Narrative review of the role of inflammation in gastroesophageal reflux disease. Can food allergies play a part?

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Abstract
Acid suppression is the accepted treatment for gastroesophageal reflux disease, despite being ineffective in one third of patients. Certain conditions presenting as reflux may later be attributed to food allergy (infant cow’s milk allergy; eosinophilic esophagitis), but the role of food allergy in adult reflux disease has rarely been investigated. The mechanisms of gastroesophageal reflux disease are examined to explore potential subgroups within the population, such as undisclosed food allergy, which may determine the responsiveness to treatment. The relevant literature was searched systematically using ProQuest Dialog, yielding 113 papers that were evaluated for quality. The extracted evidence was formed into a mechanistic diagram representing the processes of disease. As yet, insufficient research exists to evaluate the relationship between food allergies and reflux in adults. Of significance, however, is the potential for multiple variables to affect the integrity of the esophageal mucosa, thereby allowing symptoms to emerge which are independent of acid exposure. Where nonacidic drivers of inflammation exist, acid suppression is unlikely to offer adequate symptom resolution and may serve to explain the high proportion of nonresponders in this group. The review concludes that symptoms of gastroesophageal reflux may emerge in response to the coexistence of physiological reflux and esophageal mucosal inflammation. The latter may arise due to reflux-induced acid erosion, or due to alternative endogenous sources of inflammation. When a patient presents with refractory reflux and a history of allergic disease, the role of antigen-induced inflammation should be considered for further investigation. Nonallergic individuals presenting with refractory reflux symptoms may benefit from further analysis of relevant co-morbidities that have the capacity to compromise mucosal integrity, including obesity or psychological stress. The identification of specific mediators of inflammation in refractory reflux disease may enable the development of personalized treatment regimes which improve outcomes and reduce the reliance on acid suppressants.

Abbreviations: ACT, acid contact time; APT, atopic patch testing; CMA, cow’s milk allergy; DIS, dilated intercellular spaces; EoE, eosinophilic Esophagitis; ERD, Erosive Reflux Disease; GOR, Gastroesophageal Reflux; GORD, Gastroesophageal Reflux Disease; IBS, Irritable Bowel Syndrome; LOS, Lower esophageal, Lower esophageal sphincter; NERD, nonerosive reflux disease; Nrf2, nuclear factor erythroid-derived, nuclear factor erythroid-derived 2-like pathway; PPI, proton pump inhibitor; SPT, skin prick testing

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1 | INTRODUCTION

The Montreal definition of gastroesophageal reflux disease (GORD) defines it as an "array of disorders caused by the retrograde movement of gastric content into the oesophagus,\(^1\) which is largely attributed to gastric hypersecretion or increased acidic reflux events due to lower oesophageal sphincter (LOS) dysfunction, hiatal hernia, or gastric/esophageal dysmotility. As a result, acid suppression has been adopted as the mainstay of treatment, with proton pump inhibitors (PPIs) being favored due to their ability to offer a 80–85% healing rate of esophageal lesions.\(^2,^3\)

However, only 30% of GORD patients exhibit erosive disease (ERD);\(^3^–^6\) and 50% of those with nonerosive disease (NERD) have normal acid contact time (ACT),\(^4,^7\) which may explain why PPIs do not provide symptom relief in 10–40% of GORD patients,\(^5^–^10\) particularly those with NERD.\(^3\) Moreover, there is no conclusive evidence to suggest that NERD progresses to erosive disease,\(^11\) suggesting the likelihood of an alternative etiology in this group. To date, it is acknowledged that patients with refractory GORD may be considered to have functional heartburn or esophageal hypersensitivity in accordance with the Rome IV criteria\(^12\) and also that weight gain and abdominal adiposity are key factors that can contribute to the perception of reflux severity and the response to PPIs.\(^13\) Given the increasing concerns over the long-term effects of PPI therapy,\(^14^–^18\) it is important to explore the mechanisms that govern symptom perception in subgroups of the GORD population to determine whether inflammatory mechanisms which are not driven by acid exposure exist, thereby offering the potential for personalized treatment plans to be developed that provide greater efficacy and safety than acid-suppression.

In infants, the mechanism of GORD is well-documented and the disease is similarly unresponsive to acid suppression,\(^19\) but unlike adults, there is extensive literature citing cow’s milk protein allergy (CMA) as a trigger for infant reflux\(^20^–^26\) via delayed gastric emptying, dysmotility, LOS dysfunction, and neuroimmune interactions.\(^21\) Although it is maintained that most children outgrow CMA, it is reported that 70% of infants with CMA develop further food sensitivities later in life\(^24\) and late-onset symptoms often present as gastrointestinal dysfunction which may include GORD, irritable bowel syndrome (IBS), and intestinal mucosal inflammation.\(^23\)

Likewise, another condition commonly presenting as GORD is the antigen-driven inflammatory condition eosinophilic esophagitis (EoE), which currently accounts for 0.9–4% of refractory GORD patients.\(^27\) Increased acid exposure is not a characteristic feature of EoE, but GORD symptoms often occur as a result of mucosal inflammation and dysmotility and may represent the first clinical signs of disease.\(^28\)

