

Efficacy of Dietary Treatment for Inducing Disease Remission in Eosinophilic Gastroenteritis

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ABSTRACT

Objectives: Various dietary interventions have been used to treat patients with eosinophilic gastroenteritis (EGE). Concrete evidence as to the effectiveness of such treatments in inducing disease remission is, however, lacking. The aim of the study was to systematically review the efficacy of dietary therapies in inducing EGE remission.

Methods: We performed a systematic search for the MEDLINE, EMBASE, and SCOPUS libraries for studies investigating the efficacy of dietary interventions (in both histological and symptomatic remission) for children and adults with EGE and colitis.

Results: The search yielded 490 references; 30 were included in the review, with most of these references being “low-quality” individual cases or short case series. No significant publication bias was found. Elemental diets in children were linked to 75.8% of clinical improvement, but few of these patients underwent a histological evaluation. Allergy-testing results have been used scarcely in EGE. Empiric elimination of allergy-associated foods was the most commonly used option. The variable results in terms of symptom relief, however, were scarcely accompanied by histological confirmation. Clinical and methodological heterogeneity hindered the performance of quantitative summaries for the efficacy of dietary therapies in inducing disease remission.

Conclusions: Symptomatic improvements reported for dietary treatment in EGE by most of the available literature are questionable because of the lack of objective evaluation of clinical changes and the very limited assessment of histological remission. Because of the relative lack of well-designed, high-quality studies, the unequivocal use of dietary treatment for patients with EGE and colitis cannot be supported. Further research should be undertaken.

Key Words: dietary treatment, eosinophilic colitis, eosinophilic enteritis, eosinophilic gastroenteritis, eosinophilic gastrointestinal disorders, metaanalysis, systematic review

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What Is Known

- Food allergy has been involved in the origin of EGE. Therefore, avoiding the exposure to putative food triggers by dietary therapies has been repeatedly used.
- Its efficacy has not been, however, systematically analyzed yet.

What Is New

- Most of the available information comes from “low-quality” individual case reports and short case series.
- Most of dietary treatments in EGE reported symptomatic improvements, with very limited evaluation of clinical and histological remission.
- Dietary treatment for patients with EGE cannot be unequivocally supported owing to the lack of high-quality studies.

Eosinophilic gastrointestinal disorders (EGIDs) constitute a diverse group of disorders with increased eosinophil counts in 1 or more parts of the gastrointestinal tract in the absence of known causes of eosinophilia (eg, secondary infection) or an underlying systemic inflammatory disease (eg, inflammatory bowel disease) (1–5). The symptoms of EGID vary depending on the affected digestive segments and the involvement of the different layers of the digestive wall (1,5). EGID comprises eosinophilic oesophagitis (EoE)—in which the eosinophilic infiltration exclusively affects the oesophagus; eosinophilic gastroenteritis (EGE)—the affected sites typically being the stomach and small bowel, although any area of the gastrointestinal tract may virtually be involved (from the oesophagus to the rectum), occasionally manifested as eosinophilic colitis (7). A differentiation should be made between two paediatric diseases triggered by food allergen exposure and eosinophilic infiltration of the colonic mucosa—known as allergic eosinophilic proctocolitis, and food–protein-induced enterocolitis.

Since Kaijser (7) first described it in 1937, the interest in EGE has grown in recent years in line with an increasing number of case reports and case series globally (8). The currently accepted diagnostic criteria for EGE were proposed by Klein et al (8) in 1970 and updated by Talley et al (9) in 1990 and include the presence of generally recurrent gastrointestinal symptoms; demonstration of a dense eosinophilic infiltrate in biopsies performed from the gastrointestinal (GI) tract or high eosinophil content in peritoneal fluid and the absence of parasitic or extraintestinal diseases that could

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cause eosinophilia (10) such as vasculitis, drug reactions, or neoplasms. Peripheral eosinophilia is currently not required for a positive diagnosis because it is not a universal finding. There are still many aspects of the disease that remain unknown however—no definitive epidemiological figures have been established, pathophysiological data are extremely limited, there is no established natural history for EGE, and therapeutic options are mostly based on empirical experience.

