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MINIREVIEWS

Gastro-oesophageal reflux disease and eosinophilic oesophagitis: What is the relationship?

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Abstract

Eosinophilic oesophagitis (EoE) and gastro-oesophageal reflux disease (GORD) are the most common causes of chronic oesophagitis and dysphagia associated with oesophageal mucosal eosinophilia. Distinguishing between the two is imperative but challenging due to overlapping clinical and histological features. A diagnosis of EoE requires clinical, histological and endoscopic correlation whereas a diagnosis of GORD is mainly clinical without the need for other investigations. Both entities may exhibit oesophageal eosinophilia at a similar level making a histological distinction between them difficult. Although the term proton-pump inhibitor responsive oesophageal eosinophilia has recently been retracted from the guidelines, a relationship between EoE and GORD still exists. This relationship is complex as they may coexist, either interacting bidirectionally or are unrelated. This review aims to outline the differences and potential relationship between the two conditions, with specific focus on histology, immunology, pathogenesis and treatment.

Key words: Relationship; Pathogenesis; Eosinophilic oesophagitis; Histological features; Gastro-oesophageal reflux disease

Core tip: The relationship between gastro-oesophageal reflux disease and eosinophilic oesophagitis is complex as they may coexist, either interacting bidirectionally or are

unrelated. This review aims to outline the differences and potential relationship between the two conditions, with specific focus on histology, immunology, pathogenesis and treatment.

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INTRODUCTION

Eosinophilic oesophagitis (EoE) is a clinicopathological condition characterised by an antigen-driven immunologic process that manifests clinically with symptoms of oesophageal dysfunction and histologically by eosinophilic inflammation[1]. The first case report of oesophageal eosinophilia can be traced back as far as 1962 by Schreiber[2], followed by the first published case series of EoE as a distinct clinicopathological condition in 1993 by Attwood *et al*[3] In 2007, the first consensus recommendation by an international expert panel for the diagnosis and treatment of EoE was published[4]. This consensus was recently updated in 2017[5].

The recognition of EoE has increased so swiftly that it is now thought to be the most frequent eosinophilic gastrointestinal disorder as well as the second most common cause of chronic oesophagitis and dysphagia after gastro-oesophageal reflux disease (GORD)[6]. Although it is still an uncommon disease, the prevalence has been increasing over the past few years with an estimated prevalence in the general population of 13-49 cases/100000 persons[5,7]. This is also in keeping with an increasing incidence of EoE estimated at 1-20 cases/100000 persons[5,7]. Various hypotheses have been considered for this phenomenon particularly that of an increase in the recognition of the disease and an increase in volume of endoscopies performed[8-10]. However, two population-based studies have shown that the incidence and cumulative prevalence of EoE has indeed increased more than the rate of annual endoscopies during the observation period[11,12]. This, therefore, argues in favour of a true rise in the incidence and prevalence of the disease.

Attwood *et al*[3] first characterized EoE as a distinct entity from GORD in 1993 where patients with more than 20 eosinophils per high power field and dysphagia in the absence of endoscopic oesophagitis and a normal 24-h pH testing were proposed to have EoE. According to the diagnostic criteria for EoE, other diseases associated with oesophageal eosinophilia must be excluded before a diagnosis of EoE is made (Table 1), with the main differential being GORD[1,13,14]. It is important to distinguish between EoE and GORD as their pathogenesis, natural history, monitoring and treatment differ[15]. This is challenging as many of their clinical and histological features overlap[15,16]. Given the prevalence of GORD in the general population is approximately 20%, it is inevitable that there will be a high probability for EoE to co-exist with GORD[16].

Table 1 Diseases associated with oesophageal eosinophilia

GORD
Eosinophilic gastrointestinal diseases
Atopy
Coeliac disease
Crohn's disease
Oesophageal infections
Hypereosinophilic syndrome
Achalasia
Drug hypersensitivity
Vasculitis
Pemphigoid vegetans
Connective tissue disease
Graft-versus-host-disease
Oesophageal atresia

GORD: Gastro-oesophageal reflux disease.