There is clear evidence to demonstrate that dietary modification can bring about effective symptom resolution for individuals with CMA and EoE,\(^22^–^26,^29\) but there has been limited exploration into the potential for food antigens to act as nonacidic drivers of mucosal inflammation in GORD, which may be equally responsive to dietary intervention or alternative pharmacological treatment. The role of acid-induced inflammation as a trigger for GORD symptoms is well-established, and this fact remains undisputed. The purpose of this narrative review, however, is to examine the current understanding of relevant mechanisms that operate in conditions presenting as GORD, and to investigate whether food-antigen induced mucosal inflammation and dysmotility, as seen in CMA and EoE, can explain the presence of GORD-like symptoms in a proportion of patients who appear to fall into the gap between PPI-responsive GORD and EoE. In addition, given the knowledge that GORD is more prevalent in the overweight population, the potential for reflux disease to be managed through diet and lifestyle modification is explored. This is based on the hypothesis that the systemic inflammation that accompanies obesity may contribute to symptom perception and thereby respond to anti-inflammatory diet and lifestyle interventions.

2 | METHOD

A systematic search of the literature was conducted in order to avoid selection bias, and the details are presented comprehensively within the Supporting Information. The relevant search terms were established (S1 in the Supporting Information) and expanded using ProQuest thesaurus facility to provide more comprehensive search strings (S2 in the Supporting Information). For the purpose of this review, the term “food allergy” is used, as defined by the World Allergy Organisation,\(^30\) encompassing immune-mediated reactions which may include IgE, non-IgE, or mixed antibody involvement, although it is acknowledged that some authors may reserve this term solely for IgE responses, preferring the term “food hypersensitivity” for non-IgE reactions.

Preliminary searches indicated that ProQuest Dialog, utilizing Embase and Medline databases, returned the greatest number of relevant results. In all, eight searches were conducted, retrieving a total of 513 papers, of which 105 papers were selected for analysis. Any relevant primary literature cited within review papers which had fallen outside the search criteria was read and evaluated for inclusion into the review, resulting in an additional eight studies being included. The total number of papers selected for the review was 113. All papers were critically analyzed using recognized forms where possible, including both SIGN 50 and ARRIVE forms. Information detailing the rationale for each search, including the inclusion/exclusion criteria can be accessed online in S2.
TABLE 1  Breakdown of review papers retrieved and evaluated

| Area of study                                      | Number of reviews analyzed |
|---------------------------------------------------|----------------------------|
| Gastroesophageal reflux disease                    | 8                          |
| Refractory gastroesophageal reflux disease         | 14                         |
| Infant reflux and cow’s milk allergy (CMA)        | 8                          |
| Food allergies and sensitivities: adults or children| 14                         |
| Eosinophilic esophagitis                           | 13                         |
| Other papers from related areas                    | 8                          |
| Total review papers analyzed                      | 65                         |

2.1  | Review paper strategy

Due to the lack of primary literature evaluating the role of food sensitivities in GORD, it was necessary to examine the separate areas by including a greater proportion of review papers, the breakdown of which is illustrated in Table 1.

2.2  | Primary research search strategy

When initial searches for primary research relating food sensitivities with GORD in humans were unfruitful, the search criteria were widened to encompass papers more than 10 years old, animal studies and additional databases such as the Allied and Complementary Health database where appropriate.

From the preliminary searches, the significance of the esophageal mucosal integrity and the role of “dilated intercellular spaces” (DIS) emerged as key areas from which to direct later searches and the process was stopped when the final search retrieved no results. Mechanisms that were identified in the analysis of all 113 papers were then mapped onto a mechanistic diagram (Appendix A), and a fully referenced version can be found in S5/S6 in the Supporting Information.

2.3  | Limitations of search process

The lack of available primary research examining the role of food sensitivities in GORD enforced reliance upon a high number of review papers, in order that the relevant mechanisms in each area could be examined separately. DIS was chosen as the most relevant mechanism to investigate in this review, but it is acknowledged that further analysis in the areas of immune response, antibody-type, cell junction protein expression, and the role of specific inflammatory cytokines is required to facilitate further understanding in future reviews.

3  | RESULTS

One hundred thirteen full text papers were critically analyzed, and relevant mechanisms were extracted and constructed into a referenced mechanistic diagram (Appendix A; S5/S6 in the Supporting Information) The key findings most relevant to the research question are presented as follows.

