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Article

Food Allergen Component Sensitization Patterns in Eosinophilic Esophagitis: Insights from a Retrospective Comparative Study

Adam Wawrzeńczyk [1,*], Katarzyna Napiórkowska-Baran [1], Kinga Lis [1], Marta Tykwińska [1], Maciej Szota [1], Paweł Treichel [2], Justyna Durślewicz [3,4] and Zbigniew Bartuzi [1]

[1] Department of Allergology, Clinical Immunology and Internal Diseases, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland

[2] Student Research Club of Clinical Immunology, Department of Allergology, Clinical Immunology and Internal Diseases, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-067 Bydgoszcz, Poland

[3] Faculty of Medicine, Bydgoszcz University of Science and Technology, Aleje Prof. S. Kaliskiego 7, 85-796 Bydgoszcz, Poland

[4] Department of Tumor Pathology and Pathomorphology, Oncology Centre – Prof. Franciszek Łukaszczyk Memorial Hospital, 85-796 Bydgoszcz, Poland

* Correspondence: adam.wawrzenczyk@cm.umk.pl

Abstract

Eosinophilic esophagitis (EoE) is a chronic, food-driven inflammatory disorder of the esophagus in which repeated exposure to dietary antigens plays a central role, yet identification of relevant food triggers remains largely empirical. In this retrospective single-center study, molecular IgE sensitization profiles were evaluated in adult patients with EoE and compared with an allergic control group with chronic urticaria using component-resolved diagnostics. IgE sensitization was common in both cohorts and predominantly reflected inhalant-related, cross-reactive components, particularly PR-10 proteins, indicating a shared sensitization background. In contrast, sensitization to structurally stable food allergen components, including lipid transfer proteins and plant storage proteins, was observed exclusively in patients with EoE. These food-derived components are characterized by resistance to thermal processing and gastrointestinal digestion, supporting their potential relevance as markers of sustained mucosal exposure rather than acute IgE-mediated reactions. Although component-resolved diagnostics showed limited utility for direct identification of trigger foods, the selective presence of stable food ingredient sensitization may help define a distinct food-driven EoE phenotype. These findings emphasize the importance of considering molecular properties of food ingredients when interpreting sensitization patterns in chronic, diet-related inflammatory diseases. Using component-resolved diagnostics (CRD) as an immunological tool for food allergen component characterization, we highlight an emerging EoE-associated sensitization signature enriched for structurally stable, digestion-resistant allergen families. If validated prospectively, this marker pattern may support immunophenotyping and stratification of EoE patients for targeted dietary evaluation rather than stand-alone trigger identification.

Keywords: eosinophilic esophagitis; food allergy; food allergen components; component-resolved diagnostics; lipid transfer proteins; food allergen stability; elimination diet

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1. Introduction

1.1. Eosinophilic Esophagitis as a Food-Driven Allergic Disease

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disorder of the esophagus characterized by eosinophil-predominant infiltration and a strong association with atopic disease. Although EoE frequently coexists with IgE-mediated food allergy, accumulating clinical evidence indicates that it represents a distinct, food-driven condition in which dietary antigens play a central role in disease initiation and persistence [1].

The strongest evidence supporting a causal role of food exposure in EoE derives from interventional dietary studies. Empiric elimination diets targeting common food triggers induce histologic remission in approximately 50–75% of adult patients, while elemental amino acid–based diets achieve even higher response rates [2]. Systematic food reintroduction consistently results in recurrence of esophageal eosinophilia and clinical symptoms, demonstrating that specific dietary components actively drive disease activity rather than representing epiphenomena of inflammation [2–3]. Long-term follow-up studies further show that sustained avoidance of identified trigger foods can maintain histologic and clinical remission for years, underscoring the importance of continuous antigen exposure in disease maintenance [3].

Despite this clear food dependence, conventional allergy diagnostics have limited utility in identifying causative foods in EoE. Skin prick testing and serum food-specific IgE measurements show poor concordance with elimination–reintroduction outcomes, predicting only a minority of clinically relevant triggers [2]. These observations indicate that classical IgE-mediated mechanisms are not the primary drivers of esophageal inflammation in most patients with EoE.

Mechanistic studies support this distinction by demonstrating that EoE is predominantly mediated by non-IgE pathways. Interventional trials targeting IgE have failed to improve histologic or clinical outcomes, while tissue-based analyses reveal enrichment of IgG4-positive plasma cells and evidence of antigen-specific T-cell activation within the esophageal mucosa [4–5]. Collectively, these data establish EoE as a food-driven allergic disease with immunopathologic features distinct from immediate-type food allergy. Although IgE is not considered the principal effector mechanism in EoE, component-resolved IgE profiles may still capture immunological imprinting and exposure-related sensitization phenotypes that extend beyond conventional extract-based testing.

1.2. Molecular Properties of Food Allergens as Food Ingredients: Stability, Structure, and Clinical Relevance

In food allergy, the clinically relevant unit is rarely the "food" itself but rather specific proteins—food ingredients—whose molecular properties determine stability during processing and digestion, epitope presentation, and immune recognition. This distinction is directly relevant to molecular sensitization profiling, where the distribution of allergen families may provide biologically meaningful patterns. Across major allergen families, resistance to thermal denaturation and gastrointestinal proteolysis is a recurring feature of class I food allergens, which can sensitize via the gastrointestinal tract and are more often associated with systemic reactions [6–7]. In contrast, class II pollen-related food allergens—most notably PR-10 proteins and profilins—are typically heat-labile and digestion-sensitive, yet remain clinically relevant through primary inhalant sensitization and subsequent cross-reactivity with homologous food proteins [6].

Several allergen families illustrate how molecular structure and stability converge on clinical expression. Plant non-specific lipid transfer proteins (nsLTPs) are consistently described as highly resistant to heat and proteolysis, supporting their role as robust food allergens that may retain biological activity despite culinary processing and gastrointestinal conditions [6,8]. Similarly, plant seed storage proteins—including 2S albumins and members of the cupin superfamily (vicilins and legumins)—derive stability from compact folding and stabilizing intramolecular interactions, facilitating persistence during digestion [6–7]. Peanut storage proteins exemplify this paradigm: Ara h 2 and Ara h 6 demonstrate pronounced resistance to thermal stress and proteolytic degradation,

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and reduced in vitro IgE binding after enzymatic treatment does not necessarily translate into diminished allergenic potency [9].

Beyond plant-derived proteins, molecular diagnostic panels frequently include highly stable animal allergens such as shellfish tropomyosin and fish parvalbumin, both of which are resistant to processing and digestion [8,10]. Food processing does not uniformly reduce allergenicity. While extensive heating may destroy conformational epitopes in labile allergens, chemical modification during high-temperature processing—such as glycation during dry roasting—may enhance allergenic potential in selected contexts [8,10]. Gastric digestion further acts as a physiological gatekeeper: impaired digestion, including under acid suppression, has been linked to de novo IgE formation to dietary proteins, emphasizing host-related modifiers of sensitization independent of the food ingredient itself [11]. Together, these observations underscore the relevance of molecular stability when interpreting sensitization profiles in a food-science context [12].

