Proton Pump Inhibitors Partially Restore Mucosal Integrity in Patients With Proton Pump Inhibitor–Responsive Esophageal Eosinophilia but Not Eosinophilic Esophagitis

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BACKGROUND & AIMS: **Histologic analysis is used to distinguish patients with proton pump inhibitor–responsive eosinophilia (PPI-REE) from those with eosinophilic esophagitis (EoE). It is not clear whether these entities have different etiologies. Exposure to acid reflux can impair the integrity of the esophageal mucosal. We proposed that patients with EoE and PPI-REE might have reflux-induced esophageal mucosal damage that promotes transepithelial flux of allergens. We therefore assessed the integrity of the esophageal mucosal in these patients at baseline and after PPI.**

METHODS: **We performed a prospective study of 16 patients with suspected EoE and 11 controls. Patients had dysphagia, endoscopic signs of EoE, and esophageal eosinophilia (>15 eosinophils/high-power field [eos/hpf]). All subjects underwent endoscopy at baseline; endoscopy was performed again on patients after 8 weeks of treatment with high-dose esomeprazole. After PPI treatment, patients were diagnosed with EoE (>10 eos/hpf; n = 8) or PPI-REE (≤10 eos/hpf; n = 8). We evaluated the structure (intercellular spaces) and function (electrical tissue impedance, transepithelial electrical resistance, transepithelial molecule flux) of the esophageal mucosal barrier.**

RESULTS: **Compared with controls, electrical tissue impedance and transepithelial electrical resistance were reduced in patients with EoE ($P < .001$ and $P < .001$, respectively) and PPI-REE ($P = .01$ and $P = .06$, respectively), enabling transepithelial small-molecule flux. PPI therapy partially restored these changes in integrity and inflammation in patients with PPI-REE, but not in those with EoE.**

CONCLUSIONS: **The integrity of the esophageal mucosa is impaired in patients with EoE and PPI-REE, allowing transepithelial transport of small molecules. PPI therapy partially restores mucosal integrity in patients with PPI-REE, but not in those with EoE. Acid reflux might contribute to transepithelial allergen flux in patients with PPI-REE. Trialregister.nl number: NTR3480.**

Keywords: Epithelial Barrier; Pathophysiology; Transepithelial Resistance; Treatment.

Eosinophilic esophagitis (EoE) is a rapidly emerging disorder clinically characterized by dysphagia and food impaction.[1] The pathophysiology is largely unknown, although genetic and allergic components seem to play a role.[2] More recently, gastroesophageal reflux disease (GERD) also has been suggested to play a role.[3–5] A proton pump inhibitor (PPI) trial may differentiate between EoE and GERD, however, response to PPIs also has been observed in patients with typical symptoms and endoscopic and histopathologic signs of EoE; these patients now are considered to have PPI-responsive eosinophilia (PPI-REE).[4] Little is known about the differences between PPI-REE and EoE.[6] PPI-REE patients may have GERD instead of EoE,

Abbreviations used in this paper: **CCL26, eotaxin-3; EoE, eosinophilic esophagitis; eos/hpf, eosinophils/high-power field; ETIS, electrical tissue impedance spectroscopy; FLG, filaggrin; GERD, gastroesophageal reflux disease; IL, interleukin; IQR, interquartile range; mcs/hpf, mast cells/high-power field; PCR, polymerase chain reaction; POSTN, periostin; PPI, proton pump inhibitor; PPI-REE, proton pump inhibitor–responsive eosinophilia; TER, transepithelial electrical resistance.**

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however, they cannot be distinguished from EoE patients by clinical features, endoscopic signs, or histopathologic signs.[4,7]

In patients with GERD, it has been well documented that acid reflux causes impaired esophageal mucosal integrity, which has been suggested to decrease esophageal intraluminal baseline impedance.[8,9] Acid suppression with PPIs restores the esophageal mucosal integrity in GERD.[10] In EoE, esophageal baseline impedance values are decreased as well, and histologic studies also have shown dilation of intercellular spaces—a morphologic feature of epithelial permeability changes—in EoE.[11,12]

We hypothesized that acid-induced impairment of esophageal mucosal integrity facilitates permeation of food allergens, thereby promoting immune activation in patients with PPI-REE and EoE. If this hypothesis is valid, proton pump inhibition will restore the esophageal mucosal integrity and thereby reduce the passage of allergens into the epithelium. The aim of our study was to show an impaired esophageal mucosal integrity in PPI-REE and EoE patients, and to study the effect of acid suppression on the esophageal mucosal integrity.