3.1  | Reflux symptoms and food allergies/sensitivities

The link between CMA and GORD symptoms in infants is widely recognized in the literature, with 40% of infants referred for specialist management of GORD receiving a diagnosis of CMA with IgE and/or non-IgE involvement.23 However, the research into similar mechanisms occurring in older children or adults is limited. Semeniuk and colleagues orchestrated a series of studies evaluating the relationship between CMA/food allergy and GORD in a group of 138 children diagnosed with acidic reflux. The authors observed that GORD secondary to food allergy does not respond to traditional reflux treatment in the same way as primary GORD and reflux symptoms are more diverse in those children with food allergy.35 Although nearly 40% of children with GORD presented with inflammation, 28.1% of children in the control group who had food allergy without acidic reflux, also had first-degree inflammation. This suggests that an inflammatory process may be present in the esophageal mucosa of some allergic children in the absence of abnormal acid exposure.36 These children had initially presented with GORD-like symptoms but were excluded from GORD groups on the basis of pH monitoring. In 46.8% of children with GORD secondary to food allergy, eosinophils were noted at levels of 7–15/hpf, suggesting that some of this group were borderline for a diagnosis of EoE (where 15/hpf is diagnostic for EoE.28,37,38 Indeed, the authors suggest that 1–5/hpf may occur in primary GORD and 7–15/hpf may be indicative of GORD secondary to food allergy. This suggests that the potential for overlap may make it difficult to distinguish between primary/secondary reflux groups and EoE upon histological analysis. Interestingly, children with primary GORD had a significantly higher number of neutrophils in mucosal tissue (p < 0.0001) compared to the group with secondary GORD where eosinophils were predominant (p < 0.0002). Further analysis indicated that both groups with food allergy had significantly higher levels of serum IL-4 (p = 0.0001) than the primary GORD group, which is a key cytokine for influencing IgE production by upregulating Th2 lymphocyte activity.39 The authors note that mean IL-4 concentrations decreased after 12–24 months of food elimination and/or pharmacological intervention in the secondary GORD and control groups compared to the primary GORD group, which may indicate that it is possible for IL-4 to act as a marker for an allergic component to GORD.

In an observational study of a single group of children (< 2 years) with GORD symptoms (n = 81) where each received PPI treatment for 4 weeks, 66.7% responded successfully, an equivalent proportion of responders to those observed in adults. The remaining 27 patients, of which a higher proportion had respiratory symptoms, were given a cow’s milk-free diet for 4 weeks which resulted in complete resolution of symptoms. A similar correlation between GORD and allergy was evident in a cross-sectional analysis of 1828 Taiwanese adolescents where
GORD was significantly higher in asthmatics ($p < 0.0001$) and those with allergic conditions ($p < 0.0001$), particularly in relation to dairy produce.\textsuperscript{41}

Pomieciński et al., in their cross-sectional study of 65 adult GORD patients, noted that food sensitivities were present in 27.7% of subjects and were higher in asthmatics ($p = 0.008$).\textsuperscript{42} Fifteen of the patients with food sensitization, but negative for EoE, followed an elimination diet, with 80% showing clinical improvement ($p = 0.004$), particularly for heartburn and regurgitation ($p = 0.005$ and $p = 0.007$, respectively).

### 3.2 Reflux symptoms and eosinophilic esophagitis

EoE is well-recognized as an antigen-driven allergic condition, which often presents with GORD symptoms in the early stages,\textsuperscript{38,37,34} despite being rarely associated with abnormal acid exposure.

The involvement of IgE antibodies in EoE and GORD was explored by Yen et al. in a retrospective case-control study on 62 patients with EoE ($n = 19$), reflux esophagitis ($n = 22$), or controls without reflux ($n = 21$).\textsuperscript{43} The authors investigated the prevalence of FcεRI, a known IgE antibody receptor, hypothesizing that it would be upregulated in EoE due to its links with food/inhalant allergy.\textsuperscript{44,45} However, FcεRI was equally prevalent in EoE and reflux groups ($p = 0.7$/proximal; $p = 0.2$/distal) but significantly more prevalent in the EoE ($p = 0.006$/proximal) and reflux groups ($p = 0.004$/distal) compared to controls, indicating a possible upregulation of IgE activity in the mucosa of reflux patients as well as EoE patients.\textsuperscript{43} The authors did not expect to see an increase in FcεRI expression for the reflux group as well as the EoE group, and they conclude that the increased expression may have occurred in response to increased inflammation within the mucosa, rather than as a result of allergen binding. However, this reasoning assumes it was not possible for the reflux group to possess an allergic component to their pathology due to the current definition of GORD. Alternatively, one could hypothesize that the increased expression of the IgE receptor in the reflux group may exist due to a subclinical immune response in some GORD patients.

If the boundaries between primary GORD, GORD secondary to food allergy and EoE are unclear, it is helpful to examine the reasons why there might be differences in macroscopic, histological, and clinical observation observed between the conditions. There is some emerging evidence to demonstrate that EoE is associated with a specific pattern of genetic involvement, with only 40 common genes being shared between EoE and chronic esophagitis.\textsuperscript{46} Blanchard et al. describe the CCL26 gene which encodes the eosinophil-specific chemoattractant eotaxin-3 in EoE, with a single-nucleotide polymorphism in this gene being associated with EoE susceptibility.\textsuperscript{46} Eosinophils are typically much higher in EoE compared to GORD, but the population of EoE subjects studied by Blanchard et al. were shown to have widely varying levels of eosinophil infiltration, between 24 and 218 per/hpf. Since the gene encoding for eotaxin-3 was noted to be increased by 53-fold in EoE, with a strong correlation being shown between eotaxin-3 mRNA and peak eosinophil counts ($p < 0.005$),\textsuperscript{46} it is likely that genetic polymorphisms determine the nature and degree of response to allergic triggers in each individual. In addition, specific cytokines induced by inflammation can serve to determine the individual behavior of immune cells in different pathological processes, as illustrated by Byström and O’Shea who reported the ability of IL4 to influence antibody switching in favor of Type 1 IgE antibodies and IL5 to play a role in eosinophil differentiation and activation.\textsuperscript{37}

