The GerdQ questionnaire and high resolution manometry support the hypothesis that proton pump inhibitor-responsive oesophageal eosinophilia is a GERD-related phenomenon

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SUMMARY

Background
Little is known about the relationship between proton pump inhibitor-responsive oesophageal eosinophilia (PPI-REE), eosinophilic esophagitis (EoE) and gastro-oesophageal reflux disease (GERD).

Aim
To compare high resolution manometry features and symptom profiles of patients with EoE, PPI-REE and GERD.

Methods
Consecutive patients diagnosed with EoE or PPI-REE according to international criteria (presence of at least one typical symptom of oesophageal dysfunction; at least 15 eosinophils per high-power field at mid/proximal oesophagus, persistence or resolution of eosinophils after an 8-week PPI trial), and a group of patients with proven GERD and oesophageal eosinophilia, prospectively completed the GerdQ questionnaire and underwent high resolution manometry.

Results
Thirty-five patients with EoE, 17 with PPI-REE and 27 with GERD were enrolled. When compared to GERD, both EoE and PPI-REE had higher rates of dysphagia (15% vs. 94% vs. 88%, P < 0.0001), patients with EoE reported heartburn and regurgitation less frequently (26% vs. 85%, and 17% vs. 74%, respectively; P < 0.001 for each and had lower GerdQ score [1 (0–6) vs. 8 (6–12), P < 0.001] than GERD patients. There was no significant difference comparing PPI-REE and GERD patients. Patients with PPI-REE had a higher prevalence of erosive oesophagitis than patients with EoE (35% vs. 9%, P = 0.04), which was similar to that of GERD (48%, P = 0.54). Patients with EoE had a lower frequency of high resolution manometry features associated with GERD than patients with PPI-REE. There was no significant difference between PPI-REE and GERD patients.

Conclusion
GERD, as assessed by GerdQ and high resolution manometry is common in patients with PPI-REE, which may share similar pathogenic mechanisms.

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune/anti-
gen-mediated disease characterised clinically by symp-
toms related to oesophageal dysfunction and histologically by eosinophil-predominant inflamma-
tion.1, 2 Patients may present with a wide range of symp-
toms and, therefore, the upper endoscopy with the
evidence of at least 15 eosinophils per high power field
on oesophageal biopsies is mandatory for the diagno-
sis.3, 4 However, recent studies have demonstrated that
other oesophageal diseases such as gastro-oesophageal
reflux disease (GERD) may lead to dense eosinophilic
infiltrate on oesophageal biopsies similar to what is
observed in EoE.5–8 To rule out GERD, a trial of acid-
suppressants must be administered prior to establishing
a diagnosis of EoE.1, 3 Patients with a disappearance or a
reduction in eosinophilic infiltrate are described as
having proton pump inhibitor-responsive oesophageal
eosinophilia (PPI-REE).9

Although recent data indicate that EoE and PPI-REE
present similar phenotypic appearance and similar
histopathology, it is still unclear if PPI-REE is a GERD-
related phenomenon, a subtype of EoE, or a completely
unique entity. Indeed, current studies failed to observe
clinical or histopathological features able to distinguish
the two entities.5, 10 However, these investigations did
not systematically (i.e. prospectively and with validated
questionnaires) assess reflux-related symptoms. More-
over, limited data on their oesophageal function have
been provided. In particular, high resolution manometry
has been recently shown to provide new insights on
GERD pathogenesis,11, 12 but very limited data are avail-
able on patients with oesophageal eosinophilia and not
focusing on the distinction between these two enti-
ties.13, 14

The aim of this study was to compare clinical, endo-
scopic and manometric features of EoE and PPI-REE
patients with a control group of proven GERD patients,
to verify whether any difference observed may provide
further insights into the pathogenesis of the former two
conditions.

PATIENTS AND METHODS

Patients

In this prospective study, we included consecutive adult
patients diagnosed with EoE and PPI-REE who were
referred for symptoms suspected for EoE (dysphagia
and/or food impaction) to the Gastroenterology and
Surgery Units, University of Padua, between September
2013 and March 2015. Patients were excluded in case of
history of thoracic or digestive surgery, previous or cur-
rent malignancies, established diagnosis of scleroderma
or other connective tissue disorders, gastro-intestinal
bleeding, active anticoagulation, known oesophageal
varices, medical instability or multiple comorbidities.