Prior to the 2017 consensus, a lack of response to a 2-mo course of a proton-pump inhibitor (PPI) was required exclude PPI-responsive oesophageal eosinophilia (PPI-REE) and confirm the diagnosis of EoE[1]. Patients with PPI-REE presented symptomatically like a typical EoE patient, had GORD diagnostically excluded and exhibited a clinicopathologic response to PPI therapy[1]. Recent evidence, however, indicate that differentiating PPI-REE from EoE is counterintuitive as their phenotypic, molecular, mechanistic and therapeutic features cannot be reliably distinguished[15,17-20]. Also, there was no definition regarding the extent of clinical and histological response required to diagnose PPI-REE[13,15]. Thus, the most recent consensus has retracted the term PPI-REE and considers PPI therapy as a therapeutic agent, rather than a diagnostic criterion[5]. The term "PPI-responsive EoE" has been proposed to replace the now defunct PPI-REE[20].

Despites the fact that PPI responders are now considered to be within the EoE continuum, a relationship between EoE and GORD still exists[5]. Studies have suggested that up to 30%-40% of EoE patients may be PPI responsive, either due to a reduction in acid secretion in patients with co-existent GORD or by means of other still unknown anti-inflammatory mechanisms[21,22]. PPI therapy may also be helpful in patients with EoE as the altered oesophagus may be predisposed and more sensitive to acid exposure[23]. This review aims to outline the factors that differentiate between EoE and GORD as well as to evaluate the complex relationship between the two entities in term of pathophysiology and immunology.

PATHOGENESIS

The main pathogenic mechanism of GORD is increased

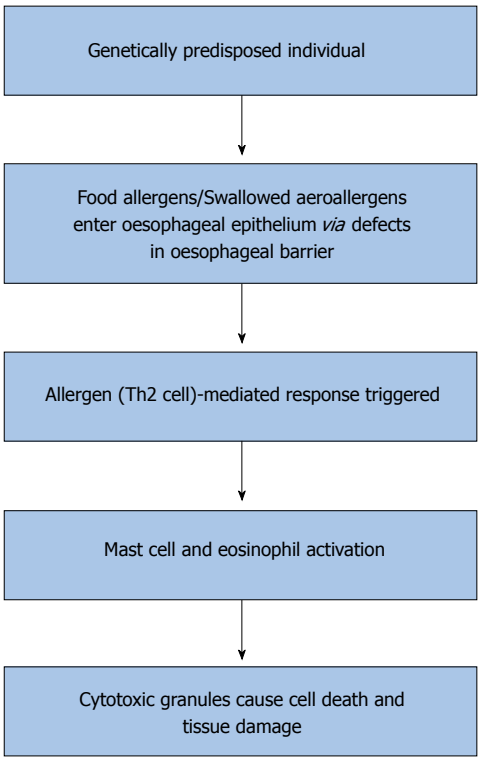

Figure 1 Proposed pathogenesis of eosinophilic oesophagitis.

transient lower oesophageal sphincter (LOS) relaxations (TLOSRs), leading to excessive reflux of gastric acid to the lower oesophageal mucosa[24]. Other potential mechanistic factors that can increase acid reflux to the oesophagus are impaired LOS resting pressure, impaired oesophageal acid clearance, delayed gastric emptying and anatomical factors, such as a hiatus hernia[24]. More recently, impaired mucosal resistance and increased visceral hypersensitivity to acid have also been reported to predispose to GORD[24]. Histologically, it was thought that erosive changes in the distal oesophagus developed due to direct chemical-induced injury of the oesophageal mucosa and death of surface cells[25]. Such injury has been shown to provoke a T-helper Type 1 (Th1) inflammatory response, activating mostly granulocytes and lymphocytes[25]. Thus, it is intriguing that oesophageal eosinophilia can occasionally be seen in GORD, and the underlying mechanism remains unclear[26]. A study showing that GORD may also be a cytokine-mediated disease lead to the discovery that oesophageal squamous cells from EoE and GORD patients exhibit similar levels of eotaxin-3 (a chemokine that attracts eosinophils) when stimulated by T-helper Type 2 (Th2) cytokines; production of which is typical of an allergic disorder[10,15,22,26,27]. This suggests that GORD may be driven to a Th2 inflammatory response when the appropriate stimulus is present leading to oesophageal eosinophilia[26]. Low intraluminal baseline impedance has been shown to be associated with dilatation of intercellular spaces and increased acid exposure in patients with GORD[28]. However, whether this damage can lead to exposure of food allergens and subsequently a Th2 response is unknown[26,29,30].

