

CLINICAL—ALIMENTARY TRACT

Efficacy of Dietary Interventions for Inducing Histologic Remission in Patients With Eosinophilic Esophagitis: A Systematic Review and Meta-analysis

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this questionnaire, successful learners will be able to distinguish the different dietary therapies used in the treatment of EoE, identify remission rates of each dietary options and recognize some important methodological aspects of systematic reviews and meta-analyses.

BACKGROUND & AIMS: Various dietary interventions have been used to treat patients with eosinophilic esophagitis (EoE), yielding varied results. This systematic review assesses the efficacy of different dietary therapies in inducing disease remission. **METHODS:** We performed a systematic search of the MEDLINE, EMBASE, and SCOPUS databases for studies investigating the efficacy of dietary interventions (reducing infiltration by immune cells <15 eosinophils/high-power field in esophageal biopsies) for pediatric and adult patients with EoE. Summary estimates, including 95% confidence intervals (CI), were calculated for exclusive feeding with amino acid-based elemental formulas, allergy test result-directed food elimination diets, and 6-food elimination diets (SFED). A fixed- or random-effects model was used depending on heterogeneity (I^2); publication bias risks were assessed by means of funnel plot analysis. **RESULTS:** The search yielded 581 references; of these, 33 were included in the quantitative summary. We analyzed data on a total of 1317 patients with EoE (1128 children and 189 adults) who received different dietary treatments. Elemental diets were effective for 90.8% of cases (95% CI, 84.7%–95.5%; $I^2 = 52.3\%$), SFED for 72.1% (95% CI, 65.8%–78.1%; $I^2 = 0$), and allergy test result-directed food elimination for 45.5% of cases (95% CI, 35.4%–55.7%; $I^2 = 75.1\%$). Additional strategies (elimination of cow's milk, gluten-free diets, and 4-food elimination diet) were also evaluated. Adults vs children had no significant differences in remission after dietary interventions (67.2% vs 63.3%). **CONCLUSIONS:** Dietary interventions are effective in producing histologic remission in patients with EoE. Elemental diets and SFEDs were the most effective, achieving <15 eosinophils/high-power field in 90.8% and 72.1% of patients, respectively.

Keywords: Esophagus; Inflammation; Immune Regulation; Therapy.

of other causes of esophageal eosinophilia, especially gastroesophageal reflux disease.¹ First characterized as a distinctive clinicopathologic disorder 20 years ago,² EoE has come to be recognized as the most prevalent cause of chronic esophageal symptoms among children and young adults,^{3,4} with an estimated prevalence of 43–56.7 cases/100,000 inhabitants in both America and Europe, affecting pediatric and adult patients alike.^{5–10} As a consequence, EoE poses a large burden to health care systems, involving multidisciplinary teams that include gastroenterologists, dietitians, and allergists in the management of the disease.

From its earliest descriptions, the origin of EoE has been linked to allergy; indeed, both pediatric and adult patients commonly present concurrent family and/or personal atopic conditions, such as asthma, rhinitis, conjunctivitis, eczema, and IgE-mediated food allergies.^{1,11} Food sensitization identified by positive results in skin prick tests (SPTs) is also commonly described in patients of all ages.^{12–14} The definitive categorization of EoE as a characteristic manifestation of food allergy came when researchers documented disease remission after feeding a series of pediatric patients exclusively with an amino acid-based elemental formula lacking any antigenic capacity, followed by disease recurrence after subjects resumed a normal diet.¹⁵

According to consensus guidelines, the treatment of EoE consists primarily of medical (corticosteroid) or dietary therapy,¹ the latter encompassing several approaches to avoid putative food triggers for EoE. Besides elemental diet, both skin allergy testing-directed food elimination and empirical restriction of the most common food antigens

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder characterized by symptoms of esophageal dysfunction and histologic evidence of eosinophil-predominant inflammation in esophageal mucosal biopsies, which persists after the exclusion

Abbreviations used in this paper: CI, confidence interval; EoE, eosinophilic esophagitis; hpf, high-power field; SFED, 6-food elimination diet; SPT, skin prick test.

from the diet have been used by different researchers with varied results. As a result, a commonly accepted algorithm for treating patients is currently lacking, and a wide variability, in both standard of care of EoE patients and adherence to proposed guidelines, has been documented in clinical practice.^{10,16}

In the short time since EoE was first described, an increasing number of publications have focused on dietary treatment of pediatric and adult EoE patients. Such research has renewed the interest in food restrictions as a drug-free alternative to topical steroids, which still constitute the most widely utilized therapy for EoE in patients of all ages.^{10,16}

However, the efficacy of the various dietary treatment modalities assayed in EoE patients has yet to be systematically analyzed in order to provide clinicians with useful evidence for making decisions concerning the complex management of EoE.