The study protocol was approved by the Internal
Review Board and performed according to the Declara-
tion of Helsinki Principles. All patients who agreed to
participate in the study gave written informed consent
before its start.

Endoscopy. All patients underwent index upper endo-
scopy off anti-secretory medication and the endoscopic
findings were recorded. Biopsies from oesophageal, gas-
tric and duodenal mucosa were taken: according to the
most recent consensus recommendations, the detection
of ≥15 eosinophils per high power field in at least one
high power field at mid-proximal oesophagus in addition
to symptoms of oesophageal dysfunction was considered
diagnostic of EoE.1 The identification of a prominent
eosinophilic infiltrate in gastric and/or duodenal biopsies
represented an exclusion criteria. After identification of
oesophageal hypereosinophilia at biopsy, all positive
patients were treated with twice-daily PPI (pantoprazole
40 mg twice daily) for at least 8 weeks. Thereafter,
patients repeated upper endoscopy plus biopsy and were
classified as affected by: EoE, in case of persistence of at
least 15 eosinophils per high power field on oesophageal
biopsies, and PPI-REE, in case of less than 15 eosino-
phils per high power field and a 50% decrease from
baseline.

Symptoms assessment. A complete clinical history was
collected, including demographics (race, age, gender),
body mass index, history of atopy and allergy (allergic
rhinitis, asthma, food allergies and seasonal allergies).
The onset and duration of EoE-related symptoms as well
as the latency from diagnosis were recorded. Structured
questionnaires based on four-point Likert scale on
GERD, dysphagia and functional dyspepsia symptoms
were administered.15, 16 Moreover, EoE and PPI-REE
patients were asked to complete the GerdQ question-
naire, blinded to the investigator.17 The questionnaire
was recently validated for the diagnosis of GERD in
comparison with endoscopy and/or pH-testing. A cut-off
value higher ≥9 was considered diagnostic for GERD.17

High resolution manometry. Before treatment, all
patients underwent out-patient high resolution
manometry in the supine position, using a 4.2-mm solid-state probe with 36 circumferential sensors at 1-cm intervals (Medtronic, Los Angeles, CA, USA). Data acquisition, display and analysis were performed using a dedicated software (Manoview analysis software; Medtronic, Duluth, GA, USA). The manometric protocol included a 5-min baseline recording to assess the oesophago–gastric junction and at least 10 single water swallows (5 mL) at 30-s intervals to evaluate the oesophageal peristalsis.18

High resolution manometry metrics analysed were: integrated relaxation pressure, distal contractile integral and distal latency, as previously defined.19 The individual swallow type was assessed and the diagnosis of the oesophageal pressure topography plots was made according to the Chicago Classification v. 3.0.20 Moreover, patients were then classified to have normal oesophago–gastric junction or hiatal hernia, based on the presence of axial cranial separation between lower oesophageal sphincter and crural diaphragm, as previously described.21, 22 Finally, oesophago–gastric junction-contractile integral, a recently introduced high resolution manometry metric to quantify the vigour of oesophago–gastric junction, was calculated according to previous papers.23, 24

For our study, we compared among our groups the high resolution manometry features that have been previously associated with GERD pathogenesis: lower oesophageal sphincter resting pressure, integrated relaxation pressure, oesophago–gastric junction morphology, oesophago–gastric junction-contractile integral and vigour of peristalsis. Also the manometry diagnoses based on Chicago Classification v. 3.0 were compared.