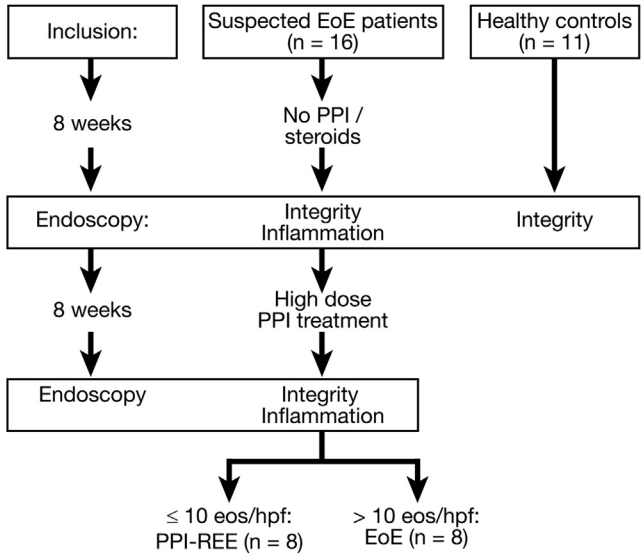

Figure 1. Study protocol and patient subgroup selection. The esophageal mucosal integrity of patients and controls was measured at baseline. In patients, the integrity and inflammation were measured after PPI treatment. Based on the eosinophil count after PPI treatment, patients were categorized as PPI-REE (≤10 eos/hpf) or EoE (>10 eos/hpf).

Methods

Study Subjects

In this prospective study, we included 16 adult patients with suspected EoE (>15 eosinophils/high-power field [eos/hpf], predominant symptoms of dysphagia and/or food impaction, and endoscopic signs of EoE), and 11 healthy controls. Based on peak eosinophil counts after PPI, patients were divided into 2 subgroups: responders (PPI-REE, ≤10 eos/hpf) and nonresponders (EoE, >10 eos/hpf) (Figure 1). Patients were recruited consecutively from the outpatient clinic of our hospital. Healthy controls were recruited by advertisement in the hospital and had no dysphagia/reflux symptoms or other gastrointestinal complaints. None of the study subjects had undergone surgery of the digestive tract. Each study subject provided written informed consent and the study protocol was approved by the Medical Ethics Committee of our institution. All authors had access to the study data and reviewed and approved the final manuscript.

Study Protocol

In all study subjects, dietary, anti-inflammatory, and acid-suppressive treatments were discontinued 8 weeks before baseline upper endoscopy. In the 24 hours preceding endoscopy, smoking and alcohol intake were not allowed. In patients, endoscopy was repeated after 8 weeks of 40 mg esomeprazole twice-daily treatment, and the frequency and severity of dysphagia for liquids and solids was assessed using a 6-grade Likert scale, in which 0 represents no dysphagia and 5 represents daily/severe dysphagia, analogous to the reflux disease questionnaire.

Upper Endoscopy

After routine inspection of the duodenum and stomach, pictures were taken of the esophagus for assessment of endoscopic signs of EoE. After this, 5 electrical tissue impedance spectroscopy (ETIS) measurements were performed in the distal esophagus 5 cm proximal to the Z-line. At the same level, 4 biopsy specimens were obtained with a large biopsy forceps (diameter, 3.7 mm) for the assessment of functional mucosal integrity in Ussing chambers. In addition, 2 large biopsy specimens were taken to evaluate dilation of intercellular spaces by transmission electron microscopy. For histopathologic analysis in patients, 6 biopsy specimens were taken, and 1 biopsy specimen was taken for gene expression profiling.

To assess endoscopic signs of EoE (white exudates, linear furrows, concentric rings, solitary ring, crepe paper mucosa, pallor, and narrow-caliber esophagus), a physician blinded to the patient's status scored the endoscopic pictures.

Esophageal Mucosal Integrity Assessment In Vivo

As a functional measure of esophageal mucosal integrity, we performed ETIS measurements to measure the extracellular esophageal impedance during endoscopy, as previously described.[13] The extracellular impedance was correlated with structural and functional in vitro parameters of esophageal mucosal integrity; ETIS is therefore a measure of esophageal mucosal integrity in vivo.[13]