1.3. Panallergens and Cross-Reactivity Patterns in Food Allergy

Panallergens are structurally conserved protein families shared across phylogenetically unrelated allergen sources and constitute the molecular basis of IgE cross-reactivity between inhalant and food allergens. Among the most clinically relevant panallergen families are lipid transfer proteins (LTPs), PR-10 proteins, profilins, tropomyosins, and parvalbumins, each characterized by distinct biochemical properties and sensitization pathways [13–14].

Lipid transfer proteins represent clinically significant plant-derived panallergens due to their resistance to thermal processing, proteolytic digestion, and acidic gastric conditions. This molecular stability supports systemic reactions and broad IgE cross-reactivity across botanically unrelated plant foods, so sensitization to a single source may translate into reactions to a wide range of fruits, vegetables, nuts, and cereals [15–17].

In contrast, PR-10 proteins and profilins are heat-labile and readily degraded during digestion. Sensitization typically arises from primary inhalant exposure—most commonly birch pollen—with subsequent IgE cross-reactivity to homologous food proteins. Although such sensitization frequently yields multiple positive molecular test results, clinical manifestations are usually mild and confined to oral allergy syndrome [13,18], and PR-10 proteins account for the majority of cross-reactive sensitizations detected in adults with combined inhalant and food allergy [18–19].

A major diagnostic challenge associated with panallergen sensitization is the discrepancy between immunological sensitization and true clinical allergy. High rates of IgE positivity—particularly involving broadly cross-reactive components—often exceed rates of clinically confirmed food allergy, highlighting the limitations of conventional diagnostics and the risk of unnecessary dietary restriction [16,20]. In diseases such as EoE, where chronic tissue-restricted inflammation is not directly driven by IgE effector pathways, panallergen sensitization may primarily reflect background cross-reactivity rather than causative food triggers, reinforcing the need to interpret molecular profiles as phenotypic markers rather than direct indicators of disease-driving antigens [21–22].

1.4. Molecular Diagnostics in Food Allergy and the Unmet Need in Eosinophilic Esophagitis

Conventional extract-based allergy diagnostics remain widely used in clinical practice but are limited by poor specificity and an inability to distinguish clinically relevant food allergy from asymptomatic sensitization, particularly in polysensitized individuals [23]. Population-based studies demonstrate that only a minority of sensitized patients develop clinically confirmed food allergy upon oral food challenge, underscoring the risk of overdiagnosis when extract-based testing is used in isolation [24].

Component-resolved diagnostics (CRD) address these limitations by enabling IgE detection against individual allergenic molecules. Across multiple food allergens, CRD has improved diagnostic accuracy through identification of stable components associated with systemic reactions,

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such as storage proteins, and through differentiation between primary food sensitization and pollen-related cross-reactivity [23,25].

Despite these advantages, the role of CRD in eosinophilic esophagitis remains insufficiently defined. Molecular profiling studies consistently demonstrate high rates of IgE sensitization in EoE—predominantly to aeroallergens and cross-reactive plant components such as PR-10 proteins and profilins—yet these patterns correlate poorly with food triggers identified by elimination diets and histologic response [26]. Currently available CRD platforms were largely developed to predict IgE-mediated anaphylaxis rather than chronic, non-IgE-driven esophageal inflammation, and allergenic components relevant to major EoE trigger foods remain incompletely characterized [27].

Accordingly, this study aimed to systematically characterize component-resolved IgE sensitization patterns in adults with eosinophilic esophagitis and to compare these profiles with those observed in a clinically relevant comparator group with chronic urticaria (CU). By focusing on sensitization to structurally stable food allergen components in contrast to predominantly inhalant-driven and cross-reactive patterns, we sought to provide a food ingredient-centered framework for interpreting molecular IgE profiles in EoE.

The conceptual relationship between extract-based diagnostics, CRD, and the unresolved diagnostic gap in eosinophilic esophagitis is summarized in Figure 1.

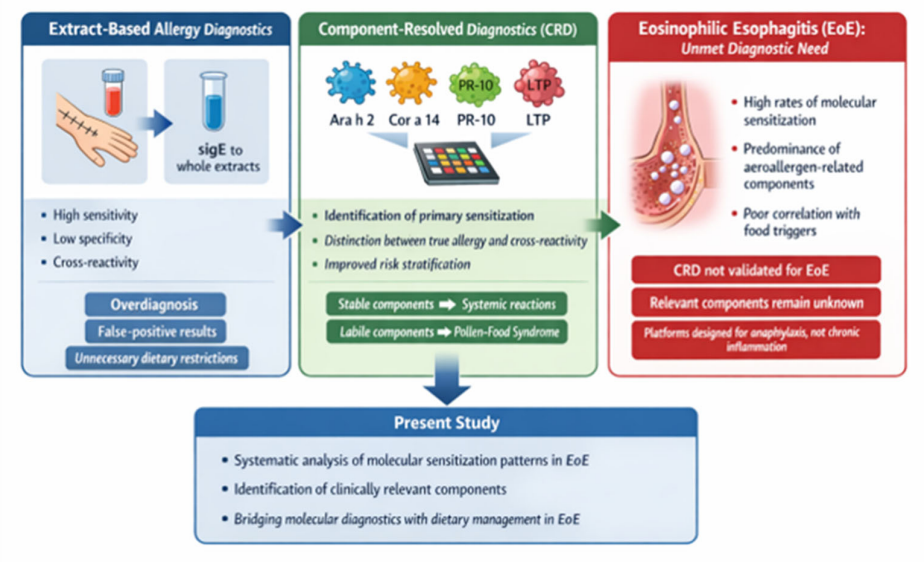

Figure 1. Conceptual framework illustrating the relationship between extract-based allergy diagnostics, component-resolved diagnostics (CRD), and the diagnostic gap in eosinophilic esophagitis (EoE). Extract-based testing is characterized by high sensitivity but limited specificity due to cross-reactivity. CRD enables identification of sensitization to individual allergenic molecules and differentiation between primary food allergy and pollen-related cross-reactivity. In EoE, molecular sensitization profiles frequently show limited concordance with food triggers identified by elimination diets, underscoring a diagnostic gap in the context of chronic, non-IgE-driven esophageal inflammation.

2. Materials and Methods

2.1. Study Design and Ethical Considerations

This study was designed as a retrospective, observational analysis based on a review of medical records from adult patients evaluated at the Department of Allergology, Clinical Immunology and Internal Diseases, Dr. Jan Biziel University Hospital No. 2 in Bydgoszcz, Poland, between 2012 and 2025.

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The study was non-interventional in nature and did not involve any additional diagnostic or therapeutic procedures, direct patient contact, or modifications of routine clinical management. All data were obtained exclusively from existing medical documentation, including clinical information, laboratory findings, and results of component-resolved IgE allergy diagnostics.

Data analysis was conducted using anonymized and coded patient records to ensure confidentiality and full compliance with applicable data protection regulations. The study protocol was approved by the Bioethics Committee of the Faculty of Medicine at Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz (approval no. KEWL 35/2025, issued on 17 December 2025), in accordance with national regulations, the General Data Protection Regulation (GDPR), and the principles of the Declaration of Helsinki.