Control group. For comparisons, a group of 27 patients [18 men; mean age 48 (21–70) years; mean body mass index 25 (19–31) kg/m²], with proven reflux disease based on erosive oesophagitis at upper endoscopy (grade A n = 8, grade B n = 3, grade C n = 1, grade D n = 2) and/or abnormal pH-testing (n = 26, with a mean oesophageal acid exposure time of 8% over 24 h) and with an oesophageal eosinophilic infiltration in distal oesophagus was used. Patients taking antisecretary drugs were asked to stop them at least 30 days before endoscopy. All patients underwent upper endoscopy with oesophageal biopsies to assess GERD-related oesophageal histological abnormalities (including eosinophilic infiltration). Moreover, they underwent high resolution manometry with the same protocol and completed the same structured questionnaires. In these patients with proven reflux disease and with distal oesophageal eosinophilic infiltration, EoE was excluded based on negative biopsies for oesophageal infiltration at mid-proximal oesophagus (at least five biopsies taken at mid/proximal oesophagus).

Statistical analysis
Data were collected and analysed using statistical software SPSS version 22 (Statistical Package for the Social Sciences, Chicago, IL, USA). Data for categorical variables are expressed as proportions and percentages and data for continuous variables are expressed as median and interquartile (25th–75th percentiles) range. Unpaired t-test and one-way ANOVA with Bonferroni correction were used for comparison of continuous variables and Kruskal–Wallis test was performed for nonparametric evaluations, where appropriate. A two-sided P value of 0.05 was considered statistically significant.

RESULTS

Basal clinical characteristics
Fifty-two consecutive patients were included. At the follow-up endoscopy plus biopsy, after 8 weeks treatment with twice-daily PPI, 35 (67%) patients were identified as having EoE, whereas 17 (33%) patients were diagnosed as PPI-REE.1 Demographical and clinical features of the study population are summarised in Table 1.

Endoscopic data
Baseline endoscopic features in EoE and PPI-RRE are illustrated in Table 2. Eighteen (51%) EoE patients had oesophageal strictures compared to 4 (24%) PPI-REE patients; the difference was not significant, although there was a positive tendency in favour of the former population (P = 0.0759). Furthermore, there was no difference regarding the other EoE-associated endoscopic features. PPI-REE patients showed an increased frequency of erosive oesophagitis [6 (35%) vs. 3 (9%), P = 0.0446], similar to that of GERD patients with oesophageal eosinophilia [6 (35%) vs. 13 (48%), P = 0.5351], whereas the latter patients had higher rate of erosive oesophagitis compared to EoE patients [13 (48%) vs. 3 (9%), P = 0.0009].

Symptoms assessment
As shown in Table 3, the two cohorts had similar dysphagia (P = 0.5890), bolus impaction (P = 1.000) and chest pain (P = 0.3094), but significantly different rates of heartburn (P = 0.0315) and regurgitation (17%, P = 0.0429). The overall GerdQ score was statistically
lower in EoE than in PPI-REE [1 (0–6) vs. 8 (2.5–11.25), \( P = 0.004 \)]. When compared to GERD patients with oesophageal eosinophilia, both EoE [33 (94%) vs. 4 (15%), \( P < 0.0001 \)] and PPI-REE [15 (88%) vs. 4 (15%), \( P < 0.0001 \)] patients showed increased rate in dysphagia, whereas EoE individuals reported less frequently heartburn [9 (26%) vs. 23 (85%), \( P < 0.001 \)], regurgitation [6 (17%) vs. 20 (74%), \( P < 0.001 \)] and overall GerdQ scores [1 (0–6) vs. 8 (6–12), \( P < 0.001 \)] than GERD patients with oesophageal eosinophilia. In contrast, no difference was found comparing PPI-REE and GERD patients with oesophageal eosinophilia as to heartburn, regurgitation and overall GerdQ score (\( P = 0.0754, 0.1083 \) and 0.720 respectively). Two (6%) EoE, 8 (47%) PPI-REE and 15 (55%) GERD patients with oesophageal eosinophilia had a total score equal or above 9 (EoE vs. PPI-REE \( P = 0.010 \), EoE vs. GERD \( P < 0.001 \) and PPI-REE vs. GERD \( P = 0.7577 \) respectively).