Although the exact pathophysiology of EoE is not fully understood, substantial evidence exists to show that EoE is an allergen (Th2 cell)-mediated response in genetically predisposed individuals (Figure 1)[10,31,32]. Defects in the oesophageal barrier are thought to facilitate the entry of food allergens or swallowed aeroallergens into the oesophageal epithelium which trigger a Th2 response and lead to mast cell activation and release of mediators such as interleukin (IL)-5, which is a known eosinophil activator[10,22]. Activated eosinophils then release cytotoxic granules which contribute to cell death and tissue damage in these patients[10,33,34]. The gene coding for eotaxin-3, *CCL26* is overexpressed in the oesophagus of patients with EoE compared to healthy controls, which correlates with the increased levels of IL-5 and IL-13 in the oesophagus and blood of EoE patients[35,36]. The development of EoE may also be associated with a genetic predisposition[10]. Hereditary collagen disorders such as Marfan and Ehlers-Danlos syndromes are the most frequent associations of EoE with an incidence of about one percent[21]. In patients with atopic dermatitis, a loss of function mutation in the gene filaggrin (2282del4) is overexpressed in EoE patients compared with healthy controls[37]. Filaggrin is a key structural, keratin-binding protein that plays an important role in the maturation of skin as an epithelial barrier by preventing keratin proteolysis[37]. EoE has been shown in paediatric patients to be associated with variants at chromosome 5q22 encompassing the gene *TSLP* (thymic stromal lymphopoetin), which encodes a cytokine that controls dendritic cell-mediated Th2-cell responses[21,38]. More recently, EoE susceptibility locus was found at 2p23 which encodes *CAPN14*, which is upregulated on exposure to IL-13[39]. However, the exact impact of these genetic abnormalities on the pathogenesis of EoE is uncertain.

EPIDEMIOLOGY AND CLINICAL PRESENTATION

A few epidemiological differences exist between GORD and EoE. GORD is typically diagnosed in the second to fifth decade of life[20]. In contrast, EoE has a bimodal age presentation, with one peak in childhood and the second in the third and fourth decade with the mean age of diagnosis of 38 years[1,33,40]. Furthermore, whilst there is no gender preponderance in GORD, EoE affects males three times more than females[1,41,42]. Both conditions have been more frequently reported in Caucasians compared with other ethnicities[1,8,41,43]. It should be noted that the prevalence of GORD is much higher than that of EoE, ranging between 10%-20% in the Western population as compared to less than 1% for EoE[8,9,40,41]. Obesity has been shown to associated with GORD whereas EoE is strongly associated with atopic diseases

Table 2 Diagnostic features of gastro-oesophageal reflux disease and eosinophilic oesophagitis

	GORD	EoE
Endoscopic	Erosive oesophagitis	Trachealization
	Peptic strictures	Felinization
	Hiatus hernia	Whitish exudates
	Barrett's oesophagus	Longitudinal furrows
		Oedema
		Diffuse oesophageal narrowing
		Narrow-calibre oesophagus
		Oesophageal lacerations
		Loss of mucosal vascular pattern
Histological	Eosinophilia < 10/hpf	Eosinophilia ≥ 15/hpf
		Eosinophilic microabscesses
		Eosinophil degranulation
		Basal cell hyperplasia
		Papillary lengthening
		Superficial layering of eosinophils
		Extracellular eosinophil granules
		Intracytoplasmic keratinocyte vacuolation
		Dilated intracellular spaces
		Lamina propria fibrosis
		Positive intrasqamous IgG4
Motor function	Non-specific	Non-specific

GORD: Gastro-oesophageal reflux disease; EoE: Eosinophilic oesophagitis.

such as asthma, food allergy, eczema, environmental allergies and chronic rhinitis[1,8,10,31,44].

GORD has been defined by the Montreal Classification as a condition that occurs due to retrograde flow of gastric contents into the oesophagus that lead to troublesome symptoms, which are typically heartburn and regurgitation[45,46]. Other less common symptoms include chest pain, dysphagia, dyspepsia, epigastric pain, nausea, bloating, belching, chronic cough, asthma, laryngitis and other respiratory symptoms[45-48]. Whilst dysphagia is infrequent in GORD, it is the most common presenting symptom for EoE along with food bolus impaction[1,10,49]. Approximately 50% of patients who present with food bolus impaction and up to 15% of patients who undergo endoscopy for non-obstructive dysphagia will have EoE[6,50]. Although some EoE patients report GORD symptoms, they may respond poorly to PPIs[51]. Fifty to eighty percent of EoE patients have a prior history of atopic symptoms[21]. Other non-specific symptoms include chest pain, heartburn, regurgitation, dyspepsia, nausea and vomiting, odynophagia, abdominal pain and non-specific throat symptoms[1,10,31,33,49,52].