A strong family or personal history of allergy, the frequent blood eosinophilia, the infiltration of the gut with eosinophilic leukocytes, and the relation of symptoms to specific foods have been cited as evidence that EGE may be an allergic reaction perhaps to food. This concept is also supported by the predominantly proximal GI location of the eosinophilic infiltration in a significant number of patients. As such, dietary therapy aimed at trying to avoid exposure to putative food triggers has been repeatedly used in patients with EGE.

Encompassing several approaches, including elemental diet, skin allergy testing–directed food elimination, and empirical restriction of the most common food antigens, the efficacy of dietary therapy in inducing clinical and histopathological remissions on EGE has not been systematically assessed. In the main this is because of the relative shortage of large case series and the lack of a commonly accepted algorithm for treating patients with EGE, which has resulted in widely different clinical management (11), and the fact that treatments administered are largely based in the medical specialty area in which each patient attends (6).

Thus, the efficacy of the various dietary treatment modals assayed in patients with EGE has yet to be systematically analyzed to provide clinicians with useful evidence for decision making with regard to the complex management of this disorder.

The aim of our study was to conduct a systematic review on the efficacy and consistency of the available dietary treatment alternatives in inducing clinical and histological remission of EGE in children and adults.

METHODS

This systematic review has been registered in the PROSPERO International prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD 42014010601) and was reported in accordance with the PRISMA statements (12).

Selection of Studies

A systematic literature search was performed independently by 2 researchers (A.A. and J.M.T.) in 3 major bibliographic databases (PUBMED, EMBASE, and Scopus) for the period up to June 2014. The search was not restricted with regard to date or language of publication. To this end, a predetermined protocol was used in accordance with the quality of reporting metaanalyses of observational studies in epidemiology (13).

Comprehensive search criteria were used to identify articles dealing with dietary treatments for EGE. We consulted the thesauri for MEDLINE (MESH) and EMBASE (EMTREE) using the following search strategy: (eosinophilic gast* OR eosinophilic ent* OR eosinophilic col*) 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 (abstract books of the annual Digestive Diseases Week, American College of Gastroenterology Meeting, the United European Gastroenterology Week, the

American Academy for Allergy, Asthma and Immunology Meeting for the period between 2004 and 2013) to identify additional relevant studies. Three reviewers (A.J.L., B.S.-M., and A.A.) independently screened the database search for titles and abstracts. If any of the reviewers felt that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

Inclusion Criteria

1. Studies were included in the systematic review if they provided original data on clinical and/or histological efficacy or effectiveness after dietary treatment.
2. Studies evaluating any kind of dietary intervention were included, such as elemental diets, hydrolyzed formulas, allergy testing–directed elimination diets, empirical elimination diets, and any kind of food exclusion, after which a clinical and/or histological evaluation was undertaken.
3. Studies providing objective quantitative data on diet efficacy in terms of clinical and/or histological response were included (EGE remission was considered to be a peak eosinophil count <20 eosinophils/high-power field [hpf] in gastric (14–17), small bowel (14,18–20), or colonic biopsies (15,21–23)) after dietary treatment.

Exclusion Criteria

1. Reviews on the treatment of EGE or eosinophilic colitis that did not provide original data on dietary therapy, along with clinical guidelines and consensus documents.
2. Studies dealing exclusively with EoE.
3. Studies not carried out on humans.
4. Studies using dietary intervention simultaneously with another therapeutic alternative capable of reducing esophageal inflammation (antiallergic drugs, topical and systemic steroids, and/or immunomodulatory drugs) were excluded.
5. Studies providing duplicated information (ie, repeated abstracts presented at different congresses or abstracts published later as a full paper).
6. Subsets of cases or controls from a previously published article by the same authors.
7. Studies reporting on allergic eosinophilic proctocolitis in infants.
8. Studies reporting nonprimary EGID, including EGE or colitis developed after transplant and immunosuppressant therapy.

Quality Assessment

Cohort studies, case series, and case reports were evaluated for quality and only included if the article described the following: the patients' demographic data, diagnostic criteria for EGE, the organ involved and type of disease, and study design.

Quality assessment was checked with a specific evaluation form for observational studies developed by the review group and based on the Strengthening the Reporting of Observational Studies in Epidemiology statements (24).

A 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. Four investigators (A.J.L., B.S.-M., A.A., and O.R.-G.) independently provided each eligible study an overall rating of high, low, or unclear risk of bias, and if disagreements emerged, a fifth reviewer (J.M.T.) was consulted.