The aim of our study was to conduct a systematic review and meta-analysis on the efficacy and consistency of the available dietary treatment alternatives in inducing histologic remission of EoE in children and adults.

Methods

Selection of Studies

Source studies were identified by systematically searching in 3 major bibliographic databases (PUBMED, EMBASE, and Scopus) for the period up to June 2013. To this end, a pre-determined protocol was used in accordance with the quality of reporting meta-analyses of observational studies in epidemiology.^{17,18}

Comprehensive search criteria were used to identify articles dealing with dietary treatments for EoE. We consulted the thesauri for MEDLINE (MESH) and EMBASE (EMTREE) using the following search strategy: eosinophilic esophagitis AND (diet OR dieta* OR diete*). For the Scopus database, only free text searches with truncations were carried out. The search was not restricted with regard to date or language of publication.

We also examined the reference lists from retrieved articles and abstracts of conference proceedings to identify relevant studies. Abstracts books of the annual Digestive Diseases Week, American College of Gastroenterology Meeting, and the United European Gastroenterology Week for the period 2004 to 2013 were also examined. Three reviewers (AA, JG-C, and AJL) independently screened the database search for titles and abstracts. If any of the reviewers believed that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

Inclusion Criteria

Randomized controlled trials, observational prospective and retrospective studies, and case series reports were included if data on histologic efficacy or effectiveness after dietary treatment were provided. Studies evaluating any kind of dietary intervention were included, including elemental diets, allergy testing-directed elimination diets, empirical 6-food elimination diets (SFEDs), and modified empirical SFEDs, as well as any kind of food exclusion, after which a histologic evaluation was undertaken. Studies providing objective

quantitative data on diet efficacy in terms of histologic response were included (EoE remission was considered to be a peak eosinophil count <15 eosinophils/high-power field [hpf] in esophageal biopsies)^{1,19} after dietary treatment.

Exclusion Criteria

Studies using dietary intervention simultaneously with another therapeutic alternative capable of reducing esophageal inflammation (topical and systemic steroids and/or immunomodulatory drugs) were excluded. Review articles on the treatment of EoE that did not provide original data on dietary therapy, clinical guidelines, and consensus documents were excluded. Studies not carried out on humans were excluded. Studies providing duplicated information were excluded (ie, repeated abstracts presented at different congresses or abstracts published later as a full paper). Subsets of cases or controls from a previously published article by the same authors were excluded.

Quality Assessment

Cohort studies, case series, and case reports were evaluated for quality only if the article described all patients, the type of dietary strategy assessed, and any additional therapeutic interventions. Likewise, peak eosinophil counts had to be specifically stated in the text as well as the time frames and the clinic or clinics in which the study was carried out. Quality assessment was checked with a specific evaluation form for observational studies developed by our group and based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.²⁰

The study was considered to be at low risk for bias if each of the bias items could be categorized as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Two investigators (AA and AJL) independently gave each eligible study an overall rating of high, low, or unclear risk of bias, and if disagreements emerged, a third reviewer (JG-C) was consulted.

Data Extraction

Three reviewers (AA, AJL, and JG-C) independently extracted relevant information from each eligible study using a standardized data extraction sheet and then proceeded to cross check the results. The data extracted included the trial study areas, the last name of the first author, publication year, type of dietary intervention assessed, age and sex of study participants, sample size, methodological design, and study period, whenever possible. At the same time, data on the key outcomes, including eosinophil count reduction to <15 eosinophils/hpf, were extracted from all included studies. Disagreements between reviewers about data extraction were resolved through discussion. The authors of the various studies were contacted by e-mail for additional information if necessary.

Statistical Analysis

Response percentages for dietary intervention were summarized with the aid of a fixed- or random-effects meta-analysis weighted for the inverse variance following DerSimonian and Laird's method. Summary estimates, including 95% confidence

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