DIAGNOSIS

A diagnosis of GORD is usually based on clinical symptoms, typically heartburn and regurgitation, in a patient who is responsive to PPI therapy[46]. Thus, upper endoscopy, routine biopsies from the distal oesophagus and ambulatory pH testing are not usually required in a patient with typical GORD symptoms in the absence of alarm symptoms such as dysphagia, odynophagia and weight loss[16,44,46]. The diagnosis of EoE on the other hand, relies on a correlation between clinical symptoms, endoscopic and histological features as there is no one pathognomonic feature of EoE[10,13]. According to the most recent consensus, it requires the presence of ≥ 15 intraepithelial eosinophils per high power field in one or more oesophageal mucosal biopsies in combination with symptoms of oesophageal dysfunction[5]. However, this definition may be too simplified as the diagnosis of EoE may be established with a lower intraepithelial eosinophil count if there is strong clinical suspicion and other histological features associated with eosinophilic inflammation are present[1,10]. Given that excessive accumulation of eosinophils in tissues is a common finding in numerous gastrointestinal disorders, other causes of oesophageal eosinophilia (Table 1) should also be excluded, particularly GORD[1,14]. The following diagnostic features that may be found in GORD and EoE and may help distinguish between the two entities are summarised in Table 2.

Endoscopic oesophageal features

Relevant endoscopic findings of GORD are erosive oesophagitis, peptic strictures, a hiatus hernia and Barrett's oesophagus[15,16,46]. Endoscopy has a high specificity for diagnosing GORD particularly when erosive oesophagitis is seen and the Los Angeles classification is used[53]. However, most patients with GORD will have normal endoscopies[15,16]. In contrast, endoscopic oesophageal features of EoE patients are trachealization, felinization, whitish exudates, longitudinal furrows, oedema, diffuse oesophageal narrowing, narrow-calibre oesophagus and oesophageal lacerations secondary to passage of the endoscope[1,10,13,16,54] (Figure 2). Loss of

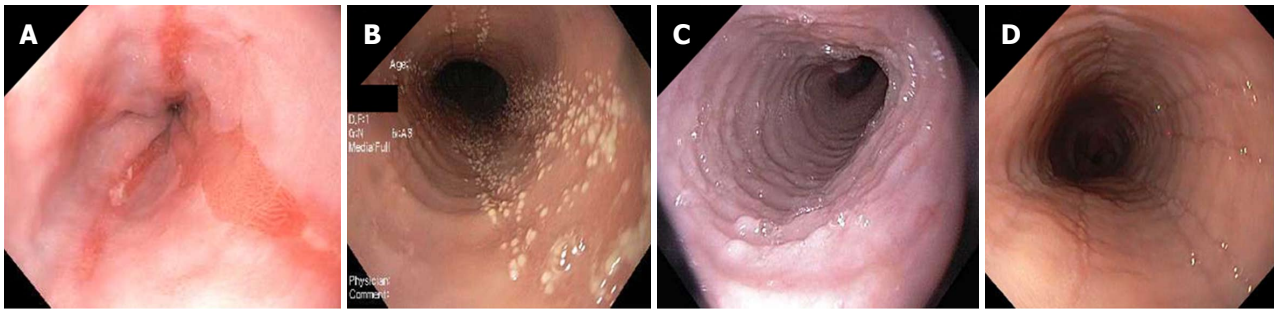

Figure 2 Endoscopic changes in patients with gastro-oesophageal reflux disease and eosinophilic oesophagitis. A: Erosive oesophagitis of gastro-oesophageal reflux disease; B: White exudates in eosinophilic oesophagitis (EoE); C: Mucosal rings or trachealization in EoE; D: Longitudinal furrows in EoE.