### 3.3 The role of acid exposure as a contributor to mucosal inflammation and dysmotility

Acid-induced esophagitis has been shown to cause significant hypomotility and peristaltic abnormalities in feline\textsuperscript{47} and murine models\textsuperscript{48} but Souza et al. observed that esophagitis in rats did not occur directly in response to acid contact. Instead, it developed over a period of 4 weeks in response to acid-induced inflammatory cytokines. They observed inflammatory characteristics occurring initially within the submucosal layer of esophageal tissue and progressing to the luminal epithelium over a period of weeks.\textsuperscript{49} The authors indicate that they would expect the first signs of an acid-induced injury to involve the death of surface epithelial cells, followed by a proliferation of basal cells in an attempt to repair the damage. However, three days after reflux was induced, they observed that there was no damage to the surface cells, but signs of inflammation had occurred within the submucosa, characterized by an increased number of T-lymphocytes. In addition, esophageal basal cell and papillary hyperplasia occurred several weeks before the loss of epithelial cells was apparent. The authors therefore conclude that esophagitis develops as an immune-mediated injury, as opposed to a caustic chemical injury, and in humans this inflammatory response is thought to be of importance not only in the development of erosive disease but also in esophageal hypersensitivity.\textsuperscript{4}

Likewise, Rocha et al. observed an interesting effect upon the muscle contractility of esophagitis isolated from guinea pigs. There was no significant difference between smooth muscle contractility in the intact esophagus of guinea pigs that had been exposed to either acid or saline ($p = 0.633$). However, contractility was significantly reduced in a group where the intact mucosa was exposed to acid, compared to a group where the mucosal layer had been removed ($p = 0.039$).\textsuperscript{50} This would suggest that bile-induced mucosal inflammation has a greater impact upon esophageal contractility than any direct effects of the bile itself\textsuperscript{50,51} and that the inflamed mucosa has the potential to signal to the smooth muscle layer acting independently of acid exposure.

Additional studies appear to support the role of inflammation as a promoter of dysmotility as observed in an in vitro study by Rieder et al. using human esophageal cells from patients with esophagitis ($n = 26$) and without ($n = 19$).\textsuperscript{52} Analysis demonstrated a higher production of inflammatory mediators (IL1β and IL6) from the mucosal cells of patients with esophagitis than controls. In particular, it was noted that IL6, which has the capability to reduce muscle contractility, rapidly increased in response to gastric refluxate of pH 2.5 and pH 4, but increased only slowly when exposed to nongastric acidic medium of pH 2.5, indicating that the acidity of the refluxate may be less influential.
than other components. Rieder et al. also noted that cytokines from epithelial cells had a greater adverse effect upon motility than those produced by muscle or fibroblast cells.52

Evidently, if mechanisms of inflammation exist within the mucosa which are not orchestrated by increased ACT, the potential for mucosal disruption and dysmotility that is unresponsive to acid suppression emerges.

### 3.4 The role of DIS in reflux disease

The process of inflammation can lead to increased DIS in the esophageal or laryngeal mucosa,53,54 which may contribute to increased symptom perception in both GORD and NERD.14 The fact that acid exposure can increase intercellular spaces in the mucosa is undisputed,55 but mechanistic evidence also exists to demonstrate that mucosal integrity may also be compromised endogenously, irrespective of acid exposure.

Chen et al. investigated the nuclear factor erythroid-derived 2-like pathway (Nrf2) which is involved in the regulation of epithelial defense and noted its increased expression in basal and superficial cells of esophageal tissue of patients with nonerosive reflux disease, compared to only superficial expression in healthy controls (p < 0.05).56 In addition, Nrf2 knockout mice without reflux were shown to have increased DIS, indicating that reduced barrier function may exist in the absence of pathological reflux. The authors support their theory by acknowledging that a genetic polymorphism GSTP1, which targets Nrf2, is associated with more aggressive esophagitis.

Interestingly, it has been demonstrated that esophageal and laryngeal DIS can be induced in animals subject to restraint stress.57 Control, nonstressed rats exposed to acid had no greater development of DIS or mucosal permeability, even to the smallest molecules, than those which were exposed to a benign solution (P = 0.16), but exposure of stressed rats to gastric acid increased permeability to all molecules (p < 0.0001). Electron microscopy showed DIS was evident only in the mucosa from stressed rats with or without exposure to acid. Stress increased the number of submucosal mast cells and increased mucosal permeability without acid exposure (p < 0.01), but acid was capable of potentiating the effect significantly (p < 0.0001). The author’s relate this finding to other studies that report increased symptoms in GORD patients when stressed,57 which suggests that more extensive research into the effects of stress upon mucosal integrity and symptom perception in humans is needed.

