Digestive and Liver Disease 54 (2022) 1143–1152

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Systematic Review: esophageal motility patterns in patients with eosinophilic esophagitis

Pierfrancesco Visaggi[a,1], Matteo Ghisa[b,1], Brigida Barberio[b], Elisa Marabotto[c], Nicola de Bortoli[a,2], Edoardo Savarino[b,2,*]

[a] Gastroenterology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[b] Gastroenterology Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy
[c] Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy

ARTICLE INFO

Article history:
Received 4 December 2021
Accepted 5 January 2022
Available online 25 January 2022

Keywords:
Eosinophilic esophagitis
High-resolution manometry
Motility disorders

ABSTRACT

Background: Eosinophilic esophagitis (EoE) is a chronic disorder of the esophagus characterized by an eosinophil-predominant inflammation and symptoms of esophageal dysfunction. Eosinophils can influence esophageal motility, leading to dysphagia worsening. The spectrum of esophageal motility in EoE is uncertain.
Aim: We performed a systematic review to investigate esophageal motility in EoE.
Methods: MEDLINE, EMBASE and EMBASE Classic were searched from inception to 16th November 2021. Studies reporting esophageal motility findings in EoE patients by means of conventional, prolonged, and/or high-resolution esophageal manometry were eligible.
Results: Studies on esophageal conventional and high-resolution manometry (HRM) found that all types of manometric motor patterns can be found in patients with EoE and investigations on 24-hour prolonged manometry demonstrated an association between symptoms and intermittent dysmotility events, which can be missed during standard manometric analysis. Panesophageal pressurizations are the most common HRM finding and may help in formulating a clinical suspicion. Some motility abnormalities may reverse after medical treatment, while other major motility disorders like achalasia require invasive management for symptoms control. HRM metrics have demonstrated to correlate with inflammatory and fibrostenotic endoscopic features of EoE.
Conclusion: Esophageal motor abnormalities are common in patients with EoE and may contribute to symptoms. The resolution of dysmotility after medical treatment corroborates that eosinophils influence esophageal motility.

1. Introduction

Eosinophilic esophagitis (EoE) is an antigen-driven immune-mediated disorder of the esophagus characterized by a chronic eosinophil-predominant inflammation, in the absence of secondary causes of eosinophilia [1]. The esophageal eosinophilic infiltrate has a patchy nature, and multiple esophageal biopsies may be necessary to prove the presence of at least 15 eosinophils/high-power field (HPF) in at least one esophageal biopsy and achieve the diagnosis [2–4]. Mast cells and T-helper type 2 lymphocytes participate in the local inflammatory process, which ultimately leads to structural and motor alterations of the esophagus with organ dysfunction [5].

In Western Countries, the estimated incidence rate is 1 patient in every 1000, while prevalence may be up to 20 in every 100.000 individuals [6]. However, the disease is often misdiagnosed, and it is estimated that the diagnosis is achieved with a delay of 36–72 months [7]. Intermittent dysphagia and food impactions represent the most common presenting symptoms associated with EoE in older children and adults [1,8]. Accordingly, a recent systematic review concluded that, in children, dysphagia and food impaction are

Abbreviations: EoE, eosinophilic esophagitis; CC, Chicago classification; PEMP, Prolonged esophageal manometry and pH-metry; PEP, panesophageal pressurization; HRM, high-resolution manometry; CM, conventional manometry; LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease; DES, distal esophageal spasm; IEM, ineffective esophageal motility; HE, hypercontractile esophagus; NE, nutcracker esophagus; NMD, nonspecific motor disorder; HPF, high-power field.

* Corresponding author at: Department of Surgery, Oncology and Gastroenterology, University of Padua, Via Giustiniani 2, 35128 Padova, Italy.
E-mail address: edoardo.savarino@unipd.it (E. Savarino).

[1] PV and MG shares first co-authorship.
[2] NdB and ES shares last co-authorship.

https://doi.org/10.1016/j.dld.2022.01.003
1590-8658/

reported in up to 60.9% and 21.7% of cases, respectively, whereas in adults dysphagia and food impactions may be present in up to 94.5% and 65.7% of patients, respectively [9].

In some patients with EoE, symptoms can be related to endoscopic findings as esophageal rings, narrowed esophageal calibre, and strictures. However, up to 33% of patients have no visible anatomic abnormality, suggesting the possibility that an esophageal motor disorder may underlie symptoms [10].

Eosinophils can cause dysmotility, although the exact mechanism is unclear. Activated eosinophils and mast cells transmurally infiltrate the esophagus and release profibrotic, myoactive, and neuroactive molecules, which can have an impact on esophageal smooth muscle contraction and fibrotic remodeling [5]. The severity of esophageal structural and ultrastructural inflammatory changes can be graded according to the EoE endoscopic reference score system [11], and the EoE histology scoring system [12], respectively; however, their correlation with symptoms is often inconsistent [13], and dysmotility may be an unrecognized contributing factor to this discrepancy.

Esophageal manometry is the test of choice to investigate esophageal motility. When EoE was first recognized as a distinct disease [14], esophageal motor function could be investigated by means of conventional manometry (CM), although there was high variability in the interpretation of manometric findings. In recent years, high-resolution manometry (HRM) has become the gold standard to accurately assess esophageal motility and investigate functional causes for esophageal symptoms based on the Chicago Classification of esophageal motility disorders (CC) [15–18].

The spectrum of esophageal motility patterns in patients with EoE undergoing esophageal manometry is uncertain. Accordingly, we performed a systematic review of the literature to summarize current knowledge on esophageal motility assessed by means of conventional, prolonged and/or high-resolution manometry in patients with EoE.

2. Methods

2.1. Search strategy

We searched MEDLINE, EMBASE and EMBASE Classic (via Ovid), from inception to 16th November 2021, to identify cohort, case-control, cross-sectional, case series, and case report studies reporting esophageal motility findings in patients with EoE. To identify potentially eligible studies published only in abstract form, conference proceedings (Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology Week) from 2000 until 16th November 2021 were also searched. The complete search strategy is provided in **Supplementary Methods**. There were no language restrictions. We screened titles and abstracts of all citations identified by our search for potential suitability and retrieved those that appeared relevant to examine them in more detail. A recursive search of the literature was performed using bibliographies of all relevant studies.

2.2. Study selection (inclusion and exclusion criteria)

The eligibility assessment was performed independently by two investigators (PV, MG) using pre-designed eligibility forms. We included in the systematic literature studies evaluating esophageal motility findings in adults and/or pediatric patients with EoE by means of conventional manometry, prolonged manometry and/or high-resolution manometry. Review articles, studies investigating esophageal motility following esophageal/thoracic/abdominal surgery or esophageal dilation, and studies not meeting the predefined eligibility criteria were excluded.