### High-resolution manometry data
At high resolution manometry testing, EoE patients had higher median integrated relaxation pressure [8 (6–11) vs. 4 (2–7), \( P = 0.006 \)] and lower oesophageal sphincter basal pressure [23 (15–29) vs. 13 (11–19), \( P = 0.006 \)], but similar median distal contractile integral [998 (657–1235) vs. 874 (501–1639), \( P = 0.751 \)] than patients with PPI-REE. Type II and III oesophago–gastric junctions were less common in EoE than in PPI-REE patients [3

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**Table 1** | Demographical and clinical characteristics of adult EoE and PPI-REE patients

<table>
<thead>
<tr>
<th>Demographical and clinical features</th>
<th>EoE patients (n = 35)</th>
<th>PPI-REE patients (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, years</td>
<td>29 (18–75)</td>
<td>38 (18–65)</td>
<td>0.0200</td>
</tr>
<tr>
<td>Age at diagnosis below 30 years, n (%)</td>
<td>23 (66)</td>
<td>6 (35)</td>
<td>0.0726</td>
</tr>
<tr>
<td>Year latency from diagnosis, years</td>
<td>4 (0–15)</td>
<td>6 (2–16)</td>
<td>0.3010</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male, n (%)</td>
<td>27 (77)</td>
<td>13 (76)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>8 (23)</td>
<td>4 (24)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21 (16–25)</td>
<td>24 (16–42)</td>
<td>0.0280</td>
</tr>
<tr>
<td>Coffee consumption, n (%)</td>
<td>22 (63)</td>
<td>7 (41)</td>
<td>0.2335</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>14 (40)</td>
<td>5 (29)</td>
<td>0.5482</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>11 (31)</td>
<td>3 (18)</td>
<td>0.1784</td>
</tr>
<tr>
<td>Peripheral eosinophilia</td>
<td>6 (17)</td>
<td>2 (12)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Peripheral eosinophils (mean cells x10⁹/L ± s.d.)</td>
<td>0.31 ± 0.21</td>
<td>0.27 ± 0.17</td>
<td>0.1560</td>
</tr>
<tr>
<td>IgE levels (mean kU/L ± s.d.)</td>
<td>243 ± 198</td>
<td>221 ± 211</td>
<td>1.0000</td>
</tr>
<tr>
<td>Maximum eosinophils count (mean ± s.d.)</td>
<td></td>
<td></td>
<td>1.0000</td>
</tr>
<tr>
<td>Before PPI trial</td>
<td>63.1 ± 20.2</td>
<td>59.6 ± 28.9</td>
<td></td>
</tr>
<tr>
<td>After PPI trial</td>
<td>48.6 ± 12.9</td>
<td>5.0 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allergy</td>
<td></td>
<td></td>
<td>0.1976</td>
</tr>
<tr>
<td>Atopy, n (%)</td>
<td>17 (49)</td>
<td>8 (47)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td>8 (23)</td>
<td>4 (24)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Allergic rhinitis, n (%)</td>
<td>12 (34)</td>
<td>5 (29)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Atopic dermatitis, n (%)</td>
<td>4 (11)</td>
<td>1 (6)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Urticaria or angioedema, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

**Table 2** | Endoscopic findings at diagnosis in adult EoE and PPI-REE patients

<table>
<thead>
<tr>
<th>Endoscopic features</th>
<th>EoE patients (n = 35)</th>
<th>PPI-REE patients (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative endoscopy, n (%)</td>
<td>8 (23)</td>
<td>4 (24)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Oesophageal rings, n (%)</td>
<td>20 (57)</td>
<td>10 (59)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Whitish exudates, n (%)</td>
<td>9 (26)</td>
<td>6 (35)</td>
<td>0.5249</td>
</tr>
<tr>
<td>Linear furrows, n (%)</td>
<td>17 (49)</td>
<td>9 (53)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Crepe paper, n (%)</td>
<td>6 (17)</td>
<td>3 (18)</td>
<td>0.6221</td>
</tr>
<tr>
<td>Strictures, n (%)</td>
<td>18 (51)</td>
<td>4 (24)</td>
<td>0.0759</td>
</tr>
</tbody>
</table>

EoE, eosinophilic esophagitis; PPI-REE, proton pump inhibitor-responsive oesophageal eosinophilia; PPI, proton pump inhibitor.
Manometric diagnoses are shown in Table 4. Median oesophago–gastric junction-contractile integral of EoE patients was higher than in PPI-REE subjects [18 (4–40) vs. 13 (0–27), P < 0.001], whereas a defective oesophago–gastric junction was more common in PPI-REE compared to EoE patients [9 (47%) vs. 8 (20%), P = 0.0250]. Considering overall the manometric alterations in terms of reduced oesophageal clearance (ineffective, fragmented and absent peristalsis), they were more common in PPI-REE than in EoE patients [9 (26%) vs. 10 (59%), P = 0.0315].

