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Perspective

Diets for diagnosis and management of food allergy

The role of the dietitian in eosinophilic esophagitis in adults and children

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Introduction

The National Institute of Allergy and Infectious Diseases (NIAID) defines a food allergy as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”¹ Within this definition, a range of food-related phenomena are captured and further categorized, such as IgE-mediated food allergies, mixed IgE- and non-IgE-mediated food allergies, and non-IgE-mediated food allergies (eg, food protein–induced enterocolitis syndrome [FPIES]). These different types of food allergies are an important consideration in deciding dietary management. The NIAID-sponsored expert panel food allergy guidelines¹ categorize eosinophilic esophagitis (EoE) as a mixed IgE- and non-IgE-mediated food allergic disorder. However, a later review reclassified EoE as a non-IgE-mediated food allergic disorder on the basis of more recent data.

The dietary management of food allergies comprises 3 phases: the elimination phase, during which potential trigger foods are removed; the subsequent food reintroduction or challenge phase; and the management phase, during which definite problematic foods remain out of the diet disease management. This article focuses on the dietary strategies used in diagnosing and managing food allergies, highlighting how EoE differs from other food allergies, and on the role of the dietitian.

Despite an effort to summarize current knowledge and give practical recommendations about the role of diet therapy in the diagnosis and management of food allergies relating to EoE, there are a number of factors that need to be taken into account when reading this review. Current dietary trials in both adults and children lack true randomization and need head to head comparison of different dietary methods and improved power. There is also a need to further investigate the role of allergy tests, such as skin prick

tests and patch tests. Until these studies are conducted, choosing one method of diagnosis or one diet over another is not possible.

Elimination Phase

The aim of diagnostic diets in food allergy is to identify the offending foods.² In terms of IgE-mediated food allergy, in which symptoms usually occur within 2 hours of food consumption, and the more severe types of non-IgE-mediated food allergies (eg, FPIES), in which symptoms occur after 2 to 4 hours, the clinical history plays a crucial role in identifying the possible offending foods. In terms of IgE-mediated food allergy, further testing, such as skin prick and specific IgE testing, can also further inform the initial exclusion diet.

This process is not particularly useful in EoE or in other eosinophilic gastrointestinal disorders (EGIDs), in which symptoms can occur hours to days after food consumption. This is further complicated by the fact that symptoms often do not correlate with clinical-pathologic findings during an endoscopy.³ Therefore, in EoE, 3 different types of diagnostic diets have been previously trialed.

The elemental diet, an amino acid–based formula that is free of allergens, is the most effective dietary therapy for EoE, resolving symptoms within 7 to 10 days, with tissue lesion regression occurring in 4 to 6 weeks.⁴ A meta-analysis by Arias et al⁵ indicated a remission rate of 90.8% in trials using an elemental diet. Efficacy in children was 90%, and the 1 small study performed in adults had a success rate of 94% (see Table 1 for the limitations of each of the dietary approaches).

Another dietary approach is the empiric diet, whereby foods are eliminated without the use of any allergy testing. Empiric diets used in EoE included the 6-food elimination diet, which excludes milk, soy or legumes, eggs, grains, peanuts or tree nuts, and fish or shellfish,⁶ or the 4-food elimination diet, which eliminates milk, egg, grains, and legumes, soy, or nut.⁷ The meta-analysis by Arias et al⁵ found a 72% efficacy of empiric diets overall, with 73% improvement in adults and 73% improvement in children after the 6-food elimination diet. In addition to the 6- and 4-food

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Table 1
Limitations of Current Dietary Approaches in EoE

Diet type	Limitations
Elemental diets	Elemental formulas are costly and may affect a patient's quality of life because of issues with palatability. Although acceptable in infants, children often refuse the formula and often have to rely on gastrostomy feeds. Adherence may also be poor in adults. Dental problems may occur because of reduced saliva production.
Empiric diets	The 6-food or 4-food elimination diet varies among studies, with different grains and legumes or nuts being avoided, making the study outcomes difficult to compare. The remaining foods that the patients are actually eating are not recorded, meaning that additional foods that affect EoE may be avoided but not clinically recognized.
Test-directed elimination diets	Testing for IgE with using specific IgE tests, skin prick tests, or CRD, have produced disappointing results in identifying the foods involved in EoE. However, the methods of studies that use test-directed diets are different, making it difficult to compare.

