



Evaluation of Methods of Gastroesophageal Reflux Disease Diagnosis in Thawra Teaching Hospital Al-Bayda -Libya

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Abstract: Gastroesophageal reflux disease (GERD) results from the reflux of gastric contents, causing symptoms and injury to esophageal tissue. In this study, we evaluate methods of diagnosis of GERD and pattern of clinical, endoscopic, and histological findings in consecutive individuals. Patients were referred to endoscopy unit of Thawra Teaching Hospital, Al-Bayda-Libya for various reasons, they have Questionnaire-based assessment scales and were examined for the presence of reflux esophagitis, via endoscopy, and microscopic via histopathology. We had 48 patients with mean age of 45.5, 30 female, 18 male. Total patients with microscopic esophagitis were 29 (60.4%), and without microscopic esophagitis 19 (39.6%). The RDQ with a score of ≥ 8 as the diagnostic criteria of GERD, is not a conclusive diagnosis of GERD in isolation, but is of value in determining the need for further investigation. A normal endoscopy does not exclude GERD when endoscopy is inconclusive, adjunctive evidence from biopsy findings can add confidence for a GERD diagnosis. The finding of glandular mucosa without intestinal metaplasia in the distal 2 cm of the tubular esophagus is regarded as normal but indicates a much chronic acid exposure of the lower esophagus.

Keywords: reflux esophagitis, GERD, ERD, NERD; Gastroesophageal Reflux Disease Questionnaire (RDQ) Los Angeles classification, endoscopy, microscopic esophagitis.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disease. The incidence of GERD is rising worldwide with a prevalence of 10-33% (Sandhu & Fass, 2018). Chronic GERD causes metaplastic changes, this may lead to intestinal metaplasia and Barrett's esophagus. Chronic reflux esophagitis is a key risk factor for the development of Barrett's esophagus, which is a precursor lesion for esophageal adenocarcinoma (Lagergren & Lagergren, 2013) (Sharma, 2009). The prevalence of Barrett's esophagus among patients undergoing endoscopic examination is 1% (Pera, 2003). American College of Gastroenterology published guidelines for diagnosis of GERD on the basis of typical symptoms, improvement of reflux symptoms on

empiric medical therapy with a proton pump inhibitor (PPI) which confirms this symptom-based diagnosis (so-called PPI test) (Katz, Gerson, & Vela, 2013; Krugmann, Neumann, Vieth, & Armstrong, 2013). The Gastroesophageal Reflux Disease Questionnaire (RDQ) is a 6-item questionnaire that helps identify patients with gastroesophageal reflux disease (GERD). (Mouli & Ahuja, 2011). Patients are asked to report frequency of symptoms over the past 7 days. The symptoms suggestive of GERD in the RDQ included heartburn, substernal chest pain, acid eructation, and food regurgitation. Erosive Reflux Disease (ERD) is the major cause of inflammation and mucosal breaks of the squamous epithelium in the distal esophagus, it is sufficient to distinguish erosive lesions of any degree by endoscopy. GERD in-

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cludes more than half of patients that show no endoscopic abnormality whatsoever, the so called Non-Erosive Reflux Disease (NERD). The accurate assessment of NERD has proved difficult, as endoscopy does not provide any useful information, symptoms may be variable or atypical, and even prolonged monitoring of esophageal pH shows no abnormality in about one-third of patients with otherwise typical symptoms (Quigley, 1992), while there are no indications for routine esophageal biopsies in patients with esophageal or extraesophageal symptoms of gastro-esophageal reflux disease (J Dent et al., 1999) and the lack of a gold standard diagnostic test for patients without macroscopic lesions (NERD) makes histology very attractive in this group of subjects (John Dent, 2007).

Aim of the study In this study, we evaluate methods of diagnosis of GERD correlation and pattern of clinical, endoscopic and histological findings in consecutive individuals who underwent routine upper endoscopy as part of a routine examination in the endoscopy unit

MATERIALS AND METHODS

patients were referred to endoscopy unit of Thawra Teaching Hospital, Al-Bayda-Libya for various reasons. Based on a standard protocol including, a questionnaire, patients were examined for the presence of reflux esophagitis, macroscopic via endoscopy and microscopic via histopathology. Demographic details of the patients were recorded including age, sex, smoking habits, tea, coffee and alcohol consumption, and concurrent medical conditions including hypertension and diabetes mellitus. All subjects completed the detailed questionnaire-based assessment scales for (GERD) with the help of a doctor before endoscopy. The Gastroesophageal Reflux Disease Questionnaire (RDQ) score was calculated as the sum of scores, giving a total score ranging from 0 to 18. Those with a score of 8 or more have a high likelihood of having Gastroesophageal Reflux Disease (GERD), and those with

less than 8 have low or no likelihood. For more detailed scoring information, see the reference in the Source section (Am Fam Physician. 2010 ; Jones et al., 2009) .