Disagreements were resolved by consensus opinion among reviewers, and the degree of agreement was measured with a kappa statistic. Ethical approval was not required because this study retrieved and synthesised data from already published studies.

2.3. Data extraction and analysis

Data were extracted independently by two authors (PV, MG) onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA). Disagreements were resolved by consensus among the reviewing authors.

The following data were collected for each study: total number of patients, type of patients (i.e., adults or children), type of manometry (i.e., conventional manometry, prolonged esophageal manometry, high-resolution manometry), type of classification used to assess manometry findings (when applicable), manometry diagnoses, and cut-off value for the diagnosis of EoE. In addition, year of publication, geographic area where the study was conducted, and type of study (prospective, retrospective, case series, case report) were also retrieved.

3. Results

The Search strategy generated 2890 citations, of which 2846 were excluded based on title and abstract screening, and 44 were retrieved for full-text evaluation. Of these, 8 were excluded: 4 were dual publications, 2 did not report outcomes of interest, and 2 reported cases of esophageal eosinophilia which was not related to EoE. Finally, 36 studies met the inclusion criteria and were eligible for data extraction. Of these, 12 used CM, one both CM and ambulatory prolonged esophageal manometry and pH-metry (PEMP), one both CM and HRM, and 22 HRM (**Fig. 1**). Agreement between investigators for assessment of study eligibility was excellent (kappa statistic = 0.85).

3.1. Studies on esophageal conventional and prolonged manometry

A wide range of motor abnormalities has been reported in patients with EoE undergoing CM (**Table 1**).

In a series of 12 patients, Lucendo et al. [19] found that 83% of patients displayed signs of esophageal manometric alterations according to the recommendations of the Spanish Group of Digestive Motility. In particular, six patients had severe impairment of peristalsis with up to 80% interrupted peristaltic movements or low-amplitude peristalsis. In contrast, three patients had hypercontractility, and one showed a primary simultaneous wave in the majority of deglutition complexes. Of these, seven patients underwent a repeated manometry following a three-month course of topical fluticasone propionate, showing a significant improvement of symptoms and peristaltic waves' pattern. Similarly, Lucendo et al. [20] reported the case of one patient with EoE and absent peristalsis, which improved with 80% effective swallows after a 12-week treatment with topical fluticasone propionate.

In 2009, Bassett et al. [21] conducted a prospective study to investigate the prevalence of esophageal dysmotility in patients with EoE. Five patients were found to have a nonspecific esophageal motor disorder with nontransmitted peristalsis in at least 30% of wet swallows, two patients had high-amplitude peristaltic waves, and 23 patients showed normal esophageal motility. Consistently, other small retrospective or case report studies that investigated motor findings at standard manometry in patients with EoE described a wide range of patterns, including absent peristalsis [22], vigorous achalasia [23], distal esophageal spasm [24–26], segmental esophageal spasm of the mid esophagus [22], nutcracker esophagus [26,27], low pressure of the LES [22], and normal peristalsis [22,24,26-28].

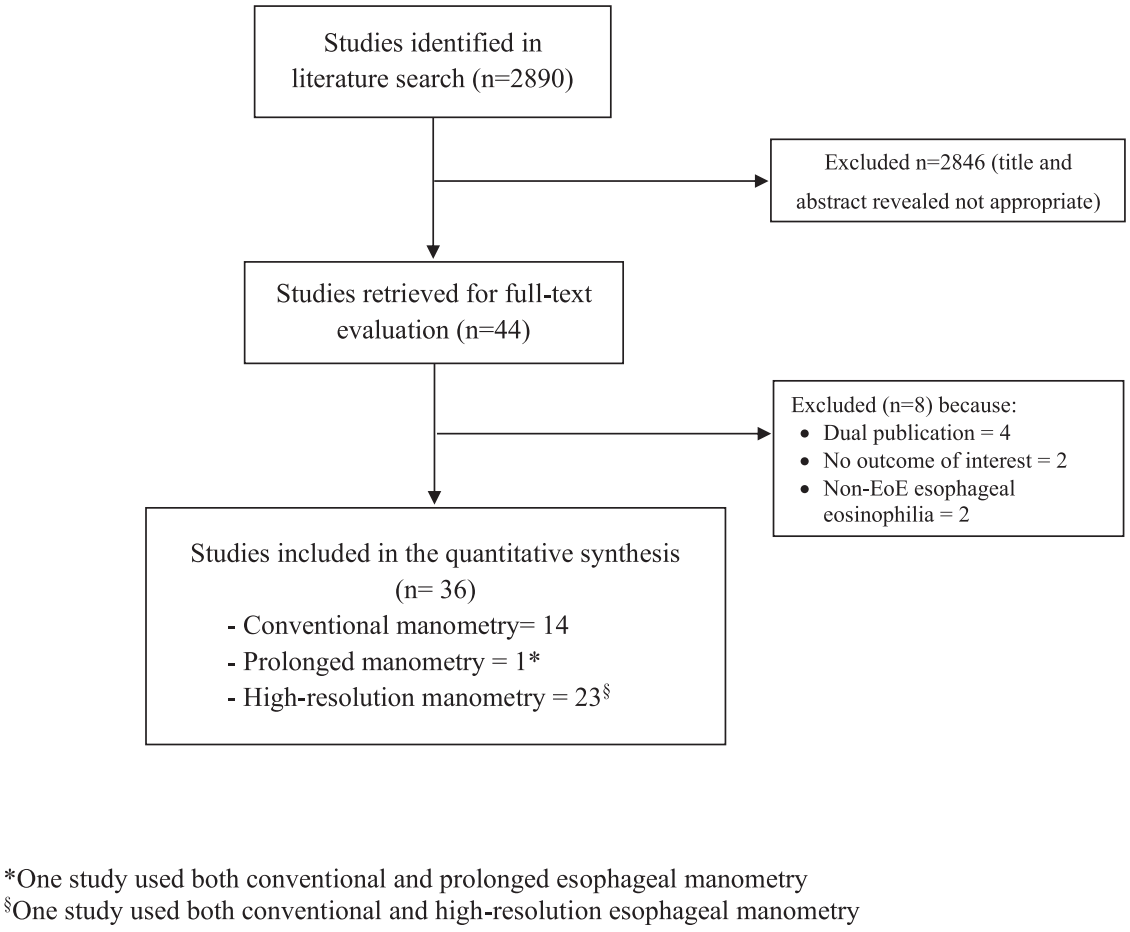

Fig. 1. Diagram of Assessment of Studies Identified for the Systematic Review.

