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Original contribution

Validation study of the Esohisto consensus guidelines for the recognition of microscopic esophagitis (*histo*GERD Trial) ☆

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Summary In patients with gastroesophageal reflux disease (GERD), histology is generally believed to be a tool of limited diagnostic value. Our study aimed to assess the prevalence of microscopic esophageal lesions as defined by the Esohisto consensus guidelines, which have proven high interobserver agreement in previous studies. In the prospective Central European multicenter *histo*GERD trial, we recruited 1071 individuals (576 females and 495 males; median age, 53 years; range, 15-93 years) undergoing gastroscopy for nonselected reasons. Biopsy material was systematically sampled from above and below the gastroesophageal junction. Overall, histologic diagnosis of mild and severe esophagitis was made in 423 (39.5%) and 296 (27.6%) individuals, respectively, whereas the squamous mucosa of 352 individuals (32.9%) was normal upon histology or showed only insignificant findings. Proliferative changes of the squamous epithelium, in particular basal cell layer hyperplasia, papillary elongation, and intercellular space dilation, were more common than inflammatory cell infiltration. The presence of microscopic esophagitis was associated with male sex ($P = .009$), patients' symptoms ($P = .003$), history of proton pump inhibitor intake ($P < .001$), and the endoscopic diagnosis of esophagitis ($P < .001$). Notably, among the 450 patients with no endoscopic signs of esophagitis (Los Angeles Category N), 41.8% and 17.1% were identified with mild and severe (microscopic) esophagitis, respectively, indicating higher sensitivity of histologic diagnosis. In conclusion, our data illustrate the

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value of histology in the workup of patients with reflux disease. We suggest that biopsies should routinely be obtained when patients undergo upper gastrointestinal endoscopy for evaluation of GERD and may particularly be beneficial in patients with nonerosive reflux disease.

1. Introduction

The prevalence of gastroesophageal reflux disease (GERD) ranges from 10% to 20% in the Western world when heartburn and/or acid regurgitation occurring at least once a week are used for definition. The prevalence in Asia is lower, accounting for less than 5% [1]. GERD comprises a wide variety of clinical manifestations, ranging from reflux symptoms without visible lesions at conventional endoscopy (ie, microscopic esophagitis) to grossly visible esophagitis with varying extent of mucosal breaks, graded according to the (modified) Los Angeles classification [2,3].

According to recently published practice guidelines of the American College of Gastroenterology, the diagnosis of GERD can be established in the setting of typical symptoms. Empiric medical therapy with a proton pump inhibitor (PPI) may be helpful in this setting (so-called PPI test). Upper endoscopy is not required in the presence of typical GERD symptoms, and routine biopsies from the distal esophagus are not recommended [4].

In patients with nonerosive reflux disease (NERD), histology is generally believed to be a tool of limited diagnostic value [5,6]. Several studies have, however, demonstrated that histology, if systematically applied, may render important diagnostic clues as at least two-thirds of NERD patients have histologic evidence of esophageal injury [7,8]. The Esohisto project is a multinational initiative for the standardized recognition of microscopic lesions in patients with GERD [9,10]. Histologic lesions evaluated were basal cell layer hyperplasia, papillary elongation, intraepithelial eosinophil, neutrophil, and mononuclear cell number, as well as necrosis/erosion, healed erosion, and dilation of intercellular spaces. The project has proven good interobserver agreement (ranging from 64% to 97%). However, a validation study, correlating the evaluated microscopic features with clinical variables, such as reflux symptoms and endoscopic features, has not been performed yet.

In the prospective Central European multicenter *histo*-GERD trial, we recruited 1130 individuals undergoing gastroscopy for various nonselected reasons. Biopsy material was systematically sampled from the gastroesophageal junction (GEJ). In this study, we aimed to assess the prevalence of microscopic esophageal lesions, as defined in the Esohisto consensus guidelines. Specifically, we related their presence to various clinical and/or endoscopic features indicative of GERD, thereby evaluating the clinical significance of the Esohisto project.

2. Materials and methods

We conducted a prospective cross-sectional study to assess the prevalence of microscopic esophageal lesions in patients with GERD and to evaluate associations between histologic and clinical data including endoscopic findings. Data will be presented following the STROBE Statement aimed at strengthening the reporting of observational studies [11].

2.1. Study population

Participants were prospectively recruited in the multicenter central European *histo*GERD trial that aimed at systematically investigating clinical, particularly endoscopic data and histologic findings in individuals with and without symptoms of reflux disease who underwent endoscopic evaluation of their upper gastrointestinal tract.

In Austria, 3 clinical departments (Department of Internal Medicine, Krankenhaus der Barmherzigen Brüder, St Veit/Glan, Department of Surgery, Division of General Surgery, and Department of Internal Medicine, Division of Gastroenterology and Hepatology, Medical University of Graz, Graz, Austria) and, in Germany, 2 private practices (Dr M. Geppert and Dr B. Schmack, Bayreuth, and Dr H. Bordel, Dr R. Müller, and Dr B. Wigginghaus, Osnabrück) participated in the investigation.

During the study period, adult men and women scheduled for elective endoscopic examination for unselected reasons were offered participation. We excluded those with previous surgery leading to abnormal anatomy in the upper gastrointestinal tract, particularly at the GEJ. In Austria, patients were recruited between November 2011 and April 2012, in Germany between December 2011 and May 2012, respectively.

The investigation was carried out in accordance with the Declaration of Helsinki. Each participant provided written informed consent. The study was approved by the Institutional Review Boards of the Medical University of Graz (EK 24–052 ex 11/12) and the University of Erlangen (EK 4571 ex 11/12), respectively, and was registered at ClinicalTrials.gov (NCT01576289).

2.2. Endoscopy

The esophagus, GEJ, and stomach of all participants were examined according to a standardized protocol devised for the study. The *GEJ* was defined as the most proximal extent