### 3.5 The role of acid suppression in the management of reflux disease

PPIs are routinely prescribed for both the treatment and differential diagnosis of GORD, and they are capable of improving overall injury scores in 90% of GORD patients and 65% of patients with laryngopharyngeal reflux.58 Though their short-term safety has been well established over the years,2,59–60 there is increasing concern over their use as a long-term treatment for GORD due to associated comorbidities.15–17

In recent years, there have been reports of PPI therapy increasing susceptibility to the development of food allergies, when reduced digestion increases the ability of food proteins to bind with specific IgE receptors. Human clinical studies have noted a 25% increase in IgE antibodies to foods in patients receiving acid suppression for 3 months,18,28,61 and there is now evidence which links the use of PPIs with EoE development.61

To explore the associations between the use of acid suppressants and food allergy, Trikha et al. conducted a large-scale retrospective cohort study using insurance codes to investigate 4,724 children treated with PPIs for GORD and compared them with the same number of children with untreated GORD, or matched controls, over a period of 12 months.62 As the authors expected, the GORD children taking acid suppressants had an increased risk of developing food allergy (1.7-fold) within 12 months, compared to those without treatment. However, the authors were surprised to note that those with untreated GORD were also more likely to develop food allergy than controls (hazard ratio (HR) 2.15; 95% confidence interval (CI): 1.21–3.81), though not as high as treated children (HR 3.67; 95% CI 2.15–6.27; p = 0.007). They explain this by suggesting that they may have consumed over-the-counter medications, but this view is founded upon their hypothesis that acid suppressants must have caused the emergence of food allergy symptoms. Alternative mechanisms accounting for these results should be further explored. It is possible, for example, that a proportion of nonmedicated patients displayed emerging, less severe GORD symptoms which were driven by low-level antigen-induced inflammation and presented themselves before overt signs of food allergy were recognized, thereby being independent of the effects of acid-suppressing medication.

### 3.6 The role of dietary intervention in the management of reflux disease

Several authors have studied the role of dietary intervention and food elimination in both CMA and EoE, but only one author who has evaluated the role of dietary exclusion specifically in GORD was identified in the search.

Caselli et al. performed a peer-reviewed double-blind randomized controlled trial on 38 refractory GORD patients to examine the effect of dietary elimination of reactive foods, as determined by leukocytotoxic testing, upon symptoms as measured by the GORD Impact Scale (GIS).63 Patients were randomly assigned to a diet sheet which excluded either their identified reactive foods or their nonreactive foods and were blind to the results of the reactivity test. After 1 month, the group receiving the personalized elimination diet had reduced symptoms (p = 0.001) compared to a significant, but much reduced, improvement in the control group (p = 0.02) which may have been due to placebo effect. Diets of the control group were then switched to the true exclusion diet, while the other group continued on their tailored exclusion diet for another 8 weeks. The original group to
follow the true exclusion diet continued to see a reduction in symptoms (−21.3%), but the GIS score did not significantly improve any further (p = 0.19), whereas the control group, who were now excluding the correct foods, saw a reduction in GIS score of −44.9% (p = 0.01). The authors suggest that T-reg cells can regulate the activity of IgE versus IgG4 antibodies, with an upregulation of T-Reg cells activating more of an IgG4 response, compared to IgE type, which can determine both tolerance and immediate versus delayed reactivity. Interestingly, these results may support a number of studies cited by the authors which have confirmed the benefit of similar test-based exclusion diets in IBS. However, it is important to recognize that leukocytotropic testing and antigen specific IgG4 tests are considered to have poor clinical specificity and sensitivity, and therefore these studies cannot be used as robust evidence to support the role of food allergy in GORD or IBS without further research.

4 | DISCUSSION

It has been suggested that the 2006 Montreal definition of GORD is a symptom-based definition "which provides a rationale for treatment with acid suppressive medications without the need for cumbersome investigations of symptom aetiology [and] which is a barrier to more precise patient management." As such conventional treatment of GORD has focused upon reducing reflux events or suppressing gastric acidity, with relatively little attention being paid to the origin of inflammation and the consequent effects of this upon mucosal integrity and symptom perception, as this has routinely been attributed to acid damage. It is evident, however, that healthy individuals can be asymptomatic, despite abnormal acid exposure, and NERD patients may experience symptoms upon exposure to saline solution, illustrating that symptom perception depends upon more than just acid contact. Although it is undisputed that mucosal damage can occur in response to gastric acid contact, which may improve with acid suppression, the fact remains that 10–40% of GORD patients fail to respond to medication, particularly in NERD where 50–85% remain symptomatic. Within a new paradigm of preventative and lifestyle medicine, this symptom-based definition prevents the appropriate investigations which have the potential to reveal underlying causes of disease that may be addressed through diet and lifestyle measures.