In a cross-sectional study on 20 patients with EoE undergoing CM, it was found that 25% had dysmotility, with IEM being present in 15%, and LES dysfunction in 10% of cases [29]. In contrast, another cross-sectional study documented normal peristalsis in all 11 patients with EoE who had been referred for dysphagia [30].

More recently, Moawad et al. [31] retrospectively evaluated the prevalence of motor disorders in a large cohort of 75 patients. The authors found that 63% of patients had normal peristalsis, 33% had ineffective esophageal motility, and 4% had a diagnosis of nutcracker esophagus. The pattern of esophageal motility were further sub-analysed based on the predominant reported symptom. Among 56 patients with dysphagia, more than a half had normal peristalsis, and the remaining subjects had either IEM or nutcracker esophagus. Similarly, among those with food impaction, 83% had normal peristalsis, and 17% had IEM. Of particular note, there was no difference in the dysphagia scores or peak eosinophil count among motility groups. Accordingly, the authors concluded that motility disorders could not be predicted by dysphagia scores in EoE, and that as much as 33% of EoE patients will have evidence of hypo- or hypercontractility on CM.

In contrast, Nurko et al. [32] hypothesized that dysphagia was related to intermittent esophageal dysmotility in a proportion of patients with EoE, and that the dysfunction could be missed when analysing only a small number of wet swallows during standard manometry. To prove this concept, the authors performed a PEMP in 17 children with EoE, 13 children with gastro-esophageal reflux disease (GERD), and 11 healthy controls, preceded by a standard CM. The PEMP lasted 20–24 h during which the patients conducted their usual daily activities and reported the occurrence of symptoms. During CM, 41% of EoE patients showed evidence of nonspecific motor disorders, compared to none of the controls and GERD group. When the PEMP tracings were analysed, all patients with abnormal CM had their motor dysfunction confirmed; additionally, dysmotility was also disclosed in a proportion of patients with normal CM. Compared to GERD and controls, children with EoE showed significantly more high-amplitude contractions in the distal esophagus and fewer complete peristaltic waves, displaying frequent ineffective peristalsis both during fasting and feeding. During prolonged registration, 13 children with EoE experienced 21 episodes of dysphagia, and all episodes were simultaneous with an event of abnormal motility. In 90% of the episodes, non-peristaltic contractions and isolated and repetitive contractions occurred, while peristaltic waves with amplitude $>$ 180 mmHg coincided with 70% of dysphagia events, demonstrating a correlation between symptoms and esophageal motor events in real life conditions.

3.2. Studies on esophageal high-resolution manometry

Recently, several studies investigated motility in patients with EoE by means of HRM (**Table 2**).

One of the first reports described a single EoE patient undergoing HRM who displayed a vigorous achalasia pattern according to CC v1.0 [16], which completely reversed to normal peristalsis with dysphagia improvement following a six-month course of topical fluticasone [22]. Subsequently, other case reports described

Table 1
Studies using conventional or prolonged manometry in patients with eosinophilic esophagitis.

Author/year	Type of study/Geographic area	Cut-off value for the diagnosis of EoE	Type of patients	Number of patients	Findings
Landres 1978 [23]	Case report/America	NA	Adult	1	• Vigorous achalasia
Attwood 1993 [26]	Retrospective/America	>20 eos/HPF	Adults	12	• 7 NMD • 2 DES • 2 NE • 1 Normal peristalsis
Vitellas 1993 [24]	Retrospective/America	NA	Adults	13	• 10 Normal peristalsis • 3 DES
Hempel 1996 [25]	Case report/America	NA	Adult	1	• DES
Arora 2003 [27]	Retrospective/America	≥ 20 eos/HPF	Adults	6	• 4 Normal peristalsis • 1 NE • 1 NMD
Cheung 2003 [30]	Retrospective/Australia	> 20 eos/HPF	Children	11	• 11 Normal peristalsis
Cantù 2005 [28]	Case series/Europe	> 20 eos/HPF	Adults	2	• 1 Normal peristalsis • 1 Absent peristalsis between 18 and 10 cm above LES
Lucendo 2006 [20]	Case report/Europe	NA	Adult	1	• Absent peristalsis
Lucendo 2007 [19]	Case series/Europe	>24 eos/HPF	Adults	12	• 6 NMD • 3 Hypercontractility • 2 Normal motility • 1 Primary simultaneous waves
Bassett 2009 [21]	Prospective/America	≥ 20 eos/HPF	Adults	30	• 23 Normal peristalsis • 5 NMD • 2 High-amplitude peristaltic waves
Nurko 2009* [32]	Prospective/America	> 15 eos/HPF	Children	17	• 10 normal peristalsis • 7 NMD
Hejazi 2010 [22]	Retrospective/America	> 15 eos/HPF	Adults	12	• 5 low LES pressure • 4 Normal peristalsis • 2 Absent peristalsis • 1 segmental spasm of mid esophagus
Moawad 2011 [31]	Retrospective/America	≥ 15 eos/HPF	Adults	75	• 47 Normal peristalsis • 25 IEM • 3 NE
Monnerat 2012 [29]	Prospective/America	≥ 15 eos/HPF	Adults	20	• 15 Normal peristalsis • 3 IEM • 2 LES dysfunction

Abbreviations. DES, distal esophageal spasm; **eos/HPF**, eosinophils per high-power field; **IEM**, ineffective esophageal motility; **LES**, lower esophageal sphincter; **NA**, not available; **NE**, nutcracker esophagus; **NMD**, nonspecific motor disorder; *This study used both conventional manometry and prolonged esophageal manometry and pH-metry.

patients with achalasia and EoE overlap. Savarino and colleagues [33] reported the case of a patient with chronic substernal discomfort and intermittent dysphagia for solids, with a manometric diagnosis of achalasia at high-resolution impedance manometry (HRIM) and severe eosinophilic infiltration at esophageal biopsies. A treatment with 50 mg prednisolone once daily was given, with dramatic improvement of symptoms and complete manometric recovery at subsequent HRIM. Another case report described a patient who was referred for dysphagia and food impaction despite a completely normal upper endoscopy [34]. Esophageal biopsies confirmed EoE, and the HRM showed an achalasia-like pattern with increased IRP and absent peristalsis. Three other case report documented the possibility of concomitant diagnoses of EoE and achalasia [35–37].