Abbreviations: CRD, component-resolved diagnostics; EoE, eosinophilic esophagitis.

approaches, Kruszewski et al⁸ recently found that using a 1-food elimination diet, removing cow's milk only, decreased peak esophageal eosinophil counts to below 15 eosinophils per high-power field in 64% of children; in comparison, 80% of patients had disease remission by this same standard when treated with swallowed fluticasone. These results from a 1-food approach are promising; however, these empirical diets are limited by the current lack of understanding about cross-reactions between foods and whether cross-reactions are of relevance at all in non-IgE-mediated diseases.⁹

The third approach is a test-directed or targeted elimination diet, which removes specific foods primarily on the basis of results of allergy skin prick,⁹ specific IgE, and atopy patch testing.¹⁰ The overall success rate of targeted diets in this review¹⁰ is the lowest at 46% efficacy, with the 2 adult studies first published reporting success rates of 27% and 35% in adults. Further studies in adults and children using the test-directed elimination diet have been published using component-resolved diagnostics. Van Rhijn et al¹¹ found that food allergen components measured by the ISAC chip could only identify the culprit food (milk) in 1 of 40 patients; however, this study was complicated by the possible effect of pollen and food cross-sensitization and the relevance (if any) to management of EoE (eg, if a patient was sensitized to apple, they were also advised to avoid pear). However, apple sensitized individuals may be Bet v 1 sensitized, and other Bet v 1 cross-reactive foods (not just pear) might have played a role in triggering EoE-related inflammation as well.

Interestingly, IgG4 is increased in the esophageal tissue of adults with EoE. Although serum levels of IgG4 were only slightly elevated in this study, IgG4 levels to specific foods were increased in those individuals who reacted to the food (wheat, egg, milk, nuts).¹² In addition, the role of IgG4 using component-resolved diagnostic testing in children with EoE is currently being investigated, with children having high levels of serum α -lactalbumin and β -lactoglobulin.¹³ These results may be explained by the recent reclassification of EoE as a non-IgE-mediated food allergy on the basis that (1) test-directed diets have low success rates; (2) omalizumab is not effective in EoE; (3) oral immunotherapy, which is effective in IgE-mediated food allergy, increases the risk of EoE; (4) children who outgrow their EoE-mediated food allergy can redevelop EoE to the

same food later on; and (5) mice devoid of mast cells are still able to develop symptoms similar to EoE.¹⁴

Reintroduction or Challenge Phase

In some cases of IgE-mediated and severe, non-IgE-mediated disease, where the history is unclear or the appropriated testing does not support the history, food reintroduction after symptoms subside is recommended to confirm the diagnosis.¹ Allergens are reintroduced during a food challenge in a hospital setting because of the risk of severe reactions. For EoE, food reintroduction may be done at home to foods avoided for non-IgE-mediated food allergy. Which food(s) are reintroduced is often decided on the basis of clinical expertise and the needs of the individual and their family instead of by testing. There are many clinical questions that dietitians face when reintroducing foods after a period of avoidance^{15,16}:

- How many foods should be reintroduced before the next endoscopy? This question is particularly important after an elemental diet because many foods need to be reintroduced.
- What is the period for reintroducing each food?
- If a patient becomes symptomatic, should food reintroduction be discontinued instead of having the patient undergo subsequent endoscopy, knowing that symptoms and biopsy results poorly correlate?
- Should each food be reintroduced separately or could groups of foods be introduced (eg, shellfish vs mollusks then crustaceans)?
- Which foods should be introduced first, low allergenicity vs high allergenicity, and how should the highly allergenic foods (eg, milk, wheat, egg, and nuts) be ranked?
- Is there a risk of more severe reactions after a period of avoidance.

Management Phase

Any of the foods identified during the food reintroduction phase may be restricted in the long term.¹⁷ There are a number of issues, discussed below, that should be taken into account when advising patients regarding food avoidance.