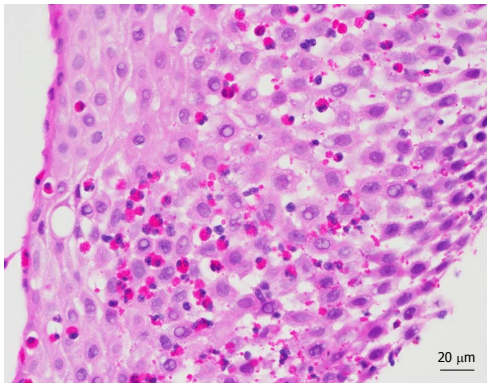

Figure 3 Histological specimen from the oesophagus (luminal aspect on left) of an eosinophilic oesophagitis patient showing marked oedema and numerous intraepithelial eosinophils in the oesophageal squamous mucosa, which are also seen in the superficial component of the mucosa.

mucosal vascular pattern has also been reported[55]. These features however, are not pathognomonic for EoE and thus histological correlation is required[1,10]. Normal endoscopic findings have been reported in up to 30% of patients with EoE[10,13].

Histological features

Patients with GORD may exhibit oesophageal eosinophilia, typically less than 10 per high power field as compared to ≥ 15 per high power field for EoE[1,10,15,56] (Figure 3). The presence of additional histological features of eosinophilic microabscesses, eosinophil degranulation, basal cell hyperplasia, papillary lengthening, superficial layering of eosinophils, extracellular eosinophil granules, intracytoplasmic keratinocyte vacuolation, dilated intracellular spaces or lamina propria fibrosis are more supportive of a diagnosis of EoE[1,10,13,16,57]. Although some of these additional histological features have been reported in biopsy specimens of patients with GORD, they are less commonly found as compared to EoE[10,13,16,57]. Recently, Zukerberg *et al*[17] showed that immunohistochemical staining of oesophageal tissue with IgG4 could help distinguish EoE from GORD, given that 76% of EoE cases were positive for intrasqamous IgG4 and none of the GORD cases were positive. The distribution of oesophageal eosinophilia may also be helpful in distinguishing the two conditions, with diffuse oesophageal eosinophilia more suggestive of EoE and distal oesophageal eosinophilia of GORD[16]. Thus, it is important to biopsy at least 2 regions of the oesophagus and accurately label the site of oesophageal biopsies.

Oesophageal motor function

Oesophageal manometry is of limited use in the diagnosis of GORD and EoE given that findings have so far been non-specific[1,13,58]. Oesophageal motility disorders found in patients with GORD have a similar type and prevalence to patients with EoE ranging between 4%-87%[14,21,33]. However, in cases where dysphagia is the main symptom, it is important to perform manometric assessment to exclude major and minor disorders of peristalsis which can sometimes mimic symptoms of GORD and EoE[18,33]. The duration of EoE has been shown to be longer in those with abnormal oesophageal motility[59].

TREATMENT

The initial management of GORD usually involves a combination of lifestyle interventions and medical therapy with the aim of eliminating symptoms, repairing any existing oesophageal mucosal injury and preventing further inflammatory injury[46,60]. Lifestyle interventions of weight loss (particularly if BMI > 25 or recent weight gain) and head of bed elevation have been proven to reduce symptoms and improve oesophageal pH values[61,62]. Other lifestyle interventions such as avoidance of late evening meals and cessation of alcohol, tobacco, chocolate, caffeine, spicy foods, citrus and carbonated drinks lack evidence and are not routinely recommended[46]. Medical therapy such as antacids, histamine-receptor antagonists (H_2RA) or PPI therapy should then be considered in patients failing lifestyle interventions alone[46,60]. PPI therapy is effective in 70%-80% of patients and has been shown to be superior to H_2RAs in regard to healing rates and decreased relapse rates[63]. Surgical therapy is as effective as medical therapy and may be contemplated in GORD patients who wish to discontinue medications, are non-compliant, have side-effects associated with medications, have a

large hiatus hernia or have refractory oesophagitis and symptoms despite optimal medical therapy[46].

The choice of initial treatment for EoE patients on the other hand is made on an individualized basis as PPI therapy, topical steroids and dietary therapy can all be considered as first-line therapeutic options[5]. All EoE patients should receive treatment to improve quality of life, prevent oesophageal remodelling secondary to active eosinophilic inflammation and prevent oesophageal injury due to the disease or endoscopic intervention[64]. 30%-40% of EoE patients may be responsive to PPIs, either due to a reduction in acid secretion in patients with co-existent GORD or by means of other still unknown anti-inflammatory mechanisms[21,22]. EoE patients can also be treated with topical steroids as it has been shown to improve symptoms and reduces oesophageal eosinophilia[21,65]. Viscous steroids have been shown to be more effective than nebulized steroids possibly due to greater mucosal contact time compared with the latter[66]. A recent meta-analysis of seven randomized controlled trials concluded that although there was an increased risk of asymptomatic oesophageal candidiasis with topical steroid therapy, it is considered safe with no evidence of adrenal suppression[67]. Dietary therapy is based on the fact that the majority of EoE patients have food allergies that may contribute to the pathogenesis of the disease[22,68]. There are 3 strategies of dietary therapy: An amino acid-based formula/elemental diet, a targeted elimination diet guided by allergy testing, and an empiric elimination diet[22,65,68]. All diets should be followed for a minimum of 6 wk and its efficacy evaluated *via* symptoms as well and oesophageal biopsies[65,69].