Tanaka et al. [38] presented a case report of a patient referred for progressive dysphagia and chest pain, whose esophageal mucosa was massively infiltrated by eosinophils. On HRM, the patient showed a DCI >8000 mmHg-cm-s in 30% of 5-ml wet swallows. According to CC v3.0 [18], the authors diagnosed a JE caused by EoE and the patient was unsuccessfully given topical fluticasone treatment. Next, oral prednisolone was prescribed, but symptoms and high-amplitude peristaltic waves persisted despite the absence of eosinophils on esophageal biopsies. Subsequently, the patient underwent a per-oral endoscopic myotomy (POEM), which led to symptom improvement and disappearance of the motor disorder. Of particular note, the POEM procedure allowed to collect biopsies of the muscular layers of the esophagus and demonstrate persistent eosinophilic infiltrates (70–80 eosinophils/HPF), which were

Table 2
Studies using high-resolution manometry in patients with eosinophilic esophagitis.

Author/year	Type of study/ Geographic area	Cut-off value for the diagnosis of EoE	Type of patients	Number of patients	CC version	Findings
Hejazi 2010 [22]	Case series/America	> 15 eos/HPF	Adult	1	V1.0	• 1 Vigorous achalasia
Martin 2011 [42]	Prospective/Europe	> 15 eos/HPF	Adults	21	V1.0	• 6 Peristaltic dysfunction • 5 Normal peristalsis • 10 PEP
Roman 2011 [41]	Retrospective/America	> 15 eos/HPF	Adults	48	V1.0	• 30 Normal peristalsis • 8 Weak peristalsis • 5 Frequent failed peristalsis • 2 Rapid contractions • 1 Absent peristalsis • 1 Hypertensive peristalsis • 1 Functional EGJ obstruction • Overall, 17 patients had abnormal esophageal pressurizations
Karkelis 2012 [55]	Case series/Europe	≥ 15 eos/HPF	Children	2	V2.0	• 2 NE
Weigt 2013 [39]	Retrospective/Europe	≥ 15 eos/HPF	Adults	10	V2.0	• 3 Normal peristalsis • 7 Weak peristalsis
Snyder 2014 [35]	Case report/America	≥ 15 eos/HPF	Adult	1	V2.0	• 1 Achalasia
Van Rhijn 2014 [40]	Retrospective/ Europe	> 15 eos/HPF	Adults	31	V2.0	• 13 Normal peristalsis • 9 Weak peristalsis • 4 Frequent failed peristalsis • 2 EGJOO • 2 Rapid contractions • 1 Weak peristalsis and rapid contractions
Colizzo 2016 [45]	Retrospective/America	> 15 eos/HPF	Adults	29	V2.0	• 23 Normal peristalsis • 2 JE • 2 Weak peristalsis • 1 EGJOO • 1 hypertensive LES
Nennstiel 2016 [43]	Prospective/Europe	≥ 15 eos/HPF	Adults	20	V1.0	• 12 Normal peristalsis • 7 early PEP • 1 compartmentalized pressurization
Savarino 2016 [44]	Retrospective/Europe	≥ 15 eos/HPF	Adults	35	V3.0	• 20 Normal • 4 Fragmented peristalsis • 3 IEM • 3 EGJOO • 2 Absent peristalsis • 2 DES • 1 Achalasia
Von Arnim 2017 [46]	Prospective/Europe	> 15 eos/HPF	Adults	24	V3.0	• 11 Normal peristalsis • 7 Weak peristalsis • 5 EGJOO • 1 Absent peristalsis
Manu 2018 [49]	Retrospective/Europe	≥ 15 eos/HPF	Adults	16	V3.0	• 9 Normal • 6 IEM • 1 EGJOO
Hosaka 2018 [48]	Retrospective/Asia	≥ 15 eos/HPF	Adults	18	V3.0	• 7 Achalasia • 3 IEM • 3 Normal • 2 EGJOO • 2 JE • 1 DES
Tanaka 2018 [38]	Case report/Asia	≥ 15 eos/HPF	Adult	1	V3.0	• 1 JE
Visaggi 2018 [47]	Retrospective/Europe	> 15 eos/HPF	Adults	2	V3.0	• 2 Absent peristalsis
Frieling 2019 [36]	Case report/Europe	≥ 15 eos/HPF	Adult	1	V3.0	• 1 Achalasia type II
Wong 2019 [53]	Prospective/Asia	≥ 15 eos/HPF	Adults	25	V3.0	• 19 Normal peristalsis • 6 IEM

(*continued on next page*)

Table 2 (*continued*)

Author/year	Type of study/ Geographic area	Cut-off value for the diagnosis of EoE	Type of patients	Number of patients	CC version	Findings
Surdea-Blaga 2019 [34]	Case report/Europe	> 15 eos/HPF	Adult	1	V3.0	• 1 Achalasia
Ahsan 2020 [54]	Case report/Europe	≥ 15 eos/HPF	Child	1	V3.0	• 1 DES
Ghisa 2020 [50]	Retrospective/Europe	≥ 15 eos/HPF	Adults	109	V3.0	• 68 Normal peristalsis • 23 IEM • 5 EGJOO • 4 Achalasia type II • 3 Achalasia type III • 2 JE • 1 Achalasia type I • 1 Fragmented peristalsis • 1 Absent peristalsis • 1 DES
Ghisa 2020 [51]	Retrospective/Europe	≥ 15 eos/HPF	Adults	50	V3.0	• 26 Normal • 10 IEM • 4 Fragmented peristalsis • 2 Absent peristalsis • 2 Achalasia type III • 2 Achalasia type II • 1 Achalasia type I • 1 EGJOO • 1 JE • 1 DES
Al-abdullah 2021 [37]	Case report/Australia	≥ 15 eos/HPF	Adult	1	V3.0	• 1 Achalasia
Visaggi 2021 [52]	Prospective/Europe	≥ 15 eos/HPF	Adults	21	V3.0	• 10 Normal • 5 EGJOO • 3 HE • 2 DES • 1 Achalasia

Abbreviations. CC, Chicago classification; **DES**, distal esophageal spasm;; **EGJOO,** esophagogastric junction outflow obstruction; **eos/HPF**, eosinophils per high-power field; **HE**, Hypercontractile esophagus; **IEM**, ineffective esophageal motility; **JE**, jackhammer esophagus; **LES**, lower esophageal sphincter; **NE,** nutcracker esophagus**; PEP**, pan-esophageal pressurization;.

suspected to be the cause for residual symptoms despite the mucosal remission of eosinophilia.

In 2013, Weigt et al. [39] reported on 10 EoE patients, of which 3 had normal peristalsis and 7 weak peristalsis. The following year, Van Rhijn et al. [40] retrospectively investigated HRM patterns in 31 EoE patients and found that 42% had normal peristalsis, while 58% showed abnormal motility, 9 patients with weak peristalsis, 4 frequent failed peristalsis, 2 EGJOO, 2 Rapid contractions, and 1 weak peristalsis and rapid contractions.