Data Extraction

Four reviewers (A.J.L., B.S.-M., A.A., and O.R.-G.) 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 last name of the first author, year of publication, age and sex of study participants, sample size, type of dietary intervention assessed, GI organs involved by eosinophilic infiltration, type of EGE according to Klein classification (8), methodological design, study period, and, whenever possible, the clinical and/or pathologic outcome after dietary intervention. Disagreements between reviewers regarding data extraction were resolved through discussion.

Statistical Analysis

Heterogeneity between studies was assessed by means of the χ^2 test (Cochran Q statistic) and quantified with the I^2 statistic. Generally, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively (25). Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed with Begg-Mazumdar rank test (26) along with the Egger (27) and Harbord tests (28).

For the primary outcomes, planned subgroup analyses were performed on the basis of the type of dietary intervention, disease type and location, and the age of the primary population studied (adults vs children).

A sensitivity analysis was performed with regard to quality (risk of bias) and type of document (full-length article vs abstract presented at conference proceedings). All calculations were made with StatsDirect statistical software version 2.7.9 (StatsDirect Ltd, Cheshire, UK).

RESULTS

The search strategy yielded 490 references; 432 documents were excluded after examining the title and abstract because they did not fulfill the inclusion criteria. Of the remaining 58 references, 31 documents were further excluded after reading the full text because of several reasons, and 5 new documents were incorporated from tracking papers' reference lists. In the end, 30 studies were included in the systematic review (Fig. 1).

The main characteristics of each study are summarized in Table 1 (29–57). Of the 30 documents analyzed, 25 were full text articles and 5 were abstracts. Overall, data from 86 individual patients (79 children, 7 adults; of which 41 were females and 45 males) receiving 89 dietary interventions were retrieved. The size of the various study populations ranged from 1 to 12 cases. Most of the documents were judged as having low methodological quality.

Clinical and Histological Response

Overall effectiveness in inducing clinical remission/clinical improvement was reported for 68 patients (87.2% of children and 88% of adults); however, no study objectively assessed changes in clinical complaints by means of validated or nonvalidated instruments.

Histological assessments after dietary treatment were made in 20 individual cases (22.5%), all of them being children. Resolution or decrease in eosinophilic infiltration was documented in 16 cases (80%), and changes were not noted in the 4 remaining patients.

Differential Analysis of Efficacy by Dietary Treatment Option

Exclusive feeding with an amino acid–based elemental formula lacking in any antigenic capacity was used in 29 patients, all of them being children (16,40,42,45,46,49–51,53,54); clinical remission was reported in 75.8% (22 patients); histological remission was only assessed for only 1 patient with small bowel involvement (53) and in a further 5 patients with eosinophilic gastritis in a single research (51), 5 of these 6 (83%) had normalized mucosal biopsies.

Semielemental diets (ie, extensively hydrolyzed formulas with reduced antigenic capacities) as the exclusive nutritional source were used in only 2 patients (34,43): clinical and histological remission was documented in only 1 patient.

Allergy test–directed food exclusion has rarely been documented in the literature because only 3 paediatric patients and 1 adult underwent this treatment option (29,39,47,56): clinical remission was described in every patient; biopsy samples after treatment were only available for 1 single child, who showed histological improvement (47).

Most of the patients in the literature had been treated using different empiric approaches, which consisted of elimination of single foods (milk and wheat were the most common foods excluded) or combinations of foods considered to be of high risk of triggering an allergic response. A milk elimination diet, a treatment strategy used by 4 authors (31,32,44,57) on 16 individual paediatric patients, resulted in a symptomatic improvement rate of 62.5%, with no histological assessment available. A gluten-free diet was used in 2 EGE patients with no clinical or histological benefits (30,37).

Several empiric elimination diets, which included empiric restriction of multiple foods, such as milk, cereals, egg, soy, seafood, and/or fruits, have been repeatedly used in the literature to treat EGE. The empirical elimination of the 6 most common food antigens from the diet (also called 6-food elimination diet) and 7-food elimination diet (excluding red meats also) has been assessed in recent years. Overall, 34 patients with EGE or colitis have been given this dietary treatment, and a symptomatic improvement has been reported in 29 (85.3%) of these patients. Histological assessments, however, have rarely been reported (35). A recent article, judged as of medium/high quality, reported histological remission of the disease after an empirical 7-food elimination diet in 5 of 6 children with eosinophilic gastritis (83.3%), and in 2 of 3 patients after diet without 1–3 foods (51).

