

Food-Dependent Exercise-Induced Anaphylaxis: A Challenging Life-threatening Condition

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ABSTRACT

Food-dependent exercise-induced anaphylaxis (FDEIA) is an uncommon but potentially life-threatening condition characterized by allergic reactions triggered by the combination of specific food ingestion and physical exertion. Despite its rarity, FDEIA poses significant diagnostic and management challenges due to its complex pathophysiology and variable clinical presentation. Diagnosis relies on careful evaluation of clinical history, symptomatology, and laboratory tests, with inherent difficulties in distinguishing FDEIA from other related conditions. Management of FDEIA involves comprehensive strategies to minimize the risk of allergic reactions through measures such as allergen avoidance, patient education, and timely administration of epinephrine. While existing treatment approaches primarily target acute reactions, ongoing research endeavors are crucial for validating emerging diagnostic and therapeutic modalities. This review offers a comprehensive overview of FDEIA, encompassing its epidemiology, underlying pathophysiology, clinical presentations, diagnostic challenges, and management approaches.

Keywords: Anaphylaxis; exercise; food allergy; food-dependent exercise-induced anaphylaxis; gluten; challenge test (Siriraj Med J 2024; 76: 655-660)

INTRODUCTION

Food-dependent exercise-induced anaphylaxis (FDEIA), first described in the 1970s, is a rare but potentially life-threatening condition characterized by allergic symptoms triggered by the combination of specific food ingestion and physical exertion.^{1,2} Evidence indicates that FDEIA constitutes a subset of food-induced anaphylactic reactions.³ Despite its relatively low incidence, FDEIA can lead to significant morbidity and mortality if not promptly recognized and managed.³ While exercise-induced and food-induced anaphylaxis are well-documented individually, their confluence in FDEIA presents unique diagnostic challenges for clinicians.⁴ FDEIA's complex pathophysiology and variable clinical presentation complicate its diagnosis and management.³ Recent research has focused on understanding the role of

mast cells, immunoglobulin E (IgE)-mediated reactions, and exercise-induced immune responses in FDEIA. Advances in diagnostic criteria, including oral food challenges with exercise provocation, have enhanced diagnostic accuracy and informed more targeted management strategies.

This review provides a comprehensive overview of FDEIA, including its epidemiology, pathogenesis and pathophysiology, causative food, augmenting factors, clinical manifestations, diagnostic criteria, and management approaches. Relevant articles on FDEIA published in the MEDLINE database from inception to March 2024 were evaluated and summarized. Our search strategy included keywords such as “food-dependent exercise-induced anaphylaxis,” “exercise-induced anaphylaxis,” and “food allergy.” We included peer-reviewed articles that provided significant insights into the epidemiology,

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pathogenesis, clinical manifestations, diagnosis, and management of FDEIA. Exclusion criteria included non-English articles, abstracts without full-text availability, and studies unrelated to FDEIA. Data extraction focused on summarizing key findings and identifying gaps in the current understanding of FDEIA.

Epidemiology

Estimating the precise prevalence and incidence of FDEIA remains challenging due to its rarity. A questionnaire survey conducted among 11,647 Japanese children reported FDEIA incidences of 0% in kindergartens, 0.06% in elementary schools and 0.21% in junior high schools.⁵ Subsequent surveys in Japanese schools found FDEIA prevalence rates of 0.017% among 76,229 junior high school students and 0.0047% among 170,146 elementary school students.^{6,7} In Korea, registry data of 558 participants across 16 centers focusing on anaphylaxis revealed that persons under 18 years accounted for 60% of registered patients, with FDEIA prevalence at 1.2% among children and 3.1% among adults.⁸ Notably, FDEIA represents 30% to 50% of exercise-induced anaphylaxis cases.^{6,9} Previously reported prevalence documented FDEIA diagnosis using questionnaire-based surveys and not confirmed by laboratory tests or food challenges.⁵⁻⁸ Most documented cases are associated with wheat and seafood ingestion.⁵⁻⁷ Although FDEIA predominantly affects adolescents and young adults, it has been reported across various age groups.⁷ The prevalence of FDEIA is likely to

vary among different populations due to differences in dietary patterns, exercise habits, and geographic exposure to allergens.

Pathogenesis and pathophysiology

The pathogenesis and pathophysiology of FDEIA involve complex interactions between allergenic proteins from ingested foods, exercise, and immune responses (Fig 1).¹⁰ Food allergens implicated in FDEIA vary among individuals, with common triggers, including wheat, shellfish, celery, and legumes.¹¹ Moreover, a broader spectrum of food categories such as meat, vegetables, fruit, seeds, and cereals, has been associated with FDEIA.^{11,12} Omega-5 gliadin, a component of wheat, is a notable allergen in FDEIA.¹³⁻¹⁵ Its molecular structure, rich in glutamine and proline, forms stable, immunogenic epitopes resistant to gastrointestinal digestion.^{13-15,16} These proteins can penetrate the intestinal mucosa and reach the systemic circulation, particularly when exercise increases intestinal permeability.^{17,18} Studies have shown that reducing omega-5 gliadins in mutant wheat cultivars significantly decreases allergenicity in patients with FDEIA, suggesting potential safe alternatives for these individuals.¹⁹ Understanding the molecular composition and reactivity of omega-5 gliadin is essential for developing targeted diagnostic and therapeutic strategies for FDEIA.

Physical exercise is an augmenting factor in FDEIA pathophysiology by increasing the permeability of blood vessels. Both strenuous and light exercise can trigger