2.2. Study Objectives and Hypothesis

The primary objective of this study was to characterize molecular IgE sensitization patterns—using component-resolved IgE diagnostics—in adult patients with eosinophilic esophagitis (EoE) diagnosed in accordance with the American College of Gastroenterology (ACG) clinical guideline, and to compare these patterns with those observed in a control group of patients with chronic urticaria (CU) diagnosed according to the international EAACI/GA²LEN/EuroGuiDerm/APAAACI urticaria guideline.

Specifically, the analysis aimed to explore differences in the prevalence and distribution of molecular IgE sensitization to food- and inhalant-derived allergen components, with particular emphasis on allergen groups differing in molecular stability and clinical relevance. The study further sought to examine potential differences between the groups in sensitization to structurally stable food allergens, such as lipid transfer proteins and plant storage proteins, compared with predominantly inhalant-related or cross-reactive allergen components.

An additional objective was to assess the coexistence of other allergic diseases and selected clinical characteristics in patients with EoE and CU in order to provide broader phenotypic context for the observed sensitization patterns.

Given the retrospective and exploratory nature of the study, we hypothesized that molecular IgE sensitization profiles in EoE differ from those observed in CU, with a potential enrichment of sensitization to structurally stable food allergen components. These analyses were intended to be hypothesis-generating rather than confirmatory and were not designed to establish causality or identify specific trigger foods.

2.3. Study Population and Eligibility Criteria

The study population consisted of adult patients diagnosed with eosinophilic esophagitis (EoE) and a control group of patients with chronic urticaria (CU) who were hospitalized or evaluated at the study center during the defined study period.

A total of 22 patients with a confirmed diagnosis of eosinophilic esophagitis and 29 patients with chronic urticaria were included in the final analysis. The number of analyzed cases was determined by the availability of complete clinical documentation and results of component-resolved allergy diagnostics.

Eligible participants were adults aged 18–75 years. Inclusion criteria comprised a documented diagnosis of eosinophilic esophagitis or chronic urticaria and the availability of molecular allergy testing results. Patients with incomplete clinical records or missing component-resolved diagnostic data were excluded from the analysis.

Eosinophilic esophagitis was diagnosed based on symptoms of esophageal dysfunction and histological confirmation of eosinophilic inflammation (≥15 eosinophils per high-power field) in esophageal biopsies, with secondary causes of esophageal eosinophilia excluded, as documented in the medical records. Chronic urticaria was defined as recurrent wheals, angioedema, or both persisting for >6 weeks, and diagnosed by an allergy specialist according to current guideline-based criteria.

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Patients with chronic urticaria (CU) were selected as a pragmatic comparator group from the same tertiary allergy setting, where component-resolved IgE testing was performed as part of routine clinical evaluation. Because CU does not involve eosinophilic gastrointestinal inflammation and is generally not a food-driven mucosal disease, it provides a clinically relevant reference for background IgE sensitization and cross-reactivity when interpreting molecular sensitization patterns observed in EoE.

2.4. Molecular Allergy Diagnostics

Molecular allergy diagnostics were performed using component-resolved IgE testing (CRD) as part of routine clinical practice. For the purposes of this study, results obtained during standard diagnostic evaluation were retrospectively analyzed. No additional laboratory testing was performed specifically for this study.

Two multiplex platforms were used for component-resolved diagnostics: the ImmunoCAP ISAC microarray (Thermo Fisher Scientific, Uppsala, Sweden) and the ALEX2 Allergy Explorer system (Macro Array Diagnostics, Vienna, Austria). Both platforms enable simultaneous measurement of specific IgE antibodies against a broad panel of purified natural and recombinant allergen components using a single serum sample.

The ISAC platform assesses IgE reactivity to more than 100 allergen molecules, including food allergens, inhalant allergens, and cross-reactive panallergens, with results reported semi-quantitatively as ISAC Standardized Units (ISU-E). The ALEX2 system includes a comparable and partially overlapping panel of allergen components and reports quantitative results expressed in kUA/L, while additionally incorporating CCD inhibition to reduce false-positive results related to cross-reactive carbohydrate determinants. Because the ISAC and ALEX2 panels only partially overlap, platform-related differences were considered a potential source of measurement heterogeneity; however, the distribution of diagnostic platforms did not differ between study groups (Table 1).

The molecular allergen panels covered major food allergens, including storage proteins (2S albumins, 7S and 11S globulins), lipid transfer proteins, and milk and egg components, as well as panallergens (profilins, PR-10 proteins, tropomyosins) and inhalant allergens (pollens, house dust mites, animal dander, and molds). This broad coverage enabled comprehensive characterization of individual IgE sensitization profiles.

Interpretation of molecular IgE results was based on manufacturer-recommended cut-off values. For ISAC, values ≥0.3 ISU-E were considered positive, whereas for ALEX2, specific IgE concentrations ≥0.35 kUA/L were regarded as indicative of sensitization. All results were interpreted descriptively for research purposes and were not reclassified or reinterpreted beyond the original clinical laboratory reports.

All laboratory analyses were conducted in certified diagnostic laboratories in accordance with quality control standards applicable at the time of testing. As this was a retrospective observational study, molecular sensitization patterns were analyzed as immunological markers of IgE reactivity and were not equated with clinically confirmed food allergy. Oral food challenges were not systematically performed and were not required for inclusion in the study.

2.5. Statistical Analysis

Statistical analyses were performed to describe and compare molecular sensitization patterns and selected clinical characteristics between patients with eosinophilic esophagitis (EoE) and the control group with chronic urticaria (CU).

Peripheral blood eosinophilia was defined as an absolute eosinophil count ≥0.55 G/L (i.e., above the upper limit of normal reported by the local laboratory) and analyzed both as a binary variable (present vs. absent) and as a continuous measure.

Continuous variables were assessed for normality of distribution using the Shapiro–Wilk test. Normally distributed data are presented as means with standard deviations, whereas non-normally

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distributed variables are reported as medians with interquartile ranges. Categorical variables are presented as absolute numbers and percentages.

Comparisons between the EoE and CU groups were conducted using the Student's t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

The primary analyses focused on differences in the prevalence of IgE sensitization to selected molecular allergen groups, including food-derived components (such as storage proteins, lipid transfer proteins, and PR-10 proteins), panallergens (profilins and tropomyosins), and inhalant allergens. Secondary analyses explored associations between molecular sensitization profiles and selected clinical features, including the presence of other allergic diseases. Additionally, sensitization to structurally stable food allergen components was also analyzed as a composite endpoint (any LTP or plant storage protein), and exploratory subgroup comparisons were performed within the EoE cohort. Sensitivity analyses stratified by CRD platform (ISAC vs. ALEX2) were also performed for the stable-component endpoint.

Given the exploratory nature of the study and the limited sample size, no formal sample size calculation was performed. All analyses were considered descriptive and hypothesis-generating. A two-sided p-value < 0.05 was considered statistically significant.