Response According to Disease Type and Extension

Most of the reported cases (42 patients with EGE) presented a mucosal type of EGE according to Klein classification (9); muscular type was only described for 1 patient, serosal/transmural type was reported in a single case; in 9 cases the type of EGE was not reported. The low proportion of patients with muscular and serosal/transmural-type EGE prevented a comparative analysis.

Regarding GI organ extension, the stomach was the most commonly involved organ (25 patients). Duodenal or more distal small bowel involvement was present in 13 and 7 patients, respectively. Colonic involvement was present in 10 patients. Multiple-organ involvement was present in 18 patients. No differences in clinical or histological remission/improvement were observed with regard to disease location or extension.

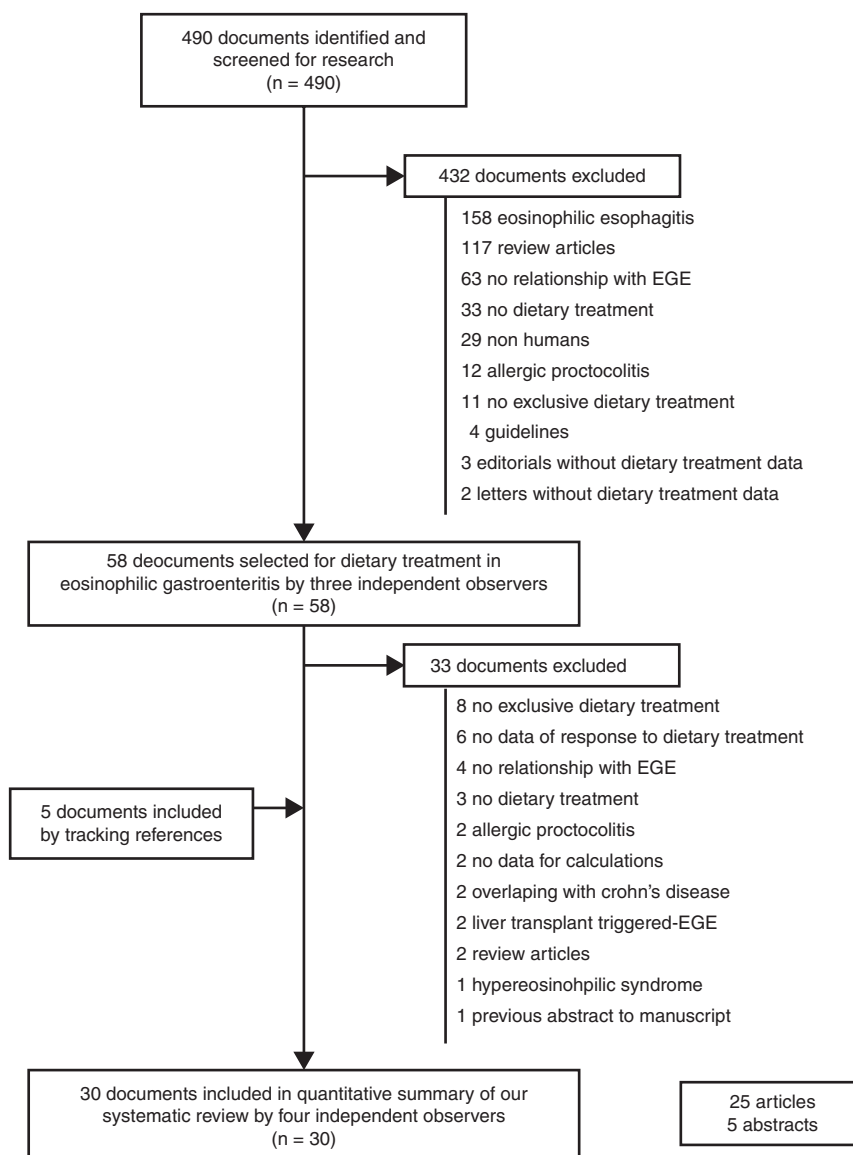


FIGURE 1. Flowchart for the process of identifying studies that were included in and excluded from the systematic review. EGE = eosinophilic gastroenteritis.