Level of Avoidance Required

Much progress has been made in recent years on establishing threshold levels for individual allergens in IgE-mediated disease (eg, eliciting doses that should be safe in not triggering an allergic reaction in 90%–95% of the population).¹⁸ In terms of non-IgE-mediated food allergies, such as FPIES, it is generally accepted that trace amounts of foods do not need to be avoided. This is based on estimated tolerance levels from food challenge studies and the fact that patients with FPIES who are breastfed do not usually react to trigger foods consumed by their mothers.¹⁹ In contrast, it is currently unclear whether patients with EoE should be advised against cross-contamination and avoid foods with precautionary advisory labeling statements. There have been reports of patients with EoE tolerating foods that contain baked milk²⁰ but also of patients lacking remission because of exposure to trace amounts of foods.^{15,21} This finding indicates that EoE may have a spectrum of disease or degree of reactivity, just as in IgE-mediated food allergy and FPIES. Measuring this level of tolerance, however, is difficult in EoE because it would involve exposing patients to different levels of an allergen for a specified period and subsequent endoscopy to confirm the presence or absence of inflammation. Current clinical practice varies among centers because some allow patients to consume foods with “may contain” statements and others do not. It may, however, be a good option to avoid foods with a “may contain” statement at least during the diagnostic phase.

Table 2
Major Allergens and Their Nutrients^a

Allergens	Main nutrients
Cow's milk	Protein, fat Calcium , magnesium, phosphorus, iodine Vitamin A, B ₆ , B ₁₂ , and D, riboflavin, pantothenic acid
Wheat	Carbohydrate Magnesium, phosphorus, potassium, zinc Frequently in enriched cereal products: iron , thiamine, niacin, riboflavin, folate
Soy	Protein, fat Calcium, phosphorus, magnesium, iron, zinc Thiamine, riboflavin, vitamin B ₆ , folate
Egg	Protein, fat Iron , selenium, choline Biotin, vitamin B ₁₂ , pantothenic acid, folate, riboflavin
Fish or shellfish	Protein, fat, Ω3 fatty acids Iodine, Choline Vitamins A and vitamin D
Peanut or tree nuts	Protein, fat Vitamin E, niacin, magnesium, chromium

^aThe main nutrients are indicated in bold.

Nutritional Deficiencies

Dietary avoidance, particularly long-term avoidance, can lead to nutritional inadequacies.²² The main allergens and their nutrients are summarized in Table 2. Nutritional deficiencies in food allergic conditions have been well described in IgE-mediated food allergy, indicating deficiencies in calories, protein, fat, vitamins (particularly B vitamins), and minerals (particularly calcium and iron).²³ Meyer et al²⁴ also reported nutritional deficiencies in patients with FPIES, particularly in vitamin D and zinc, despite vitamin and mineral supplementation; in this study, using a hypoallergenic formula significantly improved nutritional intake. In one of the few studies that included adult patients, the authors found that those with a milk allergy consumed lower intakes of calcium, zinc, and vitamin B₂.²²

Growth and Development

Over the years, reports have indicated problems with short height for age and low weight for height but also more recently the problem of high weight for height in children.²⁵ The only article investigating the effect of diet therapy in EoE on nutritional status in children indicated that the median weight for height z score did not significantly change after the dietary intervention; however, the prediet

weight for height score indicated moderate malnutrition in 10% of participants, which is of concern.²⁶ Mukkada et al²⁷ also reported on a group of 200 children with EGIDs; 21% were diagnosed as having failure to thrive or faltering growth, of whom 70% of required feeding therapy. In terms of body mass index in adults, studies indicate some weight loss during intervention trials of approximately 6%, but the baseline body mass index was not specified.^{4,28}

Feeding Skills

Food avoidance during infancy affects food intake and feeding behaviors up to a decade after the food allergy has been outgrown. In addition, children growing up on a cow's milk avoidance diet have a much more restrictive diet and tend to eat the same foods repetitively.^{29,30} Meyer et al³¹ described that a significant number of children on food avoidance diets attributable to gastrointestinal presentations of food allergies had feeding difficulties, particularly relating to symptoms of abdominal distention and bloating, vomiting, weight loss, rectal bleeding, constipation, and the number of foods avoided. In agreement with these findings, children with EoE often have poor feeding skills and maladaptive behavior. Of a group of children with EGIDs in the United States, 17% had significant feeding dysfunction, and 94% had a variety of learned maladaptive feeding behaviors.²⁷ There are no published reports on feeding dysfunction in adults, but swallowing anxiety is a problem often encountered in adults with EoE.³²