Statistical analyses were performed using Statistica (version 13.3; TIBCO Software Inc., Palo Alto, CA, USA).

3. Results

3.1. Baseline Demographic Characteristics and Type of Molecular Allergy Testing

A total of 22 patients with eosinophilic esophagitis (EoE) and 29 patients with chronic urticaria (CU) were included in the analysis. Patients with EoE were younger than those with CU, with a median age of 28 years (IQR: 23–35) compared with 39 years (IQR: 29–47) in the CU group ($p = 0.001$, Mann–Whitney U test).

Male sex was more frequent in the EoE group than in the CU group (59.1% vs. 31.0%); however, this difference did not reach statistical significance ($p = 0.053$, Fisher's exact test).

With respect to component-resolved molecular allergy diagnostics, the distribution of diagnostic platforms was comparable between groups. In the EoE cohort, 59.1% of patients were tested using the ImmunoCAP ISAC platform and 40.9% using the ALEX2 system, compared with 58.6% and 41.4%, respectively, in the CU group ($p = 1.000$, Fisher's exact test). Baseline demographic characteristics and diagnostic methods are summarized in Table 1.

Table 1. Baseline demographic characteristics and type of molecular allergy testing in patients with eosinophilic esophagitis (EoE, n = 22) and chronic urticaria (CU, n = 29).

Variable	EoE (n = 22)	CU (n = 29)	p-value
Age, years (median, IQR)	28 (23–35)	39 (29–47)	0.001
Male sex, n (%)	13 (59.1)	9 (31.0)	0.053
ISAC, n (%)	13 (59.1)	17 (58.6)	1.000
ALEX2, n (%)	9 (40.9)	12 (41.4)	1.000

3.2. Clinical Presentation of Eosinophilic Esophagitis

The distribution of self-reported clinical symptoms among patients with eosinophilic esophagitis is shown in Figure 2. Dysphagia was the most commonly reported symptom, affecting 13 of 22 patients, followed by abdominal pain reported by 8 patients. A history of food impaction, retrosternal chest pain, and heartburn was each documented in 5 patients.

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Less frequent manifestations included unintentional weight loss, reported by 2 patients, and nausea or vomiting, which was reported by 1 patient. Overall, the symptom profile was dominated by esophageal manifestations, with relatively infrequent systemic or alarm symptoms.

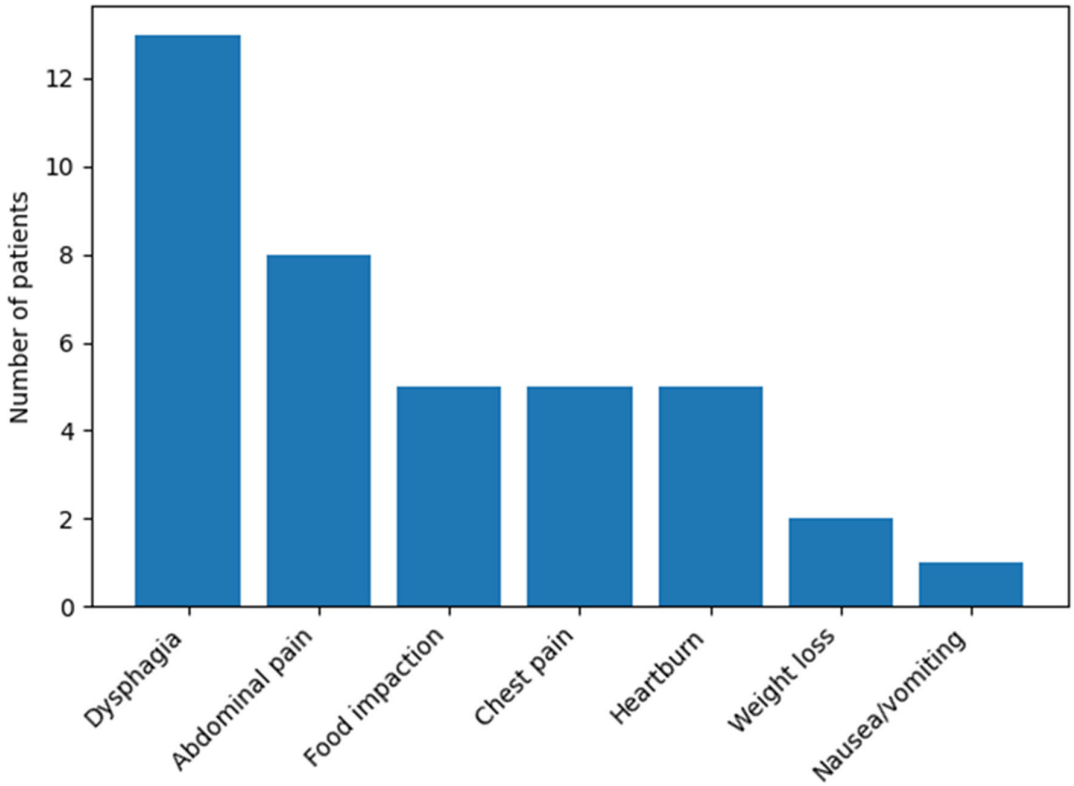

Figure 2. Clinical symptoms reported by patients with eosinophilic esophagitis (n = 22). Bars represent the number of patients reporting each symptom. Individual patients could report more than one symptom.

3.3. Other Atopic Comorbidities

The prevalence of atopic comorbidities other than eosinophilic esophagitis and chronic urticaria is summarized in Table 2. Allergic rhinitis was reported in 45.5% of patients with eosinophilic esophagitis (EoE) and in 27.6% of patients with chronic urticaria (CU), with no statistically significant difference between groups ($p = 0.140$).

Angioedema was more frequently observed in the CU group than in the EoE group (58.6% vs. 9.1%, $p < 0.001$). The prevalence of asthma did not differ significantly between patients with EoE (36.4%) and those with CU (24.1%, $p = 0.240$).

Atopic dermatitis was infrequent in both cohorts and was documented in one patient with EoE (4.5%) and in none of the patients with CU ($p = 0.430$). A history of anaphylaxis was rare and occurred with comparable frequency in the two groups (9.1% vs. 6.9%, $p = 1.000$).

Table 2. Prevalence of non-disease-defining atopic comorbidities in patients with eosinophilic esophagitis (EoE, n = 22) and chronic urticaria (CU, n = 29).

Atopic comorbidity	EoE (n = 22), n (%)	CU (n = 29), n (%)	p-value
Allergic rhinitis	10 (45.5)	8 (27.6)	0.140
Angioedema	2 (9.1)	17 (58.6)	<0.001
Asthma	8 (36.4)	7 (24.1)	0.240
Atopic dermatitis	1 (4.5)	0 (0.0)	0.430
Anaphylaxis	2 (9.1)	2 (6.9)	1.000

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3.4. Overall Detection of Molecular Allergen Components

The overall detection of molecular allergen components is summarized in Tables 3 and 4. At least one molecular component was detected in 77.3% of patients with eosinophilic esophagitis (EoE) and in 65.5% of patients with chronic urticaria (CU), with no statistically significant difference between groups (p = 0.390).