Publication Bias

Funnel plot analysis revealed no significant publication bias (P value for the Begg-Mazumdar test = 0.1533; P value for the Egger test = 0.237; P value for the Harbord test = 0.266) (Fig. 2).

DISCUSSION

This systematic review of 30 published documents, including 89 dietary interventions in 86 patients with EGE and/or eosinophilic colitis, has revealed the following: a high heterogeneity in the dietary management of patients, and in the outcomes obtained after a dietary treatment approach, as well as concern about the quality of data available. Most of the information available in the literature derives from individual case reports and short series of patients, judged to be of low methodological quality and for whom reported results were mainly restricted to clinical assessment (usually

reported as “symptomatic improvement or resolution”). No validated or nonvalidated tool was used to objectively determine such an improvement however. Histopathological assessment to demonstrate changes in the eosinophilic infiltration after treatment has rarely been used in patients with EGE and colitis, preventing the authors of this review from considering most of the reported results as reliable.

The increasing recognition of EGID, mainly motivated by the rising prevalence of EoE worldwide in recent years, has made it one of the most important areas of growing interest for gastroenterologists and allergists recently. EoE has been characterized as the second cause of chronic esophagitis in industrialized countries after gastroesophageal reflux, and the leading cause of dysphagia among young patients (58); a current prevalence of about 1/2000 cases has been reported for paediatric and adult EoE patients in Europe and the United States (59–62). In contrast, EGE and eosinophilic colitis are significantly less common entities; although

TABLE 1. Demographics and characteristics of studies on efficacy of dietary treatment for eosinophilic gastroenteritis and colitis

	Dietary treatment	Population	Outcome indicator		Design	Period	% Male	Segment	Type
			(histological remission)	(clinical remission/improvement)					
Full text articles									
Leinbach and Rubin (29)	Allergy test-direct elimination diet (egg-free diet)	Adult	NR	Subjective clinical improvement but not biochemical parameters	Case report	NR	100	G and S	M
	Elimination diet (diet with fish, chicken, and vegetables)		NR	Symptoms continued					
Dobbins et al (30)	Gluten-free diet	Adult	NR	No clinical improvement of symptoms	Case report	NR	100	O, G, and S	M
Katz et al (31)	Milk elimination diet	Children	NR	50% (6/12) clinical remission	Retrospective	NR	66.7	G (9) and S	M
Stringel et al (32)	Milk elimination diet	Children	NR	Asymptomatic	Case report	NR	100	Appendix	NR
Guerrero et al (33)	Elimination diet (diet with soy, potato, vegetables, and chicken)	Adult	NR	Asymptomatic	Case report	NR	0	S	M
Vandenplas Y et al (34)	Semi-elemental diet (Alfire + apple puree)	Children	Resolution	Clinical improvement of symptoms	Case report	NR	100	G, D, S and C	M
Agertoft et al (35)	Elimination diet (diet without milk, fish, egg, rye, and wheat)	Children	Eosinophil count fell	Clinical improvement of symptoms	Case report	NR	100	D	S
Pfaffenbanch et al (36)	Elimination diet	Adult	NR	Asymptomatic without ascites	Case report	NR	0	S	S
Justinich et al (37)	Gluten-free diet	Children	No response	No clinical improvement of symptoms	Case report	NR	100	G and S	M
	Elimination diet	Children	NR	Asymptomatic	Case report	NR	100		M
Deslandes et al (38)	Elimination diet (diet without gluten, bovine products, soy, and eggs)	Children	NR	No clinical or biochemical improvement	Case report	NR	100	G and S	M
Esteve et al (39)	Allergy test-direct elimination diet (diet without seafood) por Anisakis positivo	Children	NR	Asymptomatic	Case report	NR	100	G	M
Khan and Orenste (40)	Elemental diet (nutramigen, protein hydrolysate formula)	Children	NR	Marked clinical improvement in a few days	Case report	NR	0	G and D	Mus
Chen et al (41)	Elimination diet (diet without selffish)	Adult	NR	Symptoms resolved	Retrospective	1984–2002	0	NR	M
Ko et al (42)	Elimination diet (diet without milk, soy, eggs, and rice)	Children	NR	Clinical improvement	Case report	NR	100	G	M
Rosas Vargas et al (43)	Elemental diet (Neocate)	Children	NR	Clinical resolution					
	Semi-elemental diet (aceite de soja, aa, disacáridos)	Children	NR	No clinical improvement	Case report	NR	0	G	M
	Elimination diet (diet without carrot, apple, rice, peas, squash, and semielemental formula)		NR	Asymptomatic					