Quality of Life

IgE-mediated food allergies are known to affect quality of life due to a number of reasons, including the strain of the constant vigilance required to avoid unintentional ingestion. This is also true for EoE, in which quality-of-life scores are worse among patients with more restricted diets than unrestricted diets.³³ Children on elimination diets may become anxious or depressed, with challenging behaviors often seen in teenagers, leading to parental worries and concerns.³⁴ A recent study among parents of children with a variety of different food allergies highlighted the following as parental needs from a dietetic food allergy consultation:

- Help to protect their child from harm and maintain normality
- Advice to become an expert in looking after their children
- Reassurance about their child's nutritional intake
- Patient advocacy and emotional support

Table 3
Differences Between EoE and Other Dietary Approaches

Dietary phase	EoE	Other food allergies (IgE Mediated or FPIES)
Diagnostic	Clinical history of less relevance Temporal relationship can be days or weeks Dietary avoidance is crucial to make a diagnosis of food allergy	Clinical history very important Temporal relationship: IgE-mediated food allergies: minutes to hours FPIES (acute): 2–4 hours FPIES (chronic): hours to days In many cases, a diagnosis of food allergy can be made on the basis of: IgE-mediated food allergies: a good clinical history and supporting tests FPIES: a good clinical history
Reintroduction	Food reintroduction needs to be conducted for a specified period (days, weeks, or months) and occurs outside the clinical setting Little or no concern of severe IgE-mediated reactions after a period of avoidance	Food reintroduction needs to be performed in a period of hours and conducted in the clinical setting Some concern of severe IgE-mediated reactions after a period of avoidance
Management	Little or no evidence about threshold levels No good quality data on nutritional intake Unintentional exposure does not lead to life-threatening reactions, but it may lead to esophageal inflammation Very high prevalence of feeding dysfunction and maladaptive behavior Patients likely to avoid a number of foods Feeding gastrostomies often required	Some evidence about threshold levels A number of reports on nutritional intake in children, a few in adults Unintentional exposure can lead to life-threatening reactions, but these reactions resolve once the allergen is removed and treatment is given Moderate to high prevalence of feeding dysfunction and maladaptive feeding behavior Patients unlikely to avoid a large number of foods in the long term Feeding gastrostomies almost never required

Abbreviations: EoE, eosinophilic esophagitis; FPIES, food protein–induced enterocolitis syndrome.

In addition, a recent study by Safroneeva et al.³² indicated that EoE affects quality of life on social and emotional aspects in adults with EoE. Dietitians are particularly well suited to provide a comprehensive, individualized treatment plan, taking into account the medical condition, food avoidance strategies, nutritional requirements (which may include nutritional supplements), and family life.³⁵ Evidence also suggests that a dietetic consultation improves patient outcomes in terms of nutritional intake and nutritional status.³⁶ A summary of the differences between EoE and other presentations of food allergy is provided in Table 3.

Future Considerations

There are several considerations and needs for the future use of dietary therapy in the diagnosis and management of food allergic diseases, including the following:

- We need to find biomarkers that could be used to diagnose and monitor EoE.
- We need to learn more about an optimal elimination (eg, which foods and duration) and reintroduction process (eg, order of foods reintroduced, period of reintroduction required, and number of endoscopies).
- Threshold levels for food allergens need to be set.
- We need improved physician awareness about the important role of nutrition and the role of the dietitian in the diagnosis and management of food allergies related to EoE.
- We need to train more dietitians to be able to understand the complexities, differences, and uncertainties in food allergic conditions and how they affect the individualized dietary advice given.
- We need to gain information about long-term outcomes and tolerance of using novel or alternative proteins (eg, quinoa and hemp).
- We need to expand the range of elemental drinks to include some foods with textures and some suitable for adults.
- We need to improve methods of measuring patient adherence.
- We need to use the field of electronic diaries and software applications to improve patient food intake.
- We need to learn more about the quality of life of patients with food allergies.

There are countless remaining questions, and as we venture into the electronic realm, we need to learn how these technologies truly benefit our patients.

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