To whom and when the upper gastrointestinal endoscopy is indicated in gastroesophageal reflux disease? What is the role of routine esophageal biopsy? Which endoscopic esophagitis classification should be used?

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ABSTRACT

Gastroesophageal reflux disease (GERD) is a chronic disease characterized with heartburn and regurgitation symptoms. The prevalence of these symptoms in Turkey is reported to be as high as 20%. GERD negatively effects the quality of life along with the development of some complications due to chronic course. Upper gastrointestinal endoscopy is commonly performed for diagnosis and surveillance of complications in the context of GERD. However, there is no consensus in terms of timing and indications for endoscopy, use of esophagitis classification system, to obtain a biopsy sample or recommendation for surveillance endoscopy. In order to answer these questions, we performed a systematic literature search. In this article, we report our findings for these targeted questions and our proposals as a result of the national consensus program on GERD.

Keywords: Gastroesophageal reflux disease, endoscopy, classification, biopsy, surveillance, barrett esophagus, esophagus cancer

INTRODUCTION

Gastroesophageal reflux disease (GERD) is common condition which develops when the reflux of gastric contents causes troublesome symptoms or complications and has a negative effect on quality of life due to chronic course. In the management of GERD, the role of upper gastrointestinal endoscopy (EGD) is to make a positive diagnosis and to rule out GERD injury syndromes such as esophageal stricture, Barrett's esophagus (BE), or esophageal adenocarcinoma (AC) (1-3). Despite of the fact that endoscopy alone is no longer considered as a gold standard for the diagnosis, GERD is the most common indication for EGD, which may be a result of uncertainty of the indications in GERD, which in turn increases the number of unnecessary endoscopies and indirectly increases the cost of disease to the society.

GERD can be diagnosed by using patient reported questionnaires for heartburn and regurgitation symptoms. However, reflux symptoms are not always associated with tissue damage; on the contrary, non-erosive reflux disease is more common. The suspicion of an organic disease arises in all patients with chronic heartburn symptoms; therefore, frequency of endoscopic procedures increases in such patient group (4,5). It is an important issue to select appropriate GERD patients for which endoscopy should be performed. Based on the literature, we tried to determine a number of risk factors for a complicated course in GERD in order to diagnose and treat it earlier. We performed a systematic search for relevant information via PubMed using the following search terms: "Gastroesophageal reflux disease, indications for endoscopy, Barrett esophagus, specialized intestinal metaplasia, cancer of esophagus, heredity, biopsy, surveillance". All of the articles were reviewed and classified according to level of evidence in order to identify risk factors.

RISK FACTORS FOR ESOPHAGEAL INJURY SYNDROMES

In a multicenter prospective study conducted in Turkey (GORHEN) in 2008 for the evaluation of endoscopic findings of GERD showed that erosive reflux disease could be detected only in 34% patients (6,7). Other population based studies in the literature also support the same data; the contribution of endoscopy to the

diagnosis is limited in the presence of typical symptoms because of the low detection rate of erosive esophagitis in such patients which is one-third of the patients on average (8-11). The treatment with proton pump inhibitors seems to be a first line approach in patients with typical symptoms (4). The selection of patients with complicated course has had more importance, and it is useful to clearly examine the EGD indications. Questioning the presence of alarm symptoms is the most trustworthy approach for selection of patients. In particular, the diagnostic contribution of the alarm symptoms on determining gastrointestinal malignancies was investigated in a meta-analysis performed by Vakil et al. (12) in 2006. In total, 17 studies comprising 50,000 patients were evaluated. The sensitivity of the often-queried symptoms such as weight loss, dysphagia, and anemia was below 50%. However, the sensitivity increases to 67% in individuals who had more than one alarm symptom. When this study is evaluated with a different point of view, it provides additional invaluable information. The negative predictive value of the specified alarm symptoms is above 90%. More specifically, Bowrey (13) investigated the relationship between esophagogastric cancer and alarm symptoms. It is reported that the incidence of cancer begins to increase as of 55 years of age (p<0.0001), and alarm symptoms were present in 85% of cancer cases. The identified symptoms in this study are; epigastric mass, anemia, persistent vomiting, dysphagia, and weight loss. The negative predictive value of these alarm symptoms was also reported to be high in other similar studies (14). The presence of alarm symptoms is helpful in detecting advanced-stage cancer patients and should be queried in every patient who is a candidate for endoscopy.