The median number of detected molecular components was 12.5 (IQR: 2–23) in the EoE group and 6 (IQR: 0–18) in the CU group. This difference did not reach statistical significance (p = 0.170, Mann–Whitney U test). A wide interindividual variability in the number of detected components was observed in both cohorts.

Table 3. Number of detected molecular allergen components in patients with eosinophilic esophagitis (EoE, n = 22).

Number of detected components	Patients, n (%)
0	5 (22.7)
1–5	3 (13.6)
6–10	2 (9.1)
11–20	7 (31.8)
>20	5 (22.7)

Table 4. Number of detected molecular allergen components in patients with chronic urticaria (CU, n = 29).

Number of detected components	Patients, n (%)
0	10 (34.5)
1–5	6 (20.7)
6–10	4 (13.8)
11–20	6 (20.7)
>20	3 (10.3)

3.5. Sensitization to Panallergen Families and Selected Component Groups

Sensitization to panallergen families and selected molecular component groups is summarized in Table 5.

Among plant-derived panallergens, PR-10 proteins were the most frequently detected sensitization pattern in both cohorts. PR-10 sensitization was observed in 63.6% of patients with eosinophilic esophagitis (EoE) and in 37.9% of patients with chronic urticaria (CU); however, this difference did not reach statistical significance (p = 0.093).

Sensitization to lipid transfer proteins (LTPs) was detected in patients with EoE (18.2%) and was not observed in the CU group (p = 0.029). Sensitization to plant storage proteins was also detected in the EoE group (13.6%) and was absent in the CU cohort, without reaching statistical significance (p = 0.074).

When stable food allergen components were considered jointly (any sensitization to LTPs or plant storage proteins), sensitization to at least one stable component was present in 7/22 (31.8%) EoE patients and in none of the CU controls (0/29); this difference was statistically significant (Fisher's exact test p = 0.0015). In platform-stratified sensitivity analyses, stable-component sensitization remained restricted to EoE in both the ISAC subset (5/13 vs. 0/17, p = 0.009) and the ALEX2 subset (2/9 vs. 0/12, p = 0.171), and stable-component sensitization was not associated with diagnostic platform within the EoE cohort (p = 0.648). In an exploratory analysis within the EoE cohort, stable-component–sensitized patients (n = 7) had a higher number of detected allergen components than non-sensitized patients (median 25 [IQR: 15–34] vs. 2 [IQR: 0–12.5]; p = 0.003), while age, sex distribution, and peripheral blood eosinophilia were similar between subgroups (all p > 0.05).

Sensitization to profilins and tropomyosins was uncommon in both groups and did not differ significantly between cohorts. Animal-derived component groups, including parvalbumins, serum

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albumins, and lipocalins, were rare and showed no statistically significant differences between EoE and CU.

Table 5. Sensitization to panallergen families and selected molecular component groups in patients with eosinophilic esophagitis (EoE, n = 22) and chronic urticaria (CU, n = 29).

Component group	EoE (n = 22), n (%)	CU (n = 29), n (%)	p-value
PR-10	14 (63.6)	11 (37.9)	0.093
LTP	4 (18.2)	0 (0.0)	0.029
Profilins	2 (9.1)	1 (3.4)	0.571
Tropomyosins	1 (4.5)	0 (0.0)	0.431
Storage proteins	3 (13.6)	0 (0.0)	0.074
Parvalbumins	0 (0.0)	0 (0.0)	—
Serum albumins	1 (4.5)	1 (3.4)	1.000
Lipocalins	2 (9.1)	3 (10.3)	1.000
Stable food allergen components (LTPs or storage proteins)	7 (31.8)	0 (0.0)	0.001

3.6. Molecular Sensitization Patterns to Inhalant- and Food-Related Components

Comparative analysis of component-resolved IgE profiles identified differences in the prevalence of selected inhalant- and food-related allergen components between patients with eosinophilic esophagitis (EoE) and those with chronic urticaria (CU).

Among aeroallergen-derived components, sensitization to rBet v 1 was more frequently detected in patients with EoE than in controls (63.6% vs. 27.6%, p = 0.021). Similarly, rPhl p 5 was detected more often in the EoE group compared with the CU group (31.8% vs. 6.9%, p = 0.029). Sensitization to the mold-derived component rAlt a 1 was also observed more frequently in patients with EoE (27.3% vs. 3.4%, p = 0.034).

Within the lipid transfer protein (LTP) family, sensitization to nArt v 3 was detected in patients with EoE (18.2%) and was not observed in the CU group (p = 0.029). In contrast, sensitization to rVes v 51 was detected only in the CU group (20.7%) and was absent in patients with EoE (p = 0.031).

Several additional allergen components showed differences in prevalence between groups without reaching statistical significance. These included PR-10–related components and selected LTPs of plant origin, as well as additional inhalant allergens (Tables 6A and 6B). Given the exploratory design of the study and the limited sample size, no correction for multiple comparisons was applied, and these findings should be interpreted as hypothesis-generating.

Table 6. A. Allergen components showing statistically significant differences (p < 0.05) between patients with eosinophilic esophagitis and chronic urticaria.

Component	Allergen family	EoE (n = 22), n (%)	CU (n = 29), n (%)	p-value
rBet v 1	PR-10 (birch pollen)	14 (63.6)	8 (27.6)	0.021
rPhl p 5	Grass pollen	7 (31.8)	2 (6.9)	0.029
rAlt a 1	Mold (Alternaria)	6 (27.3)	1 (3.4)	0.034
nArt v 3	LTP (mugwort pollen)	4 (18.2)	0 (0.0)	0.029
rVes v 51	Hymenoptera venom	0 (0.0)	6 (20.7)	0.031

Table 6. B. Allergen components showing nominal differences without statistical significance (p ≥ 0.05).

Component	Allergen family	EoE (n = 22), n (%)	CU (n = 29), n (%)	p-value
nPla a 21	PR-10–related pollen	5 (22.7)	1 (3.4)	0.073
nAmb a 1	Ragweed pollen	3 (13.6)	0 (0.0)	0.074
rCor a 8	LTP (hazelnut)	3 (13.6)	0 (0.0)	0.074
nJug r 3	LTP (walnut)	3 (13.6)	0 (0.0)	0.074
rPru p 3	LTP (peach)	3 (13.6)	0 (0.0)	0.074
rPhl p 1	Grass pollen	10 (45.5)	6 (20.7)	0.074
rMal d 1	PR-10 (apple)	12 (54.5)	8 (27.6)	0.082

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3.7. Peripheral Blood Eosinophilia

Peripheral blood eosinophilia was evaluated in both study groups using binary classification (presence vs. absence) as well as absolute eosinophil counts. As summarized in Table 7, peripheral eosinophilia was more frequently observed in patients with eosinophilic esophagitis (EoE) than in patients with chronic urticaria (36.4% vs. 3.4%, respectively; p = 0.009).