Tokodi et al (44)	Milk elimination diet	Adult	NR	Asymptomatic	1	Case report	NR	100	G	M
Chehade et al (45)	Food restriction	Children	NR	Rapid resolution of clinical symptoms	1	Retrospective	1997–2005	0	D	M
	Elemental diet	Children	NR	Rapid resolution of clinical symptoms	5	Retrospective	1997–2005	60	G and D	M
Chehade et al (46)	Elemental diet (Neocate + cooked apple)	Children	Resolution	Clinical improvement	1	Case report	NR	0	O, G and D	M
Basilious and Liem (47)	Allergy test–direct elimination diet	Children	Resolution	Asymptomatic	1	Case report	NR	100	C	NR
Busoni et al (16)	Elemental diet (elemental or hypoallergenic formula)	Children	NR	4/10 (40%) clinical improvement of symptoms	10	Retrospective	2000–2010	90	O, G, D and C	NR
Gaertner et al (48)	Dietary modifications	Children	NR	Symptoms resolved	3	Retrospective	2003–2010	100	C	M
Turner et al (49)	Elemental diet	Children	NR	Transient partial clinical improvement	1	Case series	NR	100	D and C	M
Watanabe et al (50)	Elemental diet	Children	NR	Symptoms resolved	1	Case report	NR	0	C	M
Ko et al (51)	Elemental diet	Children	4/5 (80%) response	6/6 = 100% response	6	Retrospective	2005–2011	NR	O, G and D	NR
	7-FED	Children	5/6 (83.3%) response	5/6 = 83.3% response	6	Retrospective	2005–2011	NR	O, G and D	NR
	Elimination empiric diet (diet without 1–3 foods)	Children	2/3 (66.7%) response	3/5 = 60% response	5	Retrospective	2005–2011	NR	O, G and D	NR
Yamada et al (52)	Multiple-FED	Children	NR	Clinical improvement	1	Case report	NR	100	D and C	NR
Abstracts										
Nelson et al (53)	Elemental diet	Children	Resolution	Clinical improvement	1	Case Report	NR	0	Y and D	M
Sabban et al (54)	Elemental diet	Children	NR	Clinical improvement	2	Retrospective	NR	NR	NR	NR
Ortolani et al (55)	6-FED	Children	NR	Clinical remission	11	Retrospective	2006–2011	72.7	O, G and D	M
Lamendola et al (56)	Allergy test–direct elimination diet	Adult	NR	Clinical improvement of symptoms	1	Case report	NR	0	D	NR
Passoforte et al (57)	Milk elimination diet	Children	NR	Clinical improvement of symptoms	2	Case report	NR	0	S and C	M

Disease location: C = colonic involvement; D = duodenal; G = gastric; O = oesophageal; S = small bowel distal to duodenum. Disease type, according to Klein classification: FED = food elimination diet; M = mucosal; Mus = muscular; NR = nonreported; S = serosal.



FIGURE 2. Begg funnel plot of studies evaluating publication bias of articles on the efficacy of dietary interventions in inducing remission of EGE and eosinophilic colitis. Statistically significant publication bias was not demonstrated by Begg-Mazumdar, Egger, and Harbord tests. EGE = eosinophilic gastroenteritis.

no accurate epidemiological estimations for EGE exist to date, an incidence of approximately 1 case per 100,000 inhabitants has been traditionally suggested (9). These figures have been recently updated after an American electronic survey that estimated an overall prevalence of 28 per 100,000 EGE or colitis cases (11). This makes undertaking research on large series of patients with EGE much more difficult and is the reason for the limited knowledge available on these diseases despite them first being described 80 years ago. Therefore, most of the original information available in the literature consists of individual patients and small case series. Furthermore, the EGE appears as very heterogeneous disorder in terms of disease location, deep of affection within the GI wall, and derived symptoms; a range of responses to the therapeutic options should be considered therefore.