Age is cited as an important criterion for the detection of patients with complicated progress in some studies. In a case control study, for determination of risk factors; age over 50 years (OR: 1.8, 95% CI 1.1-2.4) and male gender (OR: 2.7, 95% CI 1.6-4.5) were found to be risk factors for the development of BE (15,16). It has been also reported by other studies that men are at risk in terms of development of BE (16). As the patient's age increases, this risk increases even further (OR: 1.53, 95% CI 1.05-2.25) (17,18). In a cohort study consisting of 1058 patients, the frequency and duration of heartburn symptom increase risk of BE development; presence of heartburn for more than 5 years (OR: 1.5, 95% CI 1.07-209) and the presence of daily GERD symptoms (OR: 2.33, 95% CI 1.34-4.05) were reported risk factors (19,20). The increase in the risk of detection of high-grade dysplasia is notable in long-term GERD and BE; in a cohort study consisting of 109 patients, the average was found to be 5.66 in those having complaints for more than 20 years (21). In a population-based case-control study (FINBAR) in which the relationship between GERD and BE or esophageal AC was investigated, the presence of GERD was found to be strongly associated with BE (OR: 12.0) and esophageal AC (OR: 3.48). Smoking (OR: 4.84) and obesity (OR: 2.69) were identified as important risk factors, particularly for esophageal AC (22). Later studies revealed the relationship of obesity and BMI with

GERD with complicated course. In another study in which the development of BE along with BMI in women was investigated, BMI>30 was found to be a significant risk factor (OR: 1.5, 95% CI 1.07-2.09) (23). When anthropometric measurements associated with obesity were investigated, waist-hip ratios higher than 0.8 in women and higher than 0.9 in men were found to be associated with the development of BE; moreover, the risk further increases with every 0.1 increase in this ratio (15,17). BMI >30 (OR: 1.41, 95% CI 1.06-2.22) and smoking (OR: 1.93, 95% CI 1.15-3.24) were reported as risk factors in the risk prediction model developed for BE. Smoking is an important risk factor in analyzing the development of BE and AC (18,24). Other determined risk factors are the presence of hiatus hernia longer than 6 cm (OR: 2.07-8.37) and regular consumption of alcohol (OR: 2.38, 95% CI 0.99-5.72) (25,26). *Helicobacter pylori* infection and regular use of wine are reported as the protective factors of BE and esophageal AC (OR: 0.7, 95% CI 0.20-2.20) (25).

FAMILIAL CLUSTERING

The family history of patients always affects our decision on endoscopy. Considering the situation specific to BE and esophageal AC, there is more history of cancer in the first-degree relatives of patients with BE and AC (24% and 5%, respectively, p<0.005); besides, in multivariate analysis the family history is identified as an independent risk factor (OR: 12.23). In a study in which the relatives of patients with BE-AC and only esophagitis were compared, GERD was found more common in the siblings of patients in the first group (27-30).

CLASSIFICATION OF ESOPHAGITIS

The diagnostic contribution of endoscopy is limited in the diagnosis of GERD with typical symptoms. Detection of erythema, erosion, ulceration, peptic strictures, and BE found during the endoscopy are diagnostic for GERD with a sensitivity of 95% (31). However, it should be noted, no endoscopic evidence is encountered in most of the patients (31,32). In addition, GERD symptoms and esophageal damage are not directly proportional. Therefore, endoscopic examination should be performed in GERD patients with the abovementioned risk factors. Different systems were used for the endoscopic classification of erosive esophagitis; Savary Miller, MUSE, and LA classifications are the most frequently used ones among them. It has been demonstrated that LA classification is reliable and its intra- and inter-observer agreement is high, regardless of the experience of the endoscopist (33-35). The severity of esophagitis according to LA classification has also been found to be compatible with 24-hour acid exposure in 24-hour pH monitoring studies (36). Acid exposure has been shown to increase at night in those with LA esophagitis grades C and D (36). The use of LA system in the classification of esophagitis should be recommended.