Roman et al. [41] retrospectively reviewed HRM tracings of 48 EoE patients, 48 GERD patients, and 50 healthy controls. Sixty-three percent of EoE patients had normal motility, compared to 57% of GERD patients and 90% of controls. Among EoE subjects with abnormal contractility, 17% had weak peristalsis, 10% frequent failed peristalsis, 4% had rapid contraction pattern, 2% had either absent or hypertensive peristalsis or functional EGJ obstruction. The authors also assessed the pattern of esophageal pressurization in the three groups. Around 17% of EoE patients showed early PEP >30 mmHg within 2 s of the esophageal contraction, and 19% showed compartmentalized distal pressurization, compared to 2% and 10% of GERD patients, respectively, and none of the controls. Interestingly, the pattern of early PEP was unique to EoE patients during 5 ml swallows and could be more easily elicited during large volume wet swallows of 20 ml. Similar conclusions were drawn by a subsequent prospective study on esophageal HRM patterns in patients with EoE [42]. Among 21 patients, 81% had normal LES pressure, 14.3% LES hypotension (<10 mmHg), and 4.8% LES hypertension with a normal IRP according to CCv1.0 [16]. Forty-eight percent of patients showed PEP >30 mmHg, 28% had peristaltic dysfunction defined as failed peristalsis or breaks in the 30-mmHg isobaric contour, and 24% had a normal HRM study. Of note, the authors found a statistical correlation between bolus impaction and PEP, but no correlation between the frequency of dysphagia and PEP could be seen.

In 2016, Nennstiel et al. [43] prospectively evaluated HRM findings in patients with EoE before and after an 8-week course of topical budesonide. The authors found that 35% of patients displayed early PEP, while 5% showed compartmentalized esophageal pressurizations or frequently failed peristalsis before treatment. Additionally, patients with a fibrostenotic subtype had a tendency towards higher IBP compared to those with an inflammatory phenotype. Following treatment, PEP resolved in 86% of patients, but IBP values remained stable over time.

Savarino et al. [44] prospectively assessed HRM findings according to CCv3.0 [18] in 35 consecutive patients diagnosed with EoE. Fifty-seven percent of subjects showed no abnormalities, whereas ineffective or fragmented peristalsis were seen in 20% of patients, absent peristalsis or DES in 6%, EGJOO in 9%, and achalasia in 3%.

Colizzo et al. [45] investigated whether HRM parameters could distinguish EoE endoscopic inflammatory and fibrostenotic phenotypes. Among 29 EoE patients, 20% had abnormal HRM as per CC v2.0 [17]. Within the group with fibrostenotic disease, 2 had jackhammer esophagus (JE), one weak peristalsis, and one EGJOO. Among those with an inflammatory subtype, one had hypertensive LES and one weak peristalsis. Importantly, although the DCI and IRP were similar in the overall study population, patients with a fibrostenotic phenotypes showed a significantly higher IBP, which

could segregate the two groups with 70.5% sensitivity and 75% specificity when >16 mmHg.

Conversely, von Arnim et al. [46] did not find any significant differences in IBP, DCI, IRP, DL, and CFV between the two EoE endoscopic phenotypes. However, the IBP of patients with EoE was significantly higher than that of healthy controls. Overall, among 24 patients with EoE, 57.7% showed evidence of abnormal peristalsis, including weak peristalsis, EGJ outflow obstruction, and absent peristalsis.

In 2018, a ten-year retrospective study by Visaggi et al. [47] found that 2% of patients with an identifiable cause of absent peristalsis may have EoE; however, 50% of patients without a clear cause of absent peristalsis had not undergone esophageal biopsy to rule out EoE, possibly losing the opportunity to identify the disease. In the same year, Hosaka et al. [48] described 18 patients with EoE who had undergone HRM: 3 had normal peristalsis, 7 achalasia, 3 IEM, 2 EGJOO or JE, and 1 DES. Manu et al. [49] found that, among 16 EoE patients, 9 had normal peristalsis, 6 IEM, and 1 EGJOO.

Higher rates of obstructive motor disorders were found in a more recent large cohort multicentre retrospective study by Ghisa et al. [50]. The authors assessed the HRM patterns of 109 EoE patients over a seven-year period according to CC v3.0 [18]. Overall, abnormal peristalsis was found in 38% of the cohort, displaying a range of hypo- or hypercontractile disorders. Achalasia and other obstructive motor disorders were diagnosed in approximately 15% of cases, with 8 cases of achalasia (one with type 1, four type 2 and three type 3), 5 EGJOO, 1 JE and 1 DES. Clinical features and endoscopic findings were similar among different manometric patterns but interestingly, achalasic subjects were more frequently woman and with a longer EoE diagnostic delay compared to non-achalasia patients. In another study on 50 EoE patients [51], 26 had normal peristalsis, while 10 had IEM, 4 fragmented peristalsis, 2 had either absent peristalsis, 3 achalasia, 1 EGJOO, 1 JE, and 1 DES. In 2021, Visaggi et al. [52] described that, among 21 prospectively enrolled EoE patients, 10 had normal peristalsis, 5 EGJOO, 3 HE, 2 DES, and 1 achalasia. Similarly, Wong et al. [53] prospectively assessed EoE patients using HRM: 19 had normal peristalsis, and 6 had IEM.

As regards children, Ahsan et al. [54] reported a case of JE in a patient with EoE whose esophageal HRM normalized following treatment, while Karkelis et al. reported a case series of two children who had concomitant EoE and nutcracker esophagus according to CC v2.0 [55].

4. Discussion

EoE is a relatively recent disease whose incidence has risen steadily over the past three decades. The disease predominantly presents in young males with a peak incidence between 20 and 40 years of age but can also occur in females and at any age. Adolescences and adults typically experience intermittent dysphagia and food impactions, which can be related to luminal abnormalities [1]; however, symptoms occur even when the esophagus appears endoscopically normal and a documented histological remission may not lead to the resolution of symptoms [38,56]. From a clinical point of view, a possible explanation for this phenomenon may be the presence of an underlying motor disorder of the esophagus. In support of this concept, the esophageal inflammatory infiltrate can both directly and indirectly influence esophageal contractility, potentially inducing both hypo- and hypercontractility [57,58]. For example, eosinophils release the major basic protein (MBP), which activates muscarinic M2 acetylcholine receptors and stimulates the contraction of smooth muscles in the distal two thirds of the esophagus, while eosinophilic interleukins inhibit the release of acetylcholine, reducing the contractility of smooth muscle cells [58]. Additionally, eosinophil degranulation has been shown to induce axonal necrosis [59], which impairs the effective delivery of neurotransmitters to the esophagus. In support of the causative role of eosinophils in motor disturbances, dense eosinophilic infiltrates have been found in the esophageal muscular layers of patients with JE and nutcracker esophagus [60], and in patients with gastric dysmotility [61]. **Fig. 2** reports potential factors involved in the pathogenesis of dysmotility in EoE.

