CLINICAL—ALIMENTARY TRACT

Elimination Diet Effectively Treats Eosinophilic Esophagitis in Adults; Food Reintroduction Identifies Causative Factors

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This article has an accompanying continuing medical education activity on page e14. Learning Objectives: Upon completion of this assessment, successful learners will be able to understand the evidence supporting the use of dietary therapy in adult eosinophilic esophagitis.

See Covering the Cover synopsis on page 1399; see editorial on page 1409.

BACKGROUND & AIMS: Adults with eosinophilic esophagitis (EoE) typically present with dysphagia and food impaction. A 6-food elimination diet (SFED) is effective in children with EoE. We assessed the effects of the SFED followed by food reintroduction on the histologic response, symptoms, and quality of life in adults with EoE. **METHODS:** At the start of the study, 50 adults with EoE underwent esophagogastroduodenoscopies (EGDs), biopsies, and skin-prick tests for food and aeroallergens. After 6 weeks of SFED, patients underwent repeat EGD and biopsies. Histologic responders, defined by ≤5 eosinophils/high-power field (eos/hpf) (n = 32), underwent systematic reintroduction of foods followed by EGD and biopsies (n = 20). Symptom and quality of life scores were determined before and after SFED. **RESULTS:** Common symptoms of EoE included dysphagia (96%), food impaction (74%), and heartburn (94%). The mean peak eosinophil counts in the proximal esophagus were 34 eos/hpf and 8 eos/hpf, before and after the SFED, and 44 eos/hpf and 13 eos/hpf in the distal esophagus, respectively ($P < .0001$). After the SFED, 64% of patients had peak counts ≤5 eos/hpf and 70% had peak counts of ≤10 eos/hpf. Symptom scores decreased in 94% ($P < .0001$). After food reintroduction, esophageal eosinophil counts returned to pretreatment values ($P < .0001$). Based on reintroduction, the foods most frequently associated with EoE were wheat (60% of cases) and milk (50% of cases). Skin-prick testing predicted only 13% of foods associated with EoE. **CONCLUSIONS: An elimination diet significantly improves symptoms and reduces endoscopic and histopathologic features of EoE in adults. Food reintroduction re-initiated features of EoE in patients, indicating a role for food allergens in its pathogenesis. Foods that activated EoE were identified by systematic reintroduction analysis but not by skin-prick tests.**

Keywords: Stricture; Esophagus; Food Allergy; Inflammation.

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Eosinophilic esophagitis (EoE) is one of the most common causes for dysphagia and food impactions in adults.[1–5] Recent consensus guidelines define EoE as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.[3,4] Involvement of allergic mechanisms in the pathogenesis of EoE is supported by studies showing esophageal tissue expression of mediators such as IgE, eotaxin-3, interleukin-13, and interleukin-5, and cell mediators including mast cells, dendritic cells, as well as eosinophils.[6] Furthermore, esophageal eosinophilia is induced in a murine model after allergen exposure.[7] The concept of food allergens as the primary trigger of EoE was introduced by Kelly et al[8] in a pediatric cohort with symptoms of gastroesophageal reflux disease and esophageal eosinophilia unresponsive to acid suppression or fundoplication. Both symptoms and eosinophilia resolved

Abbreviations used in this paper: EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils/high-power field; PPI, proton pump inhibitor; QOL, quality of life; SF-36, Standard Short Form-36; SFED, 6-food elimination diet; SPT, skin prick testing.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2012.03.001

after an elemental formula. This experience has been substantiated in subsequent larger pediatric series.[9,10]

Although elemental diet is effective in children, it can be costly, unpalatable, and necessitate the placement of feeding tubes. A directed elimination diet based on allergy testing showed substantial response rates in pediatric EoE but was ineffective in a small adult series.[11,12] In a retrospective pediatric study, Kagalwalla et al[10,13] reported the effectiveness of an empiric diet, selectively removing the 6 most common food allergens in EoE. In the 6-food elimination diet (SFED), patients avoid ingestion of milk, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish.

There are known phenotypic differences in adult and pediatric EoE patients, which raises the question of whether the disease process is the same in these 2 populations.[14,15] Furthermore, the role of food allergens in EoE and the utility of SFED in the therapy of EoE has not been formally evaluated in adults. The goal of the current study was to prospectively examine the effectiveness of SFED in an adult cohort to better understand the importance of food allergy, thus potentially adding dietary intervention as a novel therapeutic option for adults with EoE.