Despite this, it was found that dietary treatment has been repeatedly used for EGE to constitute a common option for many patients with EGE, alongside EoE in which it represents one of the cornerstones for managing patients (63). Much of the cumulated information on dietary treatment of EGE is in relation to amino acid-based elemental diet, consisting exclusively of feeding patients with an artificial formula lacking any antigenic capacity. Our results show a high rate of clinical improvement reported for elemental diets—over 75%. However, histological remission, which constitutes an objective and reproducible therapeutic endpoint, has been evaluated only for a minority of patients, because less of a quarter of patients fed with the elemental formulas underwent repeated biopsies to assess their effectiveness: histological remission was reported in 83% of these patients. Despite its putative remarkable success, elemental diets have multiple drawbacks, including the need to avoid all table food, its unpleasant taste, high cost, and the psychological effects produced by the social limitations that this diet entails. These have probably contributed to the fact that this dietary intervention has been restricted exclusively to paediatric patients.

Allergy testing represents an attempt to overcome the drawbacks of elemental diets for long-term use, and to improve the feasibility of dietary treatment for a greater number of patients. This fact is not reflected in the literature in which there is an extremely low use of this option. Because only 4 patients underwent allergy test—directed food restriction, its use in managing EGE cannot be recommended as reliable at this point in time.

The most extensively assessed dietary treatment option for EGE has been the empirical restriction of the most common foods associated with food allergy. Several authors have tried to manage EGE by restricting milk, wheat or both. Even when some clinical benefit has been reported, histopathological assessment has not been provided. More recently, the empirical exclusion of the 6 or 7 most common food allergens has been used in EGE, after demonstrating consistent efficacy in inducing remission in patients with EoE (63). Although symptomatic improvement was demonstrated for most of the 34 patients reported who underwent multiple food restriction, data on histological remission are extremely scarce and restricted to a single research.

The strength of our research lies in the fact that it compiles the results of an exhaustive literature search in 3 major databases and in abstracts/books of the 3 major Gastroenterology and Allergy Congresses; recovered studies were critically appraised according to their methodological aspects; and different investigators independently extracted the data from the studies included.

Unfortunately, we could not assess clinical efficacy of dietary treatment because no randomized controlled trials on dietary interventions for EGE are available. Most of the data came from observational studies involving a small number of patients who underwent variable dietary approaches. Instead, the available data only allowed us to evaluate the global effectiveness of therapeutic interventions in the management of these patients from a clinical, but not a histological point of view, as would have been wished. Dietary treatment-induced histological improvement was only reported for a minority of patients with EGE (22.5%), all of whom were children. Even the effectiveness of dietary intervention on symptomatic improvement was not objectively or structurally assessed in any of the studies included in our research. Furthermore, diagnostic criteria for EGE in terms of eosinophil density or additional histopathological features have not been universally established, so the most conservative criteria of accepting the diagnosis given by original authors in every recovered document were used, and histological disease remission was consistently considered to be decreasing eosinophils density in mucosal GI biopsies to <30 cells/hpf. Finally, the different dietary treatment strategies have been evaluated mainly in paediatric patients, so some caution should be taken when interpreting results related to the adult population with EGE.

Because of the very limited quality of reported clinical data, our research was not capable of demonstrating a difference in effectiveness or efficacy of dietary treatment according to disease location, extension, or type of EGE. Information on the long-term effectiveness or efficacy of dietary treatment in EGE is not available in the published literature recovered by our systematic search.

Because it is not possible to ascertain whether all the relevant information published on dietary treatment for patients with EGE has been recovered, this could be considered a limitation of the review. Furthermore, despite having excluded publication bias, some elements of risk bias may still remain.

In conclusion, the clinical benefit of dietary treatment in EGE reported in most of the available medical literature contrasts with the lack of an objective measure to evaluate changes in symptoms and the very limited assessment of histological remission after dietary treatment undertaken. Because of the relative lack of valid studies with sufficient methodological quality, dietary interventions cannot unequivocally be recommended as treatment for patients with EGE and eosinophilic colitis. Isolated studies with sufficient validity suggest that some options (such as elemental diet feeding or 6/7 food elimination diets) may constitute a drug-free option to achieve disease remission, at least for children and in the short term. Well-designed studies are urgently needed to verify if

dietary treatment should continue to be offered to the increasing number of patients with these conditions.

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