This systematic review individuated 36 studies evaluating esophageal manometry findings in patients with EoE. Most of the studies were retrospective and the sample size was generally small.

Studies reporting on esophageal motility in EoE by means of CM or PEMP used variegated protocols, guidelines for the interpretation, and cut-off values of eosinophils/HPF. These studies provided variegated results regarding motility patterns and did not identify any EoE-specific pattern. Evidence of various degrees of hypo- or hypercontractile motor dysfunctions have been reported in 25% to 83% of patients with EoE undergoing CM [19,29], although their correlation with symptoms occurrence remains controversial [31,32]. However, it is interesting to highlight that prolonged esophageal manometry over a 24-hour period demonstrated a strong relationship between dysphagia and intermittent dysmotility events, possibly explaining the discrepancy between manometry findings during standard protocols and symptoms in the real life.

More recently, the introduction of HRM in clinical practice disclosed previously unrecognized details of esophageal dynamics [62], including the presence of pressurizations in the esophagus that occur independent of lumen-obliterating contractions [41]. Additionally, the introduction of consensus-based interpretation guidelines allowed to overcome the low interobserver agreement in the interpretation of manometric measurements of CM. Several studies investigated EoE patients by means of HRM and found that a number of motility patterns is possible in these patients, including normal peristalsis, achalasia, JE, EGJOO, IEM, and absent peristalsis. Of note, HRM findings such as early PEP and IBP have shown potential to distinguish EoE from controls and to correlate with endoscopic features [41,45].

From a diagnostic standpoint, although esophageal motility does not appear to be disease-specific in patients with EoE, patients may display characteristic pressure patterns on HRM, such as early PEP and altered IBP, which may be helpful to suggest the diagnosis of EoE in those who do not have preliminary performed an esophago-gastroduodenoscopy with esophageal biopsies.

From a therapeutic point of view, dysmotility and esophageal pressurizations have been shown to improve following medical management in a subset of patients with EoE [19,20,43]. The resolution of esophageal pressurizations following treatment presumably reflects an increase in esophageal wall compliance rather than a change is esophageal motility. Accordingly, a study investigating esophageal secondary peristalsis during FLIP (functional luminal imaging probe) panometry found that patients with abnormal contractile responses had greater esophageal remodeling and similar esophageal eosinophil density compared to those with normal contractile responses, suggesting that decreased distensibility of the esophageal body and EGJ could be more relevant than eosinophil inflammatory intensity in the context of abnormal secondary peristalsis[63]. However, motor abnormalities may require invasive management for symptoms resolution in selected cases. In a retrospective study [50], only a minority of patients with EoE-related obstructive motor disorders achieved symptom improvement following topical steroids treatment, and invasive management (i.e., pneumatic dilation and/or laparoscopic Heller myotomy) of achalasia or other obstructive motor disorders was required for symptom relief in 50% of patients. Similarly, a case report described a patient with persistent dysphagia related to hypercontractility despite histological remission of EoE. The patient only

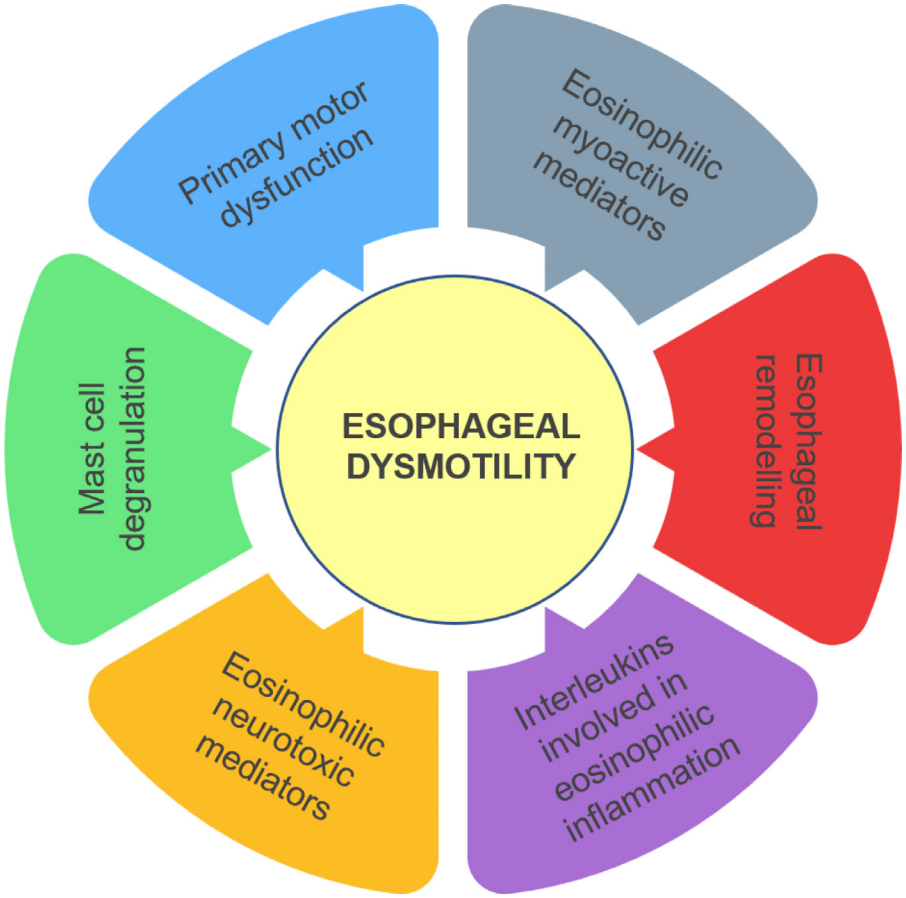

Fig. 2. Factors Potentially Involved in the Pathogenesis of Dysmotility in Eosinophilic Esophagitis.

experienced complete symptom relief following endoscopic myotomy [38]. Although several reports demonstrated that symptoms and dysmotility can improve following medical treatment for EoE [19,20,22,43], studies assessing the correlation of motor abnormalities with symptoms have reported inconsistent results [31,32]. A speculative explanation for this may be the low sensibility of current manometry protocols, that is, the assessment of a small number of low volume wet swallows. Consistently, although unique EoE HRM patterns have been described during 5-ml wet swallows, larger volume challenges demonstrated to disclose abnormalities more frequently [41]. Another reason for the discrepancy between symptoms and manometry findings may be that dysphagia has an intermittent nature in patients with EoE, and motor disturbances may not be overt at the time of manometry recording. Additionally, in real life conditions, EoE symptoms are usually elicited by solid food. In contrast, manometry is performed with wet swallows, and this might at least partially explain the absence of a significant correlation between dysphagia and HRM findings [31,32,46].