Most studies evaluating the reasons for refractory GORD have considered insufficient medication, misdiagnosis, hypersensitivity, or psychological involvement as being the primary reasons for medication failure, thereby continuing to assert that ACT is the most likely determinant of GORD symptoms. Evidence contradicts this theory, demonstrating that <10% of reflux events generate symptoms on pH monitoring, only 11–36% of pain is actually associated with acidic reflux events, and 70% of patients with heartburn are diagnosed with NERD or functional heartburn, which are associated with less acid exposure than those with reflux esophagitis. Moreover, reflux surgery has not been shown to be effective in refractory GORD, suggesting that pain perception may not be linked solely to acid or alternative components of the refluxate in this group. It is important to recognize, therefore, that a significant proportion of patients presenting with GORD in primary care may not have classic GORD, as described in the Montreal definition, and may fall into one of many subgroups, each of which requires a different management protocol.

As pediatric experts have agreed that symptoms of GORD and food allergy can be indistinguishable in infancy, the possibility has to be considered that the same may be true for adults. Given that GORD-like symptoms are observed in both infant CMA and EoE, which are both accepted to be immune-mediated, antigen-driven conditions, the evidence is discussed to explore whether antigen-driven endogenous inflammation could also account for the symptoms in a proportion of individuals presenting with refractory GORD.

4.1 Understanding GORD pathology secondary to food allergy

It is often stated that children with CMA outgrow their symptoms. As determined by skin-prick testing (SPT), atopic patch testing (APT) or parental perception of adverse events following milk ingestion. As SPT testing has a specificity of 50% and only 36% of children outgrow milk allergy is suspected. Even in IgE-mediated allergy, serum testing does not always correlate well with clinical symptoms, as IgE tends to be demonstrated that <10% of reflux events generate symptoms on pH monitoring, only 11–36% of pain is actually associated with acidic reflux events, and 70% of patients with heartburn are diagnosed with NERD or functional heartburn, which are associated with less acid exposure than those with reflux esophagitis. Moreover, reflux surgery has not been shown to be effective in refractory GORD, suggesting that pain perception may not be linked solely to acid or alternative components of the refluxate in this group. It is important to recognize, therefore, that a significant proportion of patients presenting with GORD in primary care may not have classic GORD, as described in the Montreal definition, and may fall into one of many subgroups, each of which requires a different management protocol.

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4.1 Understanding GORD pathology secondary to food allergy

It is often stated that children with CMA outgrow their symptoms. As determined by skin-prick testing (SPT), atopic patch testing (APT) or parental perception of adverse events following milk ingestion. As SPT testing has a specificity of 50% and only 36% of children outgrow milk allergy is suspected. Even in IgE-mediated allergy, serum testing does not always correlate well with clinical symptoms, as IgE tends to be demonstrated that <10% of reflux events generate symptoms on pH monitoring, only 11–36% of pain is actually associated with acidic reflux events, and 70% of patients with heartburn are diagnosed with NERD or functional heartburn, which are associated with less acid exposure than those with reflux esophagitis. Moreover, reflux surgery has not been shown to be effective in refractory GORD, suggesting that pain perception may not be linked solely to acid or alternative components of the refluxate in this group. It is important to recognize, therefore, that a significant proportion of patients presenting with GORD in primary care may not have classic GORD, as described in the Montreal definition, and may fall into one of many subgroups, each of which requires a different management protocol.

As pediatric experts have agreed that symptoms of GORD and food allergy can be indistinguishable in infancy, the possibility has to be considered that the same may be true for adults. Given that GORD-like symptoms are observed in both infant CMA and EoE, which are both accepted to be immune-mediated, antigen-driven conditions, the evidence is discussed to explore whether antigen-driven endogenous inflammation could also account for the symptoms in a proportion of individuals presenting with refractory GORD.
method depending heavily upon individual microscope quality. It is evident, however, that low-level eosinophil infiltration into the esophagus can occur in a number of other inflammatory conditions and may represent an overlap with GORD, with 6–10 eosinophils being evident in the distal esophagus of GORD patients compared to a greater number distributed along the length of the esophagus in EoE. It is possible perhaps that the point at which eosinophil infiltration becomes EoE may be determined by genetic predisposition, which may account for the male predominance in this condition, but this does not exclude similar, but less pronounced mechanisms of inflammation and dysmotility occurring in non-EoE conditions presenting with GORD. Interestingly, a number of EoE patients are shown to be responsive to PPI therapy, which may occur because PPIs also help to prevent eosinophil migration and have an anti-inflammatory action, and this may explain their success in some patients who do not have abnormal ACT but have a high mucosal inflammatory component. More recently, a relationship between functional dyspepsia and food sensitivities has been acknowledged, suggesting that immune function is characteristic of this condition and shares common processes with EoE and non-IgE food hypersensitivities such as noncoeliac gluten sensitivity. Further investigations are required to determine whether similar mechanisms may exist in functional heartburn.