Materials and Methods

Study Design

This was a prospective clinical trial from 2006 to 2010 performed at a single university medical center. The study was designed to examine the effectiveness of SFED in adults with EoE. All patients underwent an elimination diet for 6 weeks followed by esophagogastroduodenoscopy (EGD) and biopsy. Patients who achieved histologic remission underwent systematic, sequential food reintroduction with follow-up endoscopies and biopsies to identify specific food triggers.

Study End Points

The primary study end point was histologic improvement in esophageal eosinophilia after SFED defined as complete (peak eosinophil count, ≤5 eos/hpf), near complete (≤10 eos/hpf), and partial (>50% reduction of peak eosinophil count). Secondary end points included assessment of symptom response and quality of life (QOL). The study also identified causative agent(s) through the systematic reintroduction of specific foods and examined predictors of response to SFED.

Patient Selection and Eligibility

Adults older than 18 years with a diagnosis of EoE, based on the presence of esophageal symptoms and esophageal biopsy specimens showing 15 or more eosinophils/high-power field (eos/hpf) in the squamous epithelium, were eligible. A baseline endoscopy was performed on all patients with biopsy specimens obtained from the proximal and distal esophagus confirming a diagnosis of EoE (see Endoscopy, Esophageal Biopsy Specimens, and Histologic Analysis section). Before the index endoscopy, patients had completed 8 weeks of twice-daily proton pump inhibitor (PPI) therapy or had a 24-hour pH study showing normal acid exposure. Patients were recruited from an outpatient academic gastroenterology clinic (by N.G. and I.H.) and those who met entry criteria were offered treatment with SFED as an alternative to topical corticosteroids. None of the patients were treated with swallowed or systemic steroids at enrollment or during the study. Patients previously treated with topical corticosteroids had to be off therapy for at least 8 weeks with a repeat endoscopy showing persistent EoE before inclusion in the study. Patients who were on a PPI at the start of the study remained on the medication during the study period. Exclusion criteria included history of Barrett's esophagus, caustic or radiation esophagitis, achalasia or scleroderma, *Helicobacter pylori* infection, inflammatory bowel disease, use of immunosuppressive or immunomodulator therapy (ie, leukotriene inhibitors), food-associated anaphylaxis, or inability to adhere to an elimination diet. Aeroallergens were not treated concomitantly during the study, and no new allergy medication (antihistamines, nasal steroids, and so forth) was instituted.

Allergy Testing

Before the elimination diet, patients underwent skin prick testing (SPT) for food and aeroallergens. Skin testing for aeroallergens included tree, grass, ragweed, mold, house dust mite, cat, dog, and cockroach (ALO; Columbus, OH). Skin testing for food allergens included peanuts, tree nuts, fish, shellfish, egg, wheat, soy, and milk. If patients self-reported additional foods that provoked symptoms, these were tested. Saline and histamine were used as negative and positive controls, respectively. The prick tests were performed using approximately 5000 AU/mL. A positive test was considered a wheal 3 mm greater than the negative control at 20 minutes.

Diet Elimination and Reintroduction

Patients completed 6 weeks of the SFED. If they had additional food allergies based on history or SPT, these foods also were avoided. Before institution of the SFED, patients met with a dietician specifically trained in allergy diet restriction for education and were provided with sample menus and shopping guides. Patients completed a 3-day dietary log within the first 2 weeks of the initiation of the diet, which was reviewed by the dietician to document adherence and possible dietary contamination. If patients self-reported dietary contamination or indiscretion, the SFED period was extended an additional 6 weeks.

After completion of 6 weeks of dietary elimination, an EGD with proximal and distal esophageal biopsy specimens was repeated. Patients achieving the primary end point of histologic improvement underwent systematic food reintroduction to identify potential food triggers. The reintroduction phase consisted of the addition of one food group every 2 weeks. The order of food reintroduction was individualized based on allergy testing or patient preference. An EGD with biopsy specimens was repeated 4 weeks after the reintroduction of 2 food groups. If patients became symptomatic during reintroduction before the 4-week time point, an endoscopy was repeated. Food triggers were implicated if patients had histologic recurrence of EoE. If patients had evidence of recurrence based on the return of esophageal eosinophilia on repeat endoscopy, a 6-week washout period with discontinuation of the implicated food was undertaken. A repeat endoscopy after the washout period was used to confirm resolution of histologic eosinophilia before additional foods were added. This process was continued until all 6 food groups were added back to the diet.

Data Collection

Patients completed a dysphagia symptom score and QOL surveys at the time of enrollment and immediately after completion of the initial 6 weeks of the SFED. The dysphagia symptom score was a nonvalidated instrument used in a previ-