In terms of clinical history, some lines of evidence suggest that dysmotility may be a tardive manifestation of EoE. In this regard, Van Rhijn et al. [40] found that the prevalence of motility disorders in patients with EoE increases with disease duration and diagnostic delay, suggesting a progression of the disease over time. The authors compared the HRM tracings of 31 EoE patients to those of 31 GERD and healthy controls. Compared to GERD, disease duration was identified as a risk factor for abnormal motility in EoE, with an odds ratio for each year of 1.142 (95% confidence interval, 1.004–1.299). According to disease duration, the prevalence of abnormal motility increased from 36% (in those with disease duration of 0–5 years) to 83% (in those with disease duration $\geq$16 years).

In conclusion, esophageal motor abnormalities are not uncommon in patients with EoE although esophageal motility does not appear to be disease specific from currently available evidence. Of note, esophageal motility has seldom been assessed in prospective studies on EoE, and most evidence come from retrospective studies or case reports with small sample size which have been conducted mainly in adults. Recent insights suggest that dysmotility may have a role in generating symptoms and influencing treatment outcomes in EoE patients. Whether HRM should be routinely performed in patients with EoE or it should be done only in selected cases remains unclear. To this end, future studies should aim at prospectively phenotyping motility patterns in larger cohorts of patients with EoE by means of HRM with standardized protocols and assessment criteria.

Declaration of Competing Interest

Pierfrancesco Visaggi: none. Matteo Ghisa: none. Brigida Barberio: none. Elisa Marabotto: none. Nicola de Bortoli: has received lecture or consultancy fees from Malesci and Reckitt Benckiser, outside the submitted work. Edoardo Savarino: has received lecture or consultancy fees from Abbvie, Alfasigma, Amgen, Aurora Pharma, Bristol-Myers Squibb, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Johnson&Johnson, Innovamedica, Malesci, Medtronic, Merck & Co, Reckitt Benckiser, Sandoz, Shire, SILA, Sofar, Takeda, Unifarco, outside the submitted work.

Funding

None.

Guarantor of the article

Prof Edoardo Savarino

Acknowledgments

None.

Ethics committee approval

Was not required because this study retrieved and synthesised data from already published studies.

Data sharing statement

No additional data available.

ALL AUTHORS APPROVED THE FINAL VERSION OF THE MANUSCRIPT

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.01.003.