Absolute eosinophil counts were also compared between groups. Due to non-normal distribution of values, results are presented as medians with interquartile ranges. Median eosinophil counts were higher in the EoE group than in the control group (0.30 G/L [IQR: 0.17–0.61] vs. 0.13 G/L [IQR: 0.06–0.23]; p < 0.001), as shown in Table 7.

Table 7. Peripheral blood eosinophilia in patients with eosinophilic esophagitis (EoE, n = 22) and chronic urticaria (CU, n = 29).

Variable	EoE (n = 22), n (%)	CU (n = 29), n (%)	p-value
Eosinophilia present	8 (36.4)	1 (3.4)	0.009
Eosinophils, G/L, median (IQR)	0.30 (0.17–0.61)	0.13 (0.06–0.23)	<0.001

4. Discussion

4.1. Principal Findings in the Context of Food Ingredient Characterization

The present study identifies distinct molecular sensitization patterns in adult patients with eosinophilic esophagitis that are directly grounded in the observed results. Although sensitization to inhalant-related allergen components—predominantly PR-10 proteins—represented the most frequent IgE signal in the EoE cohort (Tables 5 and 6), this pattern was also common in the control group and therefore did not distinguish eosinophilic esophagitis as a disease entity. In contrast, sensitization to selected food-derived allergen components was confined to patients with EoE. Specifically, lipid transfer proteins and plant storage proteins were detected only in the EoE group and were absent in patients with chronic urticaria (Table 5), suggesting a qualitative rather than purely quantitative difference in molecular sensitization profiles.

The selective presence of food allergen components characterized by high molecular stability suggests that the immunological relevance of food exposure in eosinophilic esophagitis may depend, at least in part, on intrinsic properties of individual food ingredients. Structurally stable allergens, such as lipid transfer proteins and seed storage proteins, are more likely to withstand thermal processing and gastrointestinal digestion, thereby maintaining prolonged contact with the esophageal mucosa during repeated dietary exposure. In the context of a chronic, food-driven inflammatory disease, detection of these components—despite their lower overall prevalence compared with PR-10 sensitization—points toward a food ingredient-specific molecular signature that may be biologically relevant for disease maintenance, while not implying a direct causal role.

Beyond molecular sensitization, eosinophilic esophagitis in this cohort was associated with a higher prevalence of peripheral blood eosinophilia and increased absolute eosinophil counts compared with the control group (Table 7). Although peripheral eosinophilia is neither universal nor specific to EoE and does not directly predict disease activity or treatment response, its coexistence with selective sensitization to structurally stable food allergen components may reflect a broader systemic inflammatory imprint accompanying chronic, food-driven mucosal disease. This observation should be interpreted as a phenotypic association rather than evidence of causality.

The demographic characteristics of the EoE cohort—namely younger age and a predominance of male patients (Table 1)—are consistent with established epidemiological patterns of eosinophilic esophagitis. However, these demographic differences do not eliminate the possibility that age and sex may partially contribute to the observed sensitization profiles. In particular, younger age may influence patterns of allergen exposure and atopic background, and residual demographic confounding cannot be excluded in the absence of age- or sex-adjusted analyses. Accordingly, the

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observed food ingredient-related sensitization patterns should be interpreted as disease-associated signals rather than definitive disease-specific markers.

Overall, these findings suggest that, in eosinophilic esophagitis, the relevance of food exposure may be shaped less by the overall burden of IgE sensitization and more by the molecular properties of individual food ingredients capable of sustaining repeated antigenic contact at the esophageal mucosa.

4.2. Inhalant-Driven Sensitization as a Dominant IgE Background

In our cohort, inhalant-related sensitization signals were more frequently detected in patients with eosinophilic esophagitis, with higher prevalence of rBet v 1, rPhl p 5, and rAlt a 1 compared with the control group, alongside a high overall prevalence of PR-10 sensitization (Tables 5 and 6). These findings are consistent with the concept that, in adult EoE, molecular IgE profiles are often shaped by aeroallergen exposure and cross-reactive pathways rather than by primary sensitization to causative food ingredients. In a component-resolved study of adults with EoE, birch sensitization with cross-reactivity to food allergens was reported to predominate, supporting an inhalant-driven imprint as a common background signal in this disease [26]. Similar real-world cohorts have demonstrated high rates of aeroallergen sensitization in adults with EoE, with tree and grass pollen reactivity recurring as major contributors to the overall sensitization burden [28].

From a food ingredient perspective, dominance of PR-10 sensitization is therefore best interpreted as a marker of a cross-reactive sensitization landscape—often linked to pollen–food syndrome—rather than as an indicator of specific dietary antigens sustaining esophageal inflammation. Nevertheless, the literature indicates substantial heterogeneity within this background: PR-10 sensitization rates vary across populations and may identify subgroups enriched for oral allergy symptoms or broader polysensitization patterns [29–31]. Despite frequent molecular IgE positivity to inhalant-related components, multiple studies emphasize that sensitization profiles alone have limited utility for identifying trigger foods in EoE. This reinforces the need to distinguish between an inhalant-driven "IgE background" and food ingredient-related signatures with potentially greater relevance for chronic mucosal disease [26,28].

4.3. Structurally Stable Food Allergens as Potential Drivers of Chronic Food-Driven Inflammation

In the present study, sensitization to structurally stable food allergen components was observed preferentially in patients with eosinophilic esophagitis. Lipid transfer proteins were detected only in patients with EoE, with no LTP sensitization observed in the control group ($p = 0.029$), while sensitization to plant storage proteins was likewise confined to EoE patients, albeit without reaching statistical significance. At the molecular level, specific LTP components—including rPru p 3, rCor a 8, and nJug r 3—were identified exclusively in the EoE cohort (Table 6), representing a food ingredient-related signal that contrasts with the broadly distributed inhalant-driven sensitization background described in Section 4.2.

From a molecular perspective, lipid transfer proteins represent one of the most structurally robust classes of plant food allergens. Their compact α-helical structure, stabilized by multiple conserved disulfide bonds, confers marked resistance to thermal processing and proteolytic digestion. As a result, intact LTP molecules may persist during food processing and gastrointestinal transit, enabling repeated contact with the esophageal mucosa during routine dietary exposure. These properties distinguish LTPs from labile allergens such as PR-10 proteins and provide a biologically plausible framework by which structurally stable food ingredients could be relevant to chronic, tissue-restricted immune activation rather than exclusively to acute IgE-mediated reactions [32–35].

Although the existing literature on LTPs predominantly focuses on IgE-mediated systemic reactions and anaphylaxis, emerging mechanistic evidence suggests that immune responses to LTPs may extend beyond classical IgE effector pathways. Transcriptomic analyses in patients with LTP-associated reactions have demonstrated alterations in gastrointestinal epithelial renewal, epithelial

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barrier–related pathways, and engagement of IgG-associated immune responses, indicating that structurally stable food allergens can interact with the immune system through multiple mechanisms [36–37]. While these observations derive largely from studies of acute clinical phenotypes, they support the broader concept that persistent exposure to digestion-resistant food allergens may have immunological consequences distinct from immediate hypersensitivity.