Upper endoscopic examinations were performed using a standard video upper endoscope (Olympus GIF series). Diagnosis and classification of reflux esophagitis were based on the Los Angeles classification (Amano, Adachi, Katsube, Watanabe, & Kinoshita, 2001; Sami & Ragunath, 2013). Erosive Reflux Disease (ERD) is defined as GERD with esophageal mucosal breaks evident on routine endoscopy, whereas None-Erosive Reflux Disease (NERD) is defined as those with symptoms, but without mucosal breaks or erosions on endoscopy (Vakil et al., 2006). Endoscopic biopsies: level of the gastroesophageal, were defined by the distance from the incisor teeth. Each level had four biopsies at GE junction, 2 cm and 4 cm above.

These samples were fixed with 10% buffered formalin and biopsies were stained with Giemsa stain in addition to hematoxylin-eosin stain. The term “microscopic esophagitis” refers to a group of histological lesions observed in patients with GERD, both Erosive Reflux Disease (ERD) and None Erosive Reflux Disease (NERD) (Fiocca, Mastracci, Milione, Parente, & Savarino, 2011).

The diagnosis of microscopic esophagitis was based upon the presence of one or more of the following criteria: basal zone hyperplasia, focal or diffuse infiltration of the epithelium by polymorphonuclear (PMN) leucocytes, dense infiltration of mononuclear inflammatory cells, and/or an easily recognized infiltrate of neutrophils in lamina propria (Chandrasoma et al., 2000). Microscopic esophagitis was further graded into 5 categories based on the microscopic finding and length of esophageal involvement. Table (1).

Table (1). Microscopic esophagitis, (GEJ) Gastro Esophageal Junction)

• No Microscopic esophagitis	at GEJ
• Microscopic esophagitis With or without glandular mucosa	at GEJ
• Microscopic esophagitis without Intestinal metaplasia	at GEJ, extending to 2cm above GEJ
• Microscopic esophagitis with glandular and Intestinal metaplasia “short-segment Barrett’s esophagus”	at GEJ, extending to 2cm above GEJ
• Microscopic esophagitis with glandular and Intestinal metaplasia “long-segment, classic Barrett’s esophagus”	at GEJ, extending more than 2cm above GEJ

Statistical analysis: The data analyzed statistically, using the Chi-Square test. All tests for $p < 0.05$ and $p < 0.001$ were considered significant. SPSS version 17 was used for statistical analysis.

RESULTS

We have 48 patients with a mean age of 45.52 (Std. Deviation 16), 30 female, 18 male; mean BMI 27% , 4 (8%) male smokers. Those with a Gastroesophageal Reflux Disease Questionnaire (RDQ) score of 8 or more were 18 (37.5%), 11 (22.9%) female and 7 (14.6%) male without significant differences (P: 0.951). Taking the microscopic changes as reference, RDQ sensitivity was 50 %, specificity was 79% (Kappa value as a measure of agreement 0.267; P: 0.045). We have 13 (27%) patients with definite Erosive Reflux Disease (ERD) evident on endoscopy. Based on the Los Angeles (LA) classification, we have LA A six patients, LA B four patients and LA C two patients. Taking the microscopic changes as references for endoscopic changes, sensitivity was 54 %, and specificity 100%, (Kappa value as a measure of agreement 0.412; P: 0.000). Total patients having microscopic esophagitis were 29 (60.4%), 13 patients 45% with ERD (Microscopic esophagitis with definite Erosive Reflux Disease) and 16 patients 55% with

NERD (Microscopic esophagitis without definite Erosive Reflux Disease), and 19 patients have no microscopic esophagitis making 39.6%. See table (2).

Table (2). Microscopic esophagitis categories; (NERD: None Erosive Reflux Disease, ERD: Erosive Reflux Disease, GEJ: Gastro Esophageal junction)

Microscopic esophagitis categories	No (%)
• No Microscopic esophagitis	19 (39.6%)
• Microscopic esophagitis	29 (60.4%)
• Microscopic plus Macroscopic esophagitis (ERD)	13 (45%)
• Microscopic without Macroscopic esophagitis (NERD)	16 (55%)
• Microscopic esophagitis	29 (60.4%)
• Microscopic esophagitis (at GE junction)	16 (33%)
▪ Without Goblet cells	7 (14.6%)
▪ With Goblet cells	
• Microscopic esophagitis without Intestinal metaplasia at GEJ, extending to 2cm above GEJ	4 (08.3%)
• Microscopic esophagitis with intestinal metaplasia at GEJ, extending to 2 cm above GEJ “short-segment Barrett’s esophagus”	2(04.2%)
• Microscopic esophagitis with Intestinal metaplasia at GEJ, extending more than 2cm above GEJ “long-segment, Barrett’s esophagus”	0(00%)

We found that endoscopic finding has a positive correlation with histopathological findings and RDQ while histopathological findings do not correlate with RDQ see table (3).