References

[1] Visaggi P, et al. Eosinophilic esophagitis: clinical, endoscopic, histologic and therapeutic differences and similarities between children and adults. Therap Adv Gastroenterol 2021;14:1756284820980860.
[2] de Bortoli N, et al. Eosinophilic esophagitis: update in diagnosis and management. Position paper by the Italian Society of Gastroenterology and Gastrointestinal Endoscopy (SIGE). Dig Liver Dis 2017;49(3):254–60.
[3] Schoepfer A, et al. Eosinophilic esophagitis: latest insights from diagnosis to therapy. Ann NY Acad Sci 2018;1434(1):84–93.
[4] Visaggi P, et al. Artificial Intelligence in the Diagnosis of Upper Gastrointestinal Diseases. J Clin Gastroenterol 2021.
[5] Sciumé GD, et al. Eosinophilic esophagitis: novel concepts regarding pathogenesis and clinical manifestations. Minerva Gastroenterol Dietol 2021.
[6] Arias Á, Lucendo AJ. Epidemiology and risk factors for eosinophilic esophagitis: lessons for clinicians. Expert Rev Gastroenterol Hepatol 2020;14(11):1069–82.
[7] Lenti MV, et al. Diagnostic delay and misdiagnosis in eosinophilic esophagitis. Dig Liver Dis 2021.
[8] Visaggi P, et al. Dietary management of eosinophilic esophagitis: tailoring the approach. Nutrients 2021;13(5).
[9] Shaheen NJ, et al. Natural history of eosinophilic esophagitis: a systematic review of epidemiology and disease course. Dis Esophagus 2018(8):31.
[10] Roman S, et al. Eosinophilic esophagitis: from physiopathology to treatment. Digest Liver Dis 2013;45(11):871–8.
[11] Hirano I, et al. Endoscopic assessment of the esophageal features of eosinophilic esophagitis: validation of a novel classification and grading system. Gut 2013;62(4):489–95.
[12] Collins MH, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus 2016;30(3):1–8.
[13] Safroneeva E, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. Gastroenterology 2016;150(3):581–90 e4.
[14] Straumann A, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. Schweiz Med Wochenschr 1994;124(33):1419–29.
[15] Yadlapati R, et al. Esophageal motility disorders on high-resolution manometry: chicago classification version 4.0(©). Neurogastroenterol Motil 2021;33(1):e14058.
[16] Kahrilas PJ, Ghosh SK, Pandolfino JE. Esophageal motility disorders in terms of pressure topography: the Chicago Classification. J Clin Gastroenterol 2008;42(5):627–35.
[17] Bredenoord AJ, et al. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. Neurogastroenterol Motil 2012;24 Suppl 1(Suppl 1):57–65.
[18] Kahrilas PJ, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27(2):160–74.
[19] Lucendo AJ, et al. Manometric findings in adult eosinophilic esophagitis: a study of 12 cases. Eur J Gastroenterol Hepatol 2007;19(5):417–24.
[20] Lucendo AJ. Motor disturbances participate in the pathogenesis of eosinophilic esophagitis, beyond the fibrous remodelling of the esophagus. Aliment Pharmacol Ther 2006;24(8):1264–7.
[21] Bassett J, et al. Prevalence of esophageal dysmotility in a cohort of patients with esophageal biopsies consistent with eosinophilic esophagitis. Dis Esophagus 2009;22(6):543–8.
[22] Hejazi RA, et al. Disturbances of esophageal motility in eosinophilic esophagitis: a case series. Dysphagia 2010;25(3):231–7.
[23] Landres RT, Kuster GG, Strum WB. Eosinophilic esophagitis in a patient with vigorous achalasia. Gastroenterology 1978;74(6):1298–301.
[24] Vitellas KM, et al. Idiopathic eosinophilic esophagitis. Radiology 1993;186(3):789–93.
[25] Hempel SL, Elliott DE. Chest pain in an aspirin-sensitive asthmatic patient. Eosinophilic esophagitis causing esophageal dysmotility. Chest, 1996;110(4):1117–20.
[26] Attwood SE, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38(1):109–16.
[27] Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. Mayo Clin Proc 2003;78(7):830–5.
[28] Cantù P, et al. Ringed esophagus and idiopathic eosinophilic esophagitis in adults: an association in two cases. Digest Liver Dis 2005;37(2):129–34.
[29] Monnerat MM, Lemme EM. Eosinophilic esophagitis: manometric and pH-metric findings. Arq Gastroenterol 2012;49(2):113–17.
[30] Cheung KM, et al. Esophageal eosinophilia in children with dysphagia. J Pediatr Gastroenterol Nutr 2003;37(4):498–503.
[31] Moawad FJ, et al. Esophageal motor disorders in adults with eosinophilic esophagitis. Dig Dis Sci 2011;56(5):1427–31.
[32] Nurko S, Rosen R, Furuta GT. Esophageal dysmotility in children with eosinophilic esophagitis: a study using prolonged esophageal manometry. Am J Gastroenterol 2009;104(12):3050–7.
[33] Savarino E, et al. Achalasia with dense eosinophilic infiltrate responds to steroid therapy. Clin Gastroenterol Hepatol 2011;9(12):1104–6.
[34] Surdea-Blaga T, et al. Achalasia-like changes in eosinophilic esophagitis. J Gastrointestin Liver Dis 2019;28:146.
[35] Snyder D, Gonzalez Y, Venu M. A case of eosinophilic esophagitis with achalasia requiring myotomy. Am J Gastroenterol 2014;109(SUPPL. 2):S236.
[36] Frieling T, et al. Eosinophilic esophagitis and achalasia - just a coincidence? Z Gastroenterol 2019;57(2):151–5.
[37] Al Abdullah B, Scott D. A case of eosinophilic esophagitis and achalasia: causality or coincidence? J Gastroenterol Hepatol 2021;36(SUPPL 3):143.
[38] Tanaka S, et al. A case of Jackhammer esophagus caused by eosinophilic esophagitis in which per-oral endoscopic myotomy resulted in symptom improvement. Clin J Gastroenterol 2018;11(5):377–81.
[39] Weigt J, et al. Eosinophilic esophagitis in adults: association with esophageal motor dysfunction? Gastroenterology 2013;144(5 SUPPL. 1):S503.
[40] van Rhijn BD, et al. Prevalence of esophageal motility abnormalities increases with longer disease duration in adult patients with eosinophilic esophagitis. Neurogastroenterol Motil 2014;26(9):1349–55.
[41] Roman S, et al. Manometric features of eosinophilic esophagitis in esophageal pressure topography. Neurogastroenterol Motil 2011;23(3):208–111.
[42] Martín Martín L, et al. Esophageal motor abnormalities in eosinophilic esophagitis identified by high-resolution manometry. J Gastroenterol Hepatol 2011;26(9):1447–50.
[43] Nennstiel S, et al. High-resolution manometry in patients with eosinophilic esophagitis under topical steroid therapy-a prospective observational study (HIMEOS-study). Neurogastroenterol Motil 2016;28(4):599–607.
[44] Savarino EV, et al. The GerdQ questionnaire and high resolution manometry support the hypothesis that proton pump inhibitor-responsive esophageal eosinophilia is a GERD-related phenomenon. Aliment Pharmacol Ther 2016;44(5):522–30.
[45] Colizzo JM, Clayton SB, Richter JE. Intrabolus pressure on high-resolution manometry distinguishes fibrostenotic and inflammatory phenotypes of eosinophilic esophagitis. Dis Esophagus 2016;29(6):551–7.
[46] von Arnim U, et al. Correlation of high-resolution manometric findings with symptoms of dysphagia and endoscopic features in adults with eosinophilic esophagitis. Digest Dis 2017;35(5):472–7.
[47] Visaggi MP, et al. OWE-031 Esophageal aperistalsis is under investigated in those without achalasia or reflux. Gut 2018;67(Suppl 1):A210.
[48] Hosaka H, et al. PS01.016: esophageal dysmotility caused by esophageal eosinophilia regulates patients' symptoms and treatment requirements. Dis Esophagus 2018;31(Supplement_1):54–5.
[49] Manu K, et al. Baseline impedance on high-resolution impedance manometry correlates with severity of eosinophilic esophagitis endoscopic reference score. Gastroenterology 2018;154(6 Supplement 1):p. S.
[50] Ghisa M, et al. Achalasia and obstructive motor disorders are not uncommon in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2020.
[51] Ghisa M, et al. Esophageal motility disorders in eosinophilic esophagitis. Digest Liver Dis 2020;52(Supplement 2):S71.
[52] Visaggi P, et al. Eosinophilic esophagitis is frequently associated with disorders of peristalsis at high-resolution manometry: a prospective single-centre case-control study. United European Gastroenterol J 2021;9(SUPPL 8):292.
[53] Wong S, et al. Mo1138 – a comprehensive assessment of eosinophilic esophagitis using high-resolution manometry, mucosal biopsy and endoscopic ultrasound in adults. Gastroenterology 2019;156 S–719.
[54] Ahsan SD, et al. Distal esophageal spasm secondary to eosinophilic esophagitis in a child: response to diet therapy. Front Gastroenterol = FG 2020;11(1).
[55] Karkelis S, et al. Motility disorders in children and adolescents with eosinophilic esophagitis. Dis Esophagus 2012;25(SUPPL. 1):132A.
[56] Alexander JA, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2012;10(7):742–9 e1.
[57] Spechler SJ, Konda V, Souza R. Can eosinophilic esophagitis cause achalasia

and other esophageal motility disorders? Am J Gastroenterol 2018;113(11):1594–1599.
[58] Santander C, et al. Impaired esophageal motor function in eosinophilic esophagitis. Rev Esp Enferm Dig 2015;107(10):622–9.
[59] Nurko S, Rosen R. Esophageal dysmotility in patients who have eosinophilic esophagitis. Gastrointest Endosc Clin N Am 2008;18(1):73 -ix.
[60] Nakajima N, et al. Muscle layer histopathology and manometry pattern of primary esophageal motility disorders including achalasia. Neurogastroenterol Motil 2017;29(3).
[61] Martin ST, et al. Gastric motor dysfunction: is eosinophilic mural gastritis a causative factor? Eur J Gastroenterol Hepatol 2005;17(9):983–6.
[62] Savarino E, et al. Practice guidelines on the use of esophageal manometry - a GISMAD-SIGE-AIGO medical position statement. Dig Liver Dis 2016;48(10):1124–35.
[63] Carlson D, et al. Esophageal Dysmotility Is Associated With Disease Severity in Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2021;Nov 9:S1542-3565(21)01181-2. doi:10.1016/j.cgh.2021.11.002.