As for symptoms, EoE patients showed higher integrated relaxation pressure [8 (6–11) vs. 5 (3–7), P < 0.001] and lower oesophageal sphincter pressure [23 (15–29) vs. 10 (2–21), P < 0.001] than GERD patients with oesophageal eosinophilia and similar distal contractile integral [998 (657–1235) vs. 1104 (899–1556), P = 0.720]. Type I oesophago–gastric junction was more frequent in EoE [32 (91%) vs. 10 (37%), P < 0.0001], whereas GERD patients with oesophageal eosinophilia showed a greater incidence of oesophageal hypomotility patterns [9 (26%) vs. 15 (56%), P = 0.0205]. Finally, median oesophago–gastric junction-contractile integral of EoE patients was higher than in the PPI-REE ones [18 (4–40) vs. 11 (1–22), P < 0.001], whereas a defective oesophago–gastric junction was more common in GERD patients with oesophageal eosinophilia compared to EoE patients [16 (59%) vs. 8 (20%), P < 0.0001]. In contrast, PPI-REE patients showed similar values for integrated relaxation pressure, lower oesophageal sphincter pressure, distal contractile integral, Type I oesophago–gastric junction rate, hypomotility patterns, oesophago–gastric junction-contractile integral and defective oesophago–gastric junction frequency compared to GERD patients with oesophageal eosinophilia (P = 1.000, 0.324, 0.854, 1.0000, 1.0000, 0.720, 0.656 respectively) (Table 4).

### DISCUSSION

Eosinophilic oesophagitis has been increasingly diagnosed over the past 20 years and, actually it has reported to be the second cause of dysphagia after GERD. Together with the increasing recognition and diagnosis of EoE, oesophageal eosinophilia is being encountered more frequently and a new clinical entity has been recently recognised. However, little is known about PPI-REE. In particular, the relationship between PPI-REE and GERD is unclear and similarities and differences were investigated only in retrospective studies including patients assessed under anti-secretory therapy. Furthermore, these investigations were not focused on their motility patterns potentially highlighting their relationship with reflux disease. Thus, this represents the first study aimed to compare high resolution manometry findings in patients with EoE and PPI-RRE and to assess reflux disease presence using a disease-specific validated questionnaire. We showed in a large cohort of patients studied off-PPI therapy that high resolution manometry GERD-related patterns, typical reflux symptoms and erosive oesophagitis at upper endoscopy were more frequent in PPI-REE patients than in those with EoE, despite similarities in the two cohorts about endoscopic EoE-related features and dysphagia.
that there are evidences about an early use of more aggressive therapies (i.e. steroids and diets), prior to a course of PPIs required to establish the diagnosis of EoE, these findings are particularly relevant since patients with PPI-REE may be suspected by clinical, pathophysiological (if performed) and endoscopic findings and may obviate these treatments.30, 31

According to previous studies,5, 10 our EoE and PPI-REE patients presented similar incidence of dysphagia and bolus impaction, whereas in the GERD with oesophageal eosinophilia control group these symptoms were rare. One could argue that these two symptoms were triggered by the presence of an oesophageal lumen calibre reduction. However, strictures were common in EoE patients, but less frequent in PPI-REE subjects. Thus, different pathways for the development of these symptoms in the two cohorts could be present. We hypothesised that in EoE the role of submucosal fibrosis due to the eosinophilic infiltrate, with subsequent oesophageal body dysfunction and poor wall compliance, was more relevant than in patients with PPI-REE in whom the symptom dysphagia was more likely due to the concomitant effect of oesophageal motility abnormalities, hiatal hernia, abnormal reflux, impaired sensitisation and, of course, submucosal fibrosis. Moreover, we speculated that the lack of dysphagia and food impaction in patients with GERD and oesophageal eosinophilia was due to the absence of eosinophilic infiltration in the mid/proximal oesophagus, resulting in a better compliance of oesophageal wall. Furthermore, it is important to bear in mind that the sensitivity of the oesophagus is not the same along its length and several studies documented that stimuli occurring at proximal oesophagus are perceived more than those at the distal portion.32

So far, the high degree of inflammation in the proximal oesophagus might play a major role in determining an increased perception of symptoms such as dysphagia and bolus impaction in patients with EoE and PPI-REE.