4.2 The role of esophageal mucosal inflammation in symptom perception

Although both acid and nonacid components of refluxate have been demonstrated to be relevant in the symptom perception of GORD, it is evident that they are by no means the only contributors to mucosal inflammation, with infection, obesity, immune dysfunction, comorbidities, dysbiosis, stress, and allergic responses also potentially being relevant. A hypothetical model of the role of mucosal inflammation in GORD pathogenesis is illustrated in Figure 1, where GORD perception is determined not solely by ACT, but by the coexistence of physiological or pathological GOR alongside inflammation-induced mucosal disruption. The latter may be caused by acid-induced erosion, or a number of alternative factors, including psychological stress, obesity, pharmacological agents, dysbiosis, inflammatory or atopic disease, malnutrition, and nutrient deficiencies. Mechanistic studies have demonstrated how this mucosal inflammation and the resulting cytokines, may contribute to gastric and esophageal dysmotility by the mechanisms of hiatal hernia and reduced peristalsis, which then perpetuate the cycle of reflux disease. Further research is needed to understand how such mechanisms might impact GORD in humans, and whether esophageal dysmotility may develop in response to systemic or localized inflammatory processes.

This process can be illustrated by considering the effects of an acidic solution applied to an epidermal lesion, such as eczema. The application of acid will increase both pain and inflammation, thereby increasing symptoms perceived by the patient which will correlate with the timing of acid contact. Likewise, the removal of the acidic stimulus will prevent exacerbation of the lesion, allowing a degree of epidermal healing, but symptom resolution will depend upon controlling the inflammatory factors which are maintaining the breakdown of epidermal tissue. Acidic solution applied to healthy skin will not generate
FIGURE 2 Potential methods and effects of inflammation generation and control in gastroesophageal reflux disease

4.3 Methods for nonpharmacological management of mucosal-dominant reflux disease

Current methods of dietary management in GORD include the advice to reduce foods such as tomatoes, citrus fruits, spicy foods, coffee and mint, but this advice is based primarily on the effects upon luminal acidity or LOS relaxation, rather than the source of inflammation, and it has rarely been found to be effective. Achieving equilibrium between the processes of mucosal disruption and repair is an ultimate goal in the reduction of symptom perception, and therefore a management program which aims to reduce mucosal inflammation is likely to be of more long-term use. This offers an alternative for GORD patients who are concerned about the potential adverse effects of long-term acid suppression and eases the pressure on the healthcare budget, particularly where nonpharmacological strategies can be used as a primary method of symptom resolution.

4.4 Limitations of review and areas for further research

This review aimed to determine whether food allergies could account for the symptoms in a proportion of individuals presenting with refractory GORD, based upon the evidence that GORD-like symptoms are observed in both infant CMA and EoE, which are considered to be immune-mediated antigen-driven conditions. The literature review revealed a considerable gap of knowledge in this area, particularly for primary research which investigates the role of food allergies in adults with GORD. As a result, many of the evaluated studies in this review have been small in sample size and have frequently been observational in nature, so concrete conclusions about the role of food allergy in GORD cannot be drawn at this stage. However, it is widely acknowledged that the current understanding around the various subtypes of GORD is lacking, and patients presenting with reflux symptoms cannot be provided with a "one-size fits all" approach.

It is interesting to speculate on the reasons for this imbalance in the literature, perhaps being related to the differing ways in which medical practice has evolved with children compared to adults. Pediatric medicine is a specialism in its own right, thereby allowing a more holistic approach to diagnosis. Since a verbal history of symptom perception oftentimes cannot be gained from the patient, more exploration into presenting signs is needed. Consequently, a pediatric consultant is required to consider a number of different conditions that may present with similar symptoms, but which possess diverse etiologies. In adults however, specialties are primarily separated by organ systems, so when a patient presents with reflux-type symptoms and is referred to gastroenterology, a diagnosis is more likely to be made within the gastrointestinal system. GORD is such a well-recognized condition with a collection of established symptoms that an alternative etiology is rarely considered, particularly when symptoms of a low-grade inflammatory response and non-IgE immune responses can be subtle and easily overlooked. Since interplay between specialists in an organ-based medical paradigm is reduced, a patient presenting...
to gastroenterology with reflux symptoms may not be considered as a candidate for investigations into immune system dysfunction. It is possible therefore that the recognition of overlap between two similarly presenting conditions in pediatrics is reached much more quickly, while the two fields remain much more separate in adult medicine. This in turn may influence the patterns of research in those areas and explain the disparity in available literature on these topics.

Despite this paucity of literature, the review was able to uncover a breadth of evidence which supports a significant role for inflammation and the integrity of the esophageal mucosa in the perception of GORD symptoms, alongside acidic and nonacidic reflux events. In particular, the presence of "DIS," which are present in ERD, NERD, and EoE, appear to be significant and have been a primary focus of this review. If the identification of specific triggers of inflammation for individuals with GORD has the potential to enable more personalized treatment regimes, it is important to examine further pharmacological, dietary, and lifestyle measures that may serve to offer more options to the patient than acid suppression alone.

As a result of the review, the following areas have been identified that require further in-depth investigation in order to facilitate our understanding of GORD and the most effective management strategies for each subtype.