Table (3). correlations between RDQ, endoscopic and histologic picture.

	Correlations (Pearson)	P Value *Not significant ** Significant
Microscopic Esophagitis and RDQ	= 0.275	P=0.059*
Microscopic and Macroscopic Esophagitis	= 0.493	P= 0.000**
RDQ and Macroscopic Esophagitis	= 0.496	P= 0.000**

DISCUSSION

GERD subjects diagnosed based on RDQ score of 8 or more were 37.5%, which was high compared to other regional and international studies. In a review article based on 15 studies from 1999 to 2010, the prevalence of GERD in Iran had been reported to be about 6.8% to 33% (Delavari, Moradi, Birjandi, Elahi, & Saberifiroozi, 2012), and in a review article by El-serag *et al.* in 2013 the prevalence of GERD was 18.1%-27.8% in North America, 2.5%-7.8% in East Asia, 8.8%-25.9% in Europe, and 8.7%-33.1% in the Middle East based on the weekly occurrence of GERD symptoms. The GERD prevalence was 28.7% in Saudi Arabia (Alsuwat, Alzahrani, Alzhrani, Alkhatami, & Mahfouz, 2018).

Most studies using questionnaires might have failed to distinguish the functional heartburn (Jung, 2011). Our study sample was biased toward persons undergoing upper endoscopy, who are more likely to have more gastrointestinal symptoms than the general population and who may have GERD symptoms more frequently, it was also biased because of small sample size and this explains the low RDQ sensitivity (50%), specificity (79%). Up to 27% of our patients have positive upper gastrointestinal endoscopy findings, which is similar to other regional and international studies that reported up to 30% upper gastrointestinal endoscopy findings. (Mohamed *et al* 2014) ("[5.pdf](#)",), (Elmas Kasap, Zeybel, Aşık, Ayhan, & Yüceyar, 2011). The Los Angeles classification system is based on the detection of mucosal breaks in conventional endoscopy (Fock, Teo, Ang, Tan, & Law, 2009). Upper endoscopy is considered by many as an insensitive test for GERD as it often yields normal endoscopic findings, in our study two-thirds of patient have normal endoscopic finding. It is also more invasive and expensive. It is widely used in GERD for identifying and grading severe esophagitis, monitoring patients with Barrett's esophagus, or when other com-

plications of GERD are suspected. However, endoscopy is the gold standard for the diagnosis of erosive GERD. In this study the sensitivity of endoscopy for GERD is poor, but it has an excellent specificity of 100% (E. Kasap, Zeybel, Asik, Ayhan, & Yuceyar, 2011; Richter, 1994). The term "microscopic esophagitis" (ME) refers to a group of histological lesions observed in most patients with GERD, both ERD and NERD. Microscopic esophagitis found in 29 (60.4%), ERD (Microscopic plus Macroscopic esophagitis) 13 patients 45% and NERD (Microscopic without Macroscopic esophagitis) 16 patients 55% (E. Kasap *et al.*, 2011). This goes with who found that histopathological findings were more prevalent than the endoscopic changes. In symptomatic patients of GERD, when endoscopy does not show mucosal breaks, histopathological evaluation of distal esophageal mucosa may have a promising diagnostic value and the recognition of microscopic changes in NERD is important in some subgroups of patients (i.e., those with typical symptoms), and the histological diagnosis of GERD is generally believed to be of limited value as an initial tool for GERD evaluation (McDonald, Graham, Lavery, Wright, & Jansen, 2015; Schindlbeck, Wiebecke, Klauser, Voderholzer, & Müller-Lissner, 1996).

The finding of glandular mucosa without intestinal metaplasia in the distal 2 cm of the tubular esophagus was found in 7 (14.6%) of our patients, it is currently regarded as normal, but indicates a much chronic acid exposure of the lower esophagus. Specialized intestinal metaplasia with goblet cells in the esophagus, the lower 2 cm of the tubular esophagus "short-segment Barrett's esophagus", was found in 4.2% of our patients and also indicated a much more severe acid exposure. (Csendes *et al.*, 1993; Jain, Aquino, Harford, Lee, & Spechler, 1998).

In this study we could not find any case with long segment Barrett's esophagus, and this apparently is due to the small sample size of

our study. In 2008, Fan and Snyder conducted a retrospective study in the United States evaluating the medical records and endoscopic reports of 4,500 patients, they reported a prevalence of Barrett's esophagus of 4.4% and 1.5% in those with and without gastroesophageal reflux symptoms, respectively (Fan & Snyder, 2009). The prevalence of Barrett's esophagus was 3.77% in a Greek population undergoing upper endoscopy not referred for GERD.

