrum, there is a female preponderance. Males are believed to have more susceptibility for physical mucosal injury, whereas females have superior pain perception. Furthermore, sex-specific medicine looks to have a promising effect in order to deliver more suitable treatment for male and female GERD patients[7].

betes, alcohol use, and smoking do[8].Age, on the other hand, is a risk factor, with moderate GERD prevalence greatest among middle aged group (31–60 years), among younger and older age groups, and declining in senior patients. At this moment, the causes of the parabolic distribution of GERD prevalence with age are un-



clear. High prevalence of GERD in middle-aged people may be due to a combination of factors including high psychosocial stress, poor eating habits, lack of exercise, and family history[9].

According to the study, there is a statistically significant direct link between erosive esophagitis and male gender and age group (greater in age 30-35), but no link between higher risk of esophagitis with infection by *H. pylori* or medication use. Erosive esophagitis has been linked to a substantial rise in presence of reflux symptoms. There is a direct relationship between PH positive patients' age, male gender, smoking, and coffee use, however no link is found between *Pylori*, medication intake, or BMI. This is similar to findings's[10].

Male individuals has a higher rate of erosive esophagitis than female subjects. Additionally, the significance of coffee as a risk factor for GERD is uncertain; coffee may exacerbate heartburn in some GERD patients, but the mechanism is unknown, and it could be related to caffeine, rather than coffee itself. Coffee does not seem to be a significant risk factor. Other research, on the other hand, suggest that the link between lifestyle factors (such as smoking and coffee) and GERD is still uncertain and weak[11,12]. Sex has now been identified as a risk factor. Nasseri-Moghaddam et al. studied epidemiology of GERD in the past and discovered that sex has a role. GERD was shown to be 1.55 times more prevalent in women than in men. A meta-analysis recently corroborated this conclusion, showing that overall prevalence of GERD among women is somewhat increased[13]. Furthermore, prior study has revealed that symptomatic GERD mostly affects women with the disparity becoming more pronounced during perimenopause[14,15].

There is a good correlation between frequent reflux symptoms and age, female sex in the two study groups, and also a positive correlation with coffee use and smoking in this research. Presence of a hiatus hernia is linked to a high frequency of symptoms. *H. pylori* infection, BMI, and drug use are not found to increase the

likelihood of frequent reflux symptoms. The incidence and severity of esophagitis are greater in participants who have more frequent reflux symptoms according to the Los Angeles Classification. discovered a connection between frequent smoking and higher risk of GERD symptoms[16]. Despite the fact that the role of these lifestyle variables is disputed, the majority of GERD cases may be treated and avoided by adjusting one's lifestyle. It is essential to increase awareness of the public about different factors contributing in GERD occurrence[9].

In the present paper, *H. pylori* infection is found in 41 patients (22 men and 18 females) in our study, accounting for 58.6% of patients, and in 11 persons (36.7%) among control group. No significant correlation between infection by *H. pylori* and the increased risk of esophagitis found, and it does not raise the likelihood of frequent reflux symptoms. Epidemiological studies have found a negative relationship between the prevalence of *H. pylori* infection and the occurrence and severity of GERD, but this does not prove causation. According to international, national, or local recommendations, infection by *H. pylori* must be sought and eradication medication administered where required[17]. Another study conducted by discovered that *H. pylori* eradication has no influence on clinical outcomes in the short term as well as long-term post-eradication GERD incidence, and no correlation is found between *H. pylori* eradication and the development of GERD[18].

Among other studies, infection with *H. pylori* is revealed to be a definite risk factor for the development of erosive esophagitis[19]. A statistically significant difference is found in BMI between the two groups in this study (the patients' group had a higher BMI). The risk of frequent reflux symptoms is not linked to BMI. Lagergren et al and Zagari et al both conducted population-based investigations that corroborate this information. Silent GERD, on the other hand, is a prevalent problem among MO people, and these people also have a lower esophageal sensitivity to acid[20,21,22]. found that there is substantial



evidence to suggest that obesity/overweight is linked to GERD, as evidenced by particular symptoms and endoscopic results. Furthermore, it has been shown that controlled weight loss (through diet or surgery) can significantly improve GERD symptoms and/or clinical-endoscopic indicators[23].

A statistically significant direct correlation is found between the occurrence of erosive esophagitis and hiatus hernia (as determined by endoscopy) in the present study. The presence of a hiatus hernia is likewise substantially linked to a high frequency of symptoms. This backs up the findings of a previous study that identified male sex, smoking, obesity, and hiatus hernia to be four separate risk factors for erosive esophagitis[10]. This might be explained by the physiological dysfunction of the LES and anatomic distortion of the gastroesophageal junction that occurs with hiatus hernia[24].

In this study, there is a statistically significant difference in the percentage of basal cell hyperplasia, papillary elongation, necrosis/or erosion, intraepithelial neutrophil infiltration, intercellular space dilatation, and intraepithelial eosinophils infiltration between the two studied groups. The histopathological findings of this investigation are consistent, indicating that most individuals with verified aberrant reflux have histological changes. Histopathology has a high sensitivity (85%) among GERD patients and a high specificity (86%) among healthy participants, showing that it is a useful diagnostic tool for GERD patients. The pathology findings also show that the global severity score (GSS), which is calculated based on the total number of lesions, is capable of effectively distinguishing between GERD and controls, and that it overcomes problem of mild le-

CONCLUSION: There is a clear relationship between the global severity score calculated of the biopsies and the time spent below pH 4.0 throughout the monitoring time. Furthermore, there is a clear relationship between the global severity score and DeMeester Score. As a result, role of histology to make GERD diagnosis among young participants should be reas-

sions in controls (in particular mild basal cell hyperplasia near to the Z-line).

The duration elapsed below pH 4.0 for the whole monitored period has a direct correlation with the global severity score obtained for all biopsies. Also, the global severity score and the 24-hour composite pH score have a clear relationship (DeMeester Score). As a result, we may deduce that the histological lesions seen are mostly due to acid reflux. Patients with NERD pH -ve (normal endoscopy and normal pH testing) but with GERD symptoms measured using a validated questionnaire, however, show substantial histological alterations. This means that histology can offer an objective diagnosis in around half of the people who have functional heartburn.

Nonacid reflux may also aid in the detection of histological lesions among participants who have a pH within normal level. Electrical impedance in conjunction with pH-metry may help for the confirmation of this theory, which make us able to differentiate the reflux episodes related to acid or not based on contemporaneous changes in impedance and intra-esophageal pH[25].

We recommend doing the Upper GI endoscopy with multiple esophageal biopsies in all patients with GERD. We recommend thorough histopathological examination of the biopsies for early diagnosis of the pre-neoplastic Barrett's oesophagus in young adult patients with GERD symptoms. Further controlled, multi-center studies should be performed for better assessment of the various diagnostic tools in GERD patients.

essed. The sensitivity of GERD pathological analysis would be increased by utilizing a global severity score rather than specific pathological criteria for histopathological assessment.

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