4.5 Food elimination

Although elimination diets in CMA and EoE have been found to be effective, there has been insufficient research into the effect of elimination diets in GORD. However, when GORD patients present with a strong allergic history, further investigations into food allergy are warranted, not only to eliminate a diagnosis of EoE but also to consider whether effective allergy management may help to reduce their reflux symptoms. Specific allergen testing to inform elimination diets may not always be reliable and should not be used as a sole method for determining sensitization and clinical allergy, but it may offer some useful information as part of a holistic assessment. Further studies should be conducted to examine whether professionally guided elimination diets have the potential to be as effective in refractory GORD as they are in EoE.

4.6 Anti-inflammatory dietary regime

Research has recognized strong associations between food/lifestyle choices and inflammatory conditions and has demonstrated that specific dietary patterns, such as the Mediterranean diet, can be an effective strategy to reduce inflammation. A growing body of research supports the anti-inflammatory effects of plant-based diet high in phytonutrients with specific foods capable of reducing inflammation, and there is a call for further understanding of how personalized nutrition may be used to modulate inflammatory disorders by way of epigenetics. Further research is required to determine whether individualized dietary patterns may also be helpful specifically in the management of reflux disease.

4.7 Weight management

Weight gain and obesity have long being associated with reflux severity, but is this has largely been attributed to the pressure exerted upon the stomach by visceral adiposity, without acknowledgment of the systemic inflammation that coexists with excess weight gain. There is some emerging research to demonstrate that obesity is associated with increased DIS, even in the absence of acid reflux so it is wise to consider weight control as an integral part of the management program for patients with a BMI over 25 kg/m², where trials have shown increased mucosal healing following weight loss. Of recent interest during the COVID 19 pandemic, has been the observation of increasing tendencies towards "emotional eating" as a coping mechanism, which has led to increased weight gain in some populations. The subsequent effect upon comorbidities and systemic inflammation are yet to be explored, but the coexistence of weight gain, psychological stress, and poor diet and lifestyle choices that are more prevalent during the pandemic may have an impact upon the incidence and severity of GORD in vulnerable populations.

4.8 Lifestyle and stress

The role of alcohol and tobacco use upon the severity of reflux is well accepted, patients should be guided to modify these behaviors where appropriate, and there is also evidence to show that poor sleep quality can be relevant in symptom perception.

Psychological factors are well acknowledged in refractory reflux disease, and it is thought that the connection between psychological distress and gastrointestinal disease may be influenced by the stress-induced effect upon mucosal barrier function, which may be mediated by corticotrophin-releasing hormone operating via activation of mucosal mast cells. It is also reported that dysautonomia, downregulation of the parasympathetic nervous system, and vagal nerve dysfunction are relevant factors in reflux disease and obesity. This may support the use of a stress management program as an appropriate adjunct to the management of mucosal-dominant reflux disease which, when controlled, could have the potential to allow greater mucosal healing and reduction of DIS.

5 CONCLUSION

The esophagus is a natural highway for both food and gastric reflux, each of which can be tolerated without adverse effect in the majority of the population. For those who are symptomatic, the disease state of GORD is diagnosed, with gastric acid portrayed as the chief offender. It is proposed, however, that the current model of reflux disease is too simplistic and fails to recognize a wider range of exogenous and
endogenous inflammatory triggers. Although acid suppression can resolve or improve symptoms in a proportion of patients, this may only be achieved when acid erosion is responsible for the failure of the mucosal defense system. In a systemic inflammatory state, it is possible for acid to act as a trigger or mediator of symptoms, but successful resolution of symptoms could depend more upon achieving and maintaining the integrity of mucosal tissue, which may require alternative treatment strategies.

At present, insufficient evidence has been conducted to firmly conclude that food allergies can play a role in the pathogenesis of adult refractory GORD, but there is enough evidence to indicate that further investigations are warranted, particularly in patients who have a history of atopic or allergic disease while failing to meet the histological criteria for EoE. Although SPT/APT and serum IgE testing may be used to guide clinical decision making, in many cases it cannot be used as a definitive measure of clinical allergy or sensitivity. Where increased ACT is shown to be an exacerbating factor, acid suppression should be seen as an adjunct to holistic management of the condition which has the potential to hasten mucosal healing, but for individuals with allergic history, the routine prescription of PPIs as a diagnostic tool should be reconsidered, due to the potential for increased risk of allergic disease in these patients.

Additional research is required to explore the specific mechanisms and drivers of mucosal inflammation, and with further understanding, it is possible that symptoms previously attributed to reflux disease may actually be recognized as symptoms of low-grade inflammatory disease, where acid contact may or may not be influential. For such cases, the resolution of symptoms must depend upon the successful identification and control of relevant triggers for each individual, utilizing skills from the wider multidisciplinary team, including experts in gastroenterology, immunology, nutrition, and lifestyle medicine. The role of diet and lifestyle intervention in GORD requires further exploration but may have the potential to offer a range of effective management strategies for some patients who prefer nonpharmacological therapies. With a greater choice of treatment options available, the potential to offer personalized care plans which include bespoke combinations of pharmacological and lifestyle strategies may offer improved outcomes at reduced cost for those presenting with gastroesophageal reflux disease.

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No conflicts of interest to declare.

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The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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