The histologic lesions in GERD are usually limited to the distal esophagus. Standard sampling should include the last 2 cm above the Z line (2 biopsies at 2 cm and 2 biopsies on the esophageal side of the Z line) (Schneider NI, et al 2015). More proximal biopsies are less informative. Endoscopy has a good correlation with clinical symptoms and histopathology findings, but no correlation was observed between clinical symptoms and histological findings, see table (3). Our results are comparable to the literature published in 2005 in Pakistan (Zuberi BF, 2005).

CONCLUSION

The Gerd Q questionnaire with a score of ≥ 8 as the diagnostic criteria of GERD is not a conclusive diagnosis of GERD in isolation, but is of value in determining the need for further investigation. Endoscopy is not a necessary prerequisite to therapy for typical reflux symptoms, but it is indicated at the first presentation for patients with alarm symptoms referable to the upper gastrointestinal tract. A normal endoscopy does not exclude GERD when endoscopy is inconclusive, adjunctive evidence from biopsy findings can add confidence for a GERD diagnosis. The disease follows a rather benign course in most patients, the finding of glandular mucosa without intestinal metaplasia in the distal 2 cm of the tubular esophagus is currently regarded as normal, but indicates a much chronic acid exposure of the lower esophagus (Gyawali et al., 2018). The histologic lesions in GERD are usually limited to the

distal esophagus, more proximal biopsies are less informative.

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تقييم طرق تشخيص الجزر المريئي بمستشفى الثورة التعليمي البيضاء/ ليبيا

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المستخلص: مرض الجزر المريئي ناتج عن انعكاس أو ارتجاع لمحتويات المعدة مسبباً أعراضاً وإصابات لأنسجة المريء، ومن طرق التشخيص، استبيان خاص بمرض الجزر بني على تسجيل نقاط محسوبة، ويعتبر مجموع نقاط الاستبيان لأكثر من 8 كافياً سريريا لتشخيص المرض (الاستبيان خضع لما يعانيه المريض من أعراض). ولكن يظل تنظير المريء عاملاً مساعداً لتأكيد تشخيص التهاب الجزر (الارتجاعي) لتآكل المريء ومن ثم تحديد درجة العطب النسيجي. من الدراسات السابقة، أكثر من نصف المرضى الذين يعانون من التهاب المريء الجزري (الارتجاعي) لا توجد لديهم أية تغيرات أو عطب نسيجي وقت التنظير (يسمى: جزراً مريئياً بدون تآكل)، الأمر الذي جعل التحليل المجهرى النسيجي مطلوباً لتلك المجموعة. في هذه الدراسة قمنا بتقييم طرق تشخيص الجزر المريئي وأنماطه الإكلينيكية، و نتائج المنظار (حسب تقسيمات لوس أنجلوس لتقييم تآكل المريء بالمنظار)، وكذلك نتائج التحليل المجهرى النسيجي. تم دراسة المرضى المحالين إلى وحدة المناظير بمستشفى الثورة التعليمي بالبيضاء لغرض إجراء منظار لعدة أسباب حيث تم سؤالهم عن طريق استبيان معدّ مسبقاً لتقصّي مرض الجزر المريئي وحساب نقاط الاستبيان، بعدها جرى المنظار ثم تؤخذ عينات نسيجية من أماكن مختلفة وترسل إلى المعمل لغرض الفحص المجهرى للأنسجة. عدد الذين أجريت عليهم الدراسة 48 مريض، متوسط أعمارهم (45.5)، 30 منهم من النساء و15 من الرجال. مجموع المرضى ممن وجد لديهم تغيرات نسيجية 29 مريضاً بنسبة (60.4%) وبدون تغيرات نسيجية 19 مريضاً بنسبة (39.6%). وجدنا أن مجموع نقاط الاستبيان أكثر من 8 نقاط لا يعتبر دقيقاً لتشخيص الجزر المريئي بمفرده ولكنه ذو قيمة للمضي إلى فحوصات أخرى دقيقة. وكذلك خلو فحص المنظار من تآكل الأنسجة لا يفي أو لا يستبعد التهاب الجزر المريئي، وعند إضافة أخذ عينات نسيجية لغرض التحليل ممكن أن يزيد مدى دقة التشخيص. عند إجراء الفحص النسيجي ووجود النسيج الغدّي بدون وجود تغيرات نسيجية معوية مهاجرة على مسافة 2سم من الجزء السفلي من المريء تعتبر طبيعية ولكنها تدل على تعرض الجزء الأسفل للمريء للأحماض والعصارة المعدية.

الكلمات المفتاحية: التهاب الجزر المريئي، الجزر المريئي، التهاب المريء غير الجزري، استبيان مرض الجزر المريئي، تقسيمات لوس أنجلوس، المنظار، التهاب المريء المجهرى.

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