However, the present findings do not establish a direct mechanistic link between IgE sensitization to structurally stable food allergens and the pathogenesis of eosinophilic esophagitis. Rather, the selective presence of LTPs and plant storage proteins in EoE patients, combined with their well-characterized molecular stability, suggests that such food ingredients may serve as qualitative markers of a food-driven EoE phenotype. In this context, these components may reflect sustained antigenic exposure at the mucosal interface rather than acting as direct disease triggers identifiable by conventional IgE-based diagnostics. This interpretation aligns with a food ingredient-centered perspective on eosinophilic esophagitis and underscores the need for future studies specifically addressing the role of structurally stable allergens in non-IgE-mediated and chronic inflammatory disease contexts. A conceptual model summarizing these relationships is presented in Figure 3.

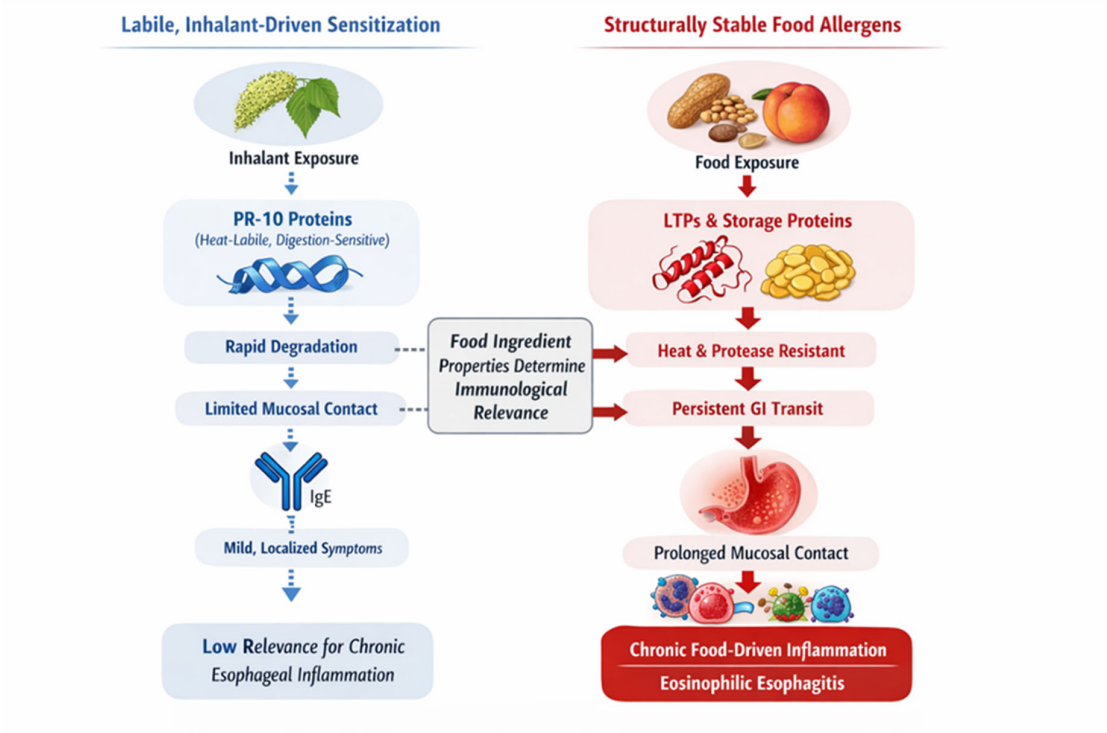

Figure 3. Conceptual model illustrating how molecular stability of food allergen components may influence immune relevance in eosinophilic esophagitis. Labile inhalant-related allergens, such as PR-10 proteins, are rapidly degraded during digestion and primarily reflect an inhalant-driven IgE sensitization background. In contrast, structurally stable food allergens, including lipid transfer proteins and plant storage proteins, resist thermal processing and proteolysis, enabling prolonged mucosal contact during gastrointestinal transit.

4.4. Molecular Properties of Food Ingredients Beyond Classical IgE-Mediated Allergy

Although IgE sensitization to multiple food and inhalant components was frequently observed in the present cohort, classical IgE-mediated effector reactions did not define the clinical phenotype of eosinophilic esophagitis. Episodes of anaphylaxis were infrequent and occurred with comparable prevalence in the control group, indicating that acute systemic reactions were neither dominant nor specific to EoE. This dissociation between IgE sensitization profiles and clinical expression suggests

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that IgE reactivity alone is insufficient to account for the chronic, tissue-restricted inflammatory course of the disease [38–39].

Growing evidence indicates that the immunological relevance of food allergens is influenced not only by IgE-binding capacity but also by intrinsic molecular properties of individual food ingredients. Structural stability, resistance to digestion, and susceptibility to processing-induced modification determine whether food-derived proteins persist during gastrointestinal transit and repeatedly interact with the mucosal immune system [38,40]. Many major food allergens belong to protein families characterized by compact folding, disulfide bond stabilization, or oligomerization, features that promote survival in the gastrointestinal environment [39,41].

Thermal processing further modulates these properties in an allergen-specific manner. While extensive heating may reduce allergenicity of labile proteins, processing of intrinsically stable allergens can generate structurally modified molecules with enhanced immunostimulatory potential. In particular, glycation through Maillard reactions promotes aggregation and formation of advanced glycation end products, which may be recognized by innate immune receptors such as RAGE, triggering pro-inflammatory signaling pathways independent of classical IgE-mediated mechanisms [40–42].

In addition, structurally altered food allergens can interact with intestinal epithelial cells, inducing stress responses and release of epithelial-derived cytokines that amplify local immune activation [43]. At the adaptive level, processing and digestion may reduce IgE-binding epitopes while preserving linear T-cell epitopes, potentially shifting immune responses from acute effector reactions toward sustained, low-grade inflammation [38,40].

Taken together, these observations support the concept that eosinophilic esophagitis may represent a disease model in which molecular properties of food ingredients contribute to chronic immune activation beyond classical IgE-mediated allergy. This framework should be interpreted as hypothesis-generating, underscoring the need for immunological characterization approaches that extend beyond serological IgE profiling to better capture mechanisms relevant to chronic, tissue-restricted inflammation [38–40].

4.5. Diagnostic and Translational Implications of CRD in Food-Driven Diseases

The present study indicates that component-resolved diagnostics (CRD) have limited ability to identify clinically relevant trigger foods in eosinophilic esophagitis. Although molecular IgE sensitization was frequently detected, CRD profiles showed no consistent correlation with foods implicated by dietary interventions, and substantial interindividual heterogeneity in the number and composition of sensitized components was observed (Results 3.4). Together, these findings suggest that CRD primarily reflects patterns of sensitization rather than disease-driving mechanisms in EoE.

Evidence from previous studies supports this interpretation. CRD performance in EoE appears to be compromised by both false-positive and false-negative results, driven by low specific IgE titers, incomplete panel coverage, and frequent cross-reactivity between inhalant and food allergens [27,44–45]. In adult EoE, birch pollen–driven sensitization is common and may lead to misattribution of plant-derived foods as causative triggers if cross-reactive PR-10 patterns are not adequately recognized [46]. Conversely, allergenic proteins relevant to major EoE triggers, particularly wheat, remain incompletely characterized or absent from current CRD panels, further limiting diagnostic accuracy in this disease context [44,47].