Oesophageal dilation, either *via* through-the-scope balloons or by Savary bougies can lead to long-lasting symptom improvement in EoE patients with structuring disease or impaired oesophageal distensibility due to subepithelial fibrosis[21,22]. Clinical improvement post dilation occurred in 75% of patients[70]. A meta-analysis evaluating the clinical efficacy and safety of oesophageal dilation in these patients showed that it is a safe procedure with a < 1% rate of serious complications[70]. However, it does not result in a decreased in eosinophil infiltration or histologic improvement and thus should not be used as a sole therapeutic option in these patients[5,71]. Several other treatment options for EoE have been assessed namely Montelukast (leukotriene receptor antagonist), Infliximab (anti-tumour necrosis factor), Mepolizumab (anti-IL-5), Azathioprine or 6-mercaptopurine, Reslizumab (IL-5 neutralizing antibody), Omalizumab (anti-IgE), QAX576 (anti-IL-13) and OC000459 (prostaglandin D2 receptor antagonist)[34,64,72-80] Although studies of these agents have shown changes in the biological behaviour of EoE disease markers, they have not yet displayed sufficient clinical benefit for widespread use[81].

RELATIONSHIP BETWEEN EoE AND GASTROESOPHAGEAL REFLUX DISEASE

The interaction between EoE and GORD is complex and may be bidirectional[5]. An approximate prevalence of GORD in the general population of 20% is sufficiently high enough to make the coexistence of EoE and GORD plausible[16]. In patients with refractory GORD symptoms, EoE was found in approximately 4%[10,56]. Four hypotheses to account for interactions between oesophageal eosinophilia and GORD have been proposed: Eosinophilia as a marker of GORD; GORD and EoE coexist but are unrelated, EoE contributes or causes GORD; and GORD contributes to or causes EoE[16,20,82,83].

Eosinophilia as a marker of GORD

GORD is thought to cause a mild eosinophilia in the absence of EoE[16,82]. Acid exposure was thought to cause oesophageal injury which results in chronic inflammation, including the presence of oesophageal eosinophils that are recruited *via* an increase in expression of adhesion molecules, release of chemokines that attract eosinophils and increase in blood flow[16]. However, the role of these adhesion molecules and chemokines in the pathogenesis of GORD is yet unclear[16]. A study also showed that dense oesophageal eosinophilia in GORD was uncommon[3].

GORD and EoE coexist but are unrelated

As mentioned above, due to a high prevalence of GORD in the general population, the coexistence of EoE and GORD due to chance alone is plausible[16,83]. Oesophageal pH studies have shown that 25%-50% of EoE patients have increased oesophageal acid exposure, thus supporting the notion that the two entities can coexist[1,16].

EoE contributes or causes GORD

This hypothesis is based on the fact that eosinophils secrete a number of agents that affect the integrity of the mucosal barrier and the function of oesophageal smooth muscle as well as producing a direct cytotoxic effect on the mucosa[16,20]. Remodelling effect in EoE may contribute to increased acid exposure due to effects on the LOS or impaired oesophageal clearance of refluxed contents[16,20].

GORD contributes to or causes EoE

An unproven hypothesis has suggested that GORD may contribute to the pathogenesis of EoE by causing changes in the integrity of the oesophageal mucosa, promoting trans-epithelial allergen permeation followed by allergic immune activation[5,84].

CONCLUSION

The relationship between EoE and GORD is complex as

they are different entities that may coexist. Distinguishing between the two remains challenging given that it has multiple overlapping features. At present, the combination of clinical, endoscopic and histological features, as well as response to PPI therapy, may help to differentiate the two conditions. Further studies into the immunopathophysiology are needed to elucidate more objective diagnostic testing that can reliably differentiate between the two disease processes.

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