ESOPHAGEAL BIOPSY AND SURVEILLANCE ENDOSCOPY

Additional contribution of biopsy to the diagnosis of GERD is low in patients with typical esophagitis findings. The sensitiv-

ity of biopsy for GERD was found to be 30% in a series of 178 patients, and its positive predictive value was calculated as 67% (37). An incomplete definition of the histopathological criteria for esophagitis and the use of several different parameters restrict the use of routine biopsies (38). In a prospective study to evaluate the contribution of biopsy in non-erosive reflux disease, while histological changes were detected in nearly all the patients with erosive esophagitis, consistent histological findings could be detected in 76% patients with non-erosive reflux disease, even though there were no endoscopic findings. Therefore, it should be noted that biopsy of the esophagus may be beneficial in the diagnosis of non-erosive reflux disease (39). However, it is not recommended due to the lack of data to support routine esophageal biopsies in heartburn patients with no compatible symptoms in endoscopy. Hence, for which patients is esophageal biopsy beneficial? In our general endoscopy practice, whether or not there is a complaint of GERD, we recommend biopsy in the presence of esophageal mass, deep ulcers, nodularity, or malignancy and also in cases where alternative diagnoses are investigated. Follow-up endoscopy is not recommended in GERD, but endoscopic examination should be undertaken in unresponsive patients despite adequate medical treatment (40). It may be difficult to assess BE or dysplasia histopathologically in the presence of severe esophagitis; the detection rates of BE may increase up to 12% in a second endoscopic examination after appropriate treatment (41-43). Therefore, follow-up endoscopy is recommended to detect BE in patients with severe erosive esophagitis or in the follow-up of patients known to have BE.

CONCLUSION AND RECOMMENDATIONS

Endoscopy should be performed in patients with typical gastroesophageal reflux disease (GERD) symptoms in the following cases:

- The contribution of esophagogastroduodenoscopy (EGD) to the diagnosis of reflux is limited in symptomatic patients. It contributes to the diagnosis of reflux in about one-third of the patients with typical complaints of reflux (Level of evidence: 2b).
- Endoscopy should be performed in patients who are above 50 years of age and/or whose symptoms have lasted longer than 5 years. In addition, male gender, smoking status, having a body mass index (BMI) >30, waist-hip ratio above 0.9 for men and 0.8 for women, and showing symptoms every day are factors that increase the risk of complications, and endoscopy indication should be evaluated according to (Level of evidence: 2b).
- It should be performed in patients with alarm symptoms, namely, dysphagia, odynophagia, involuntary weight loss, and anemia, which cannot be explained with other reasons or persistent vomiting* (Level of evidence: 2b, 3, *5).

- EGD should be performed in the presence of PPI unresponsiveness in GERD patients without alarm symptoms (Level of evidence: 5).
- It should be performed in patients whose one of the first-degree relatives has Barrett's esophagus or upper gastrointestinal tract cancer (Level of evidence: 2b).
- Esophageal biopsy is not required in the presence of typical symptoms, but biopsy can be taken in cases in which Barrett's esophagus or alternative diagnoses are investigated (Level of evidence: 2b).
- Los Angeles (LA) classification should be used for the assessment of the severity of esophagitis (Level of evidence: 1b).

In reflux patients, follow-up endoscopy is recommended only in the following cases:

- Follow-up of the patients known to have Barrett's esophagus and in patients diagnosed with severe erosive esophagitis, investigating Barrett's esophagus after the treatment (Level of evidence: 2b).

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