CRD findings correlate poorly with clinical outcomes in EoE. High rates of molecular sensitization do not reliably predict response to elimination diets, and IgE-targeted therapies such as anti-IgE monoclonal antibodies have not demonstrated clinical benefit, underscoring the limited pathogenic role of IgE-mediated mechanisms in eosinophilic esophagitis [27,44]. While some studies report symptomatic improvement following CRD-guided dietary interventions, the absence of direct comparisons with empiric elimination strategies and the persistence of non-responders despite positive CRD results highlight the limited and context-dependent predictive value of this approach [45].

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From a translational perspective, these limitations reflect the fact that current CRD platforms were developed primarily to assess the risk of acute, IgE-mediated reactions, including anaphylaxis. Eosinophilic esophagitis represents a distinct disease model, characterized by chronic, tissue-restricted inflammation driven by repeated exposure to food ingredients rather than immediate hypersensitivity. Accordingly, future diagnostic strategies may benefit from moving beyond serological IgE profiling toward food ingredient-focused approaches that integrate molecular stability, mucosal relevance, and biomarkers of chronic immune activation to better inform dietary and therapeutic decision-making in EoE.

Nevertheless, the present findings suggest that component-resolved diagnostics may still have a role as a supportive tool in selected clinical contexts. In particular, the selective detection of structurally stable food allergen components, such as lipid transfer proteins, exclusively in patients with eosinophilic esophagitis raises the possibility that CRD-informed phenotyping could help identify subgroups of patients in whom food-driven antigenic exposure is more prominent. Rather than guiding elimination diets directly, molecular sensitization profiles may assist in prioritizing dietary evaluation or tailoring empiric elimination strategies in a more individualized manner. Such an approach would require prospective validation and integration with clinical response, dietary exposure, and biomarkers of chronic inflammation, but may represent a step toward more rational and patient-centered dietary management in eosinophilic esophagitis.

Within the framework of immunological characterization of food allergen components, our findings position CRD as a pragmatic readout that links molecular allergen families to a clinically defined, food-driven inflammatory phenotype. The novelty of this work is not the identification of new allergen molecules, but the emerging marker pattern in EoE—selective IgE reactivity to structurally stable, digestion-resistant components—superimposed on a cross-reactive inhalant background. If confirmed in prospective cohorts, this pattern could contribute to biomarker-driven stratification (e.g., “stable-component–positive” vs. “cross-reactive inhalant–dominant” profiles) and inform more individualized dietary work-up.

4.6. Strengths and Limitations

The present study has several strengths that enhance the interpretability of its findings. The demographic characteristics of the study population were broadly representative of adult eosinophilic esophagitis, including a predominance of younger male patients, consistent with established disease epidemiology (Table 1). The real-world study design enabled comprehensive assessment of molecular sensitization profiles alongside clinical characteristics, allowing evaluation of component-resolved diagnostics in a routine clinical setting. Inclusion of a comparator group with chronic urticaria provided an important reference population with an allergic background but without eosinophilic gastrointestinal involvement, facilitating contextual interpretation of sensitization patterns observed in EoE.

Several limitations should also be acknowledged. The retrospective observational design precludes assessment of temporal relationships and limits causal inference, particularly with respect to dietary triggers and treatment response. The relatively small sample size reduces statistical power and may have limited the detection of weaker associations. The study cohort reflects all adult patients with eosinophilic esophagitis who met inclusion criteria and had available component-resolved diagnostic data at a single tertiary center during the study period; therefore, sample size was determined by real-world data availability rather than a priori recruitment. Notably, patients with eosinophilic esophagitis were significantly younger than those in the control group, and age-related differences in allergen exposure, atopic background, or immune maturation may have partially influenced observed sensitization profiles. Although the demographic distribution reflects known epidemiological features of EoE, residual confounding by age and sex cannot be excluded in the absence of matching or multivariable adjustment.

In addition, the use of two component-resolved diagnostic platforms (ISAC and ALEX2), while reflective of routine clinical practice, introduces methodological heterogeneity related to partial panel

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overlap, differences in allergen representation, and platform-specific technical features such as CCD inhibition. Although platform distribution did not differ between study groups, stable-component sensitization remained restricted to EoE in platform-stratified sensitivity analyses, suggesting that the observed signal was not attributable to a single platform. However, storage protein sensitization was detected only in the ISAC-tested EoE subgroup, highlighting the impact of incomplete panel overlap and limited subgroup sizes. This heterogeneity may have contributed to variability in detected sensitization profiles. Furthermore, multiple component-level comparisons were performed in an exploratory framework without formal correction for multiple testing; therefore, nominal p-values should be interpreted cautiously and require validation in larger, independent cohorts. Finally, the absence of prospective dietary validation and longitudinal follow-up limits the ability to directly link molecular sensitization patterns with clinical outcomes or treatment response. Moreover, detailed EoE disease severity data (e.g., endoscopic findings and histologic activity measures) were not uniformly available; therefore, potential phenotypic differences, including disease severity, between stable-component-sensitized and non-sensitized EoE patients remain to be studied.

5. Conclusions

In this exploratory study, molecular IgE sensitization profiles in adult eosinophilic esophagitis were characterized by a predominant inhalant-driven background, accompanied by a selective presence of structurally stable food allergen components. While sensitization to aeroallergen-related molecules, particularly PR-10 proteins, was frequent, these patterns were not disease-specific and are more likely to reflect cross-reactive IgE imprinting rather than causative dietary triggers.

In contrast, sensitization to lipid transfer proteins and plant storage proteins was confined to patients with eosinophilic esophagitis, suggesting that molecular properties of individual food ingredients may be relevant for defining disease-associated immunological phenotypes. These findings do not support the use of component-resolved diagnostics as a stand-alone tool for identifying trigger foods in eosinophilic esophagitis. Instead, they highlight its potential value as a complementary approach for immunological phenotyping when interpreted within a broader, food ingredient-centered framework.

From a dietary perspective, molecular sensitization profiles may help support individualized evaluation of food exposure in selected patient subgroups, particularly when integrated with empiric elimination strategies rather than used to guide dietary restriction directly. If confirmed in larger, prospectively validated cohorts, CRD panels could be used adjunctively to identify EoE patients with a stable-component sensitization phenotype for more targeted dietary work-up or monitoring, rather than to prescribe elimination based on IgE positivity alone. Future studies integrating molecular sensitization data with dietary exposure, allergen stability, and biomarkers of chronic mucosal inflammation are needed to refine the role of component-resolved diagnostics in the management of food-driven inflammatory diseases such as eosinophilic esophagitis.

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Informed Consent Statement: Patient consent was waived due to the retrospective study design and the use of anonymized data from existing medical records, as approved by the Bioethics Committee.

Data Availability Statement: No new data were created during this study. De-identified data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to approval by the institutional ethics committee and in compliance with GDPR. The data are not publicly available due to privacy restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

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