In our cohort, patients with PPI-RRE and GERD controls reported similar frequency of typical reflux symptoms and had more commonly erosive oesophagitis at upper endoscopy, whereas patients with EoE complained of heartburn and regurgitation less commonly, suggesting a potential role of GER in favouring dysphagia in PPI-RRE patients, according to our above-mentioned hypothesis. The mechanisms of dysphagia in patients with reflux disease are uncertain and different hypotheses have been formulated, including direct stimulation of acid at sub-mucosal level, development of motility abnormalities and mucosal injuries, peptic stenotic

<table>
<thead>
<tr>
<th>High resolution manometry features</th>
<th>EoE patients (n = 35)</th>
<th>PPI-REE patients (n = 17)</th>
<th>GERD patients (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS resting pressure, mmHg</td>
<td>23 (6–11)</td>
<td>13 (11–19)*</td>
<td>10 (2–21)+</td>
</tr>
<tr>
<td>Integrated relaxation pressure (IRP), mmHg</td>
<td>8 (6–11)</td>
<td>4 (2–7)*</td>
<td>5 (3–7)+</td>
</tr>
<tr>
<td>Median DCI (25th–75th percentiles), mmHg<em>cm</em>s</td>
<td>998 (657–1235)</td>
<td>874 (501–1639)*</td>
<td>1104 (899–1556)+</td>
</tr>
<tr>
<td>OGJ-CI, mmHg</td>
<td>18 (4–40)</td>
<td>13 (0–27)*</td>
<td>11 (1–22)+</td>
</tr>
<tr>
<td>Patients with defective OGJ-CI (&lt;13 mmHg), n (%)</td>
<td>7 (20)</td>
<td>9 (47)*</td>
<td>16 (59)+</td>
</tr>
<tr>
<td>OGJ morphology</td>
<td></td>
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<td></td>
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<tr>
<td>OGJ Type I, n (%)</td>
<td>32 (91)</td>
<td>7 (42)*</td>
<td>10 (37)+</td>
</tr>
<tr>
<td>OGJ Type II + Type III, n (%)</td>
<td>3 (9)</td>
<td>10 (58)*</td>
<td>18 (67)+</td>
</tr>
<tr>
<td>Motility pattern</td>
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<tr>
<td>Normal peristalsis, n (%)</td>
<td>20 (57)</td>
<td>6 (35)</td>
<td>10 (37)</td>
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<tr>
<td>Ineffective peristalsis, n (%)</td>
<td>3 (9)</td>
<td>6 (35)</td>
<td>6 (22)</td>
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<tr>
<td>Fragmented peristalsis, n (%)</td>
<td>4 (11)</td>
<td>3 (18)</td>
<td>7 (26)</td>
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<td>Absent peristalsis, n (%)</td>
<td>2 (6)</td>
<td>1 (6)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Distal oesophageal spasm, n (%)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Achalasia, n (%)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Outflow obstruction, n (%)</td>
<td>3 (9)</td>
<td>1 (6)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

EoE, eosinophilic esophagitis; PPI-REE, proton pump inhibitor-responsive oesophageal eosinophilia; LOS, lower oesophageal sphincter; GERD, gastro-oesophageal reflux disease; DCI, distal contractile integral; OGJ-CI, oesophago–gastric junction-contractile integral.

*P < 0.05 for PPI-REE vs. EoE.
†P < 0.05 for GERD vs. EoE.
‡P < 0.05 for GERD vs. PPI-REE.
disease and also abnormal sensitisation. Nevertheless, the resolution of dysphagia with heartburn after PPI treatment has been considered an additional criterion to attribute dysphagia to GERD. Thus, it is reasonable that the same mechanisms may contribute to the elicitation of dysphagia in PPI-REE patients. It is relevant to note that previous studies failed to observe differences in terms of typical reflux symptoms between EoE and PPI-REE patients. However, one of the major strengths of our study is its prospective design that allowed us to use validated instruments for investigating the presence of typical reflux symptoms in our patients, whereas in the previous two studies there is no mention about how reflux symptoms were collected. The importance of having and applying specific disease questionnaires has been demonstrated in several studies to overcome the limitations related to the patient self-report of symptoms and, in fact, the International Eosinophilic Esophagitis Activity Index Study Group recently suggested the use of an EoE scoring system based on seven patient-reported outcome items to assess symptoms over a 7-day recall period. Thus, we believe that an accurate evaluation of reflux symptoms by means of a validated questionnaire may permit to observe differences between EoE and PPI-REE in terms of reflux symptoms and support the need of administering PPIs, by avoiding more aggressive therapies.

This is the first study aimed to assess differences in terms of high resolution manometry findings between EoE and PPI-REE, since the only two investigation applying high resolution manometry in EoE did not differentiate PPI-REE from EoE patients. In particular, Roman et al. studied by means of high resolution manometry 48 EoE patients and found that 13 (27%) of them had weak or frequent failed peristalsis. Our data in EoE patients are in agreement with those reported by Roman et al. and van Rhijn et al. given that ineffective and fragmented peristalsis were present in 20% of our EoE patients. Furthermore, using high resolution manometry and the more recent diagnostic criteria, we investigated and compared oesphago–gastric junction features and morphologies in our patients. We found that EoE patients showed a higher median lower oesophageal sphincter basal pressure and an higher median integrated relaxation pressure than in PPI-REE patients and GERD with oesophageal eosinophilia. Also, a minor incidence of type II and III oesphago–gastric junction morphology and a lower rate of defective oesphago–gastric junction, as assessed by oesphago–gastric junction contractile integral, were observed in EoE. In contrast, patients with PPI-REE and GERD with oesophageal eosinophilia presented similar values for these features, suggesting that the presence of a “disrupted” oesphago–gastric junction and, therefore, gastro-oesophageal reflux occurrence, may play an important role in symptoms and disease development in PPI-REE, similarly to what happens in GERD patients.

Strengths of this study include the use of the state-of-the-art method to assess oesophageal motility and the prospective design with the possibility to administer validated instruments to assess reflux symptoms and the possibility to differentiate EoE and PPI-REE based on international objective criteria. A further strength relied on the exclusion of patients under recent or current anti-secretory therapy at index endoscopy and first visit, in contrast to the study of Dellon et al. This allowed us to avoid a wrong misclassification of our patients as normals when they actually had PPI-REE and to find erosive oesophagitis at endoscopy because the healing effect of PPIs was lacking. Moreover, it is reasonable to believe that also the lack of PPI administration increased the possibility to detect more patients complaining of heartburn and regurgitation at first visit. On the other hand, the lack of reflux monitoring studies and the single centre design, with the consequent limited sample size, may be regarded as limitations. However, reflux monitoring in EoE has not been proven to date as an effective measure to predict response to therapy and, so far, it is not considered in the diagnostic algorithm of suspected EoE patients. Moreover, the physiological nature of the study precluded to enrol a big number of patients.

In conclusion, our data suggest that typical reflux symptoms, erosive oesophagitis and high resolution manometry GERD-related features are more common in patients with PPI-REE than in patients with EoE, whereas endoscopic EoE-associated features and the presence of dysphagia as well as food impaction or chest pain were not able to distinguish between the two groups. These data support the hypothesis that PPI-REE and GERD may share similar pathogenic mechanisms, suggesting a close relationship between these two entities. Furthermore, our data emphasise the need of undergoing a PPI trial in patients with oesophageal eosinophilia to rule out GERD and PPI-REE and avoiding an incorrect and prolonged administration of topical or systemic steroids. Further larger prospective studies are needed to confirm these findings.

**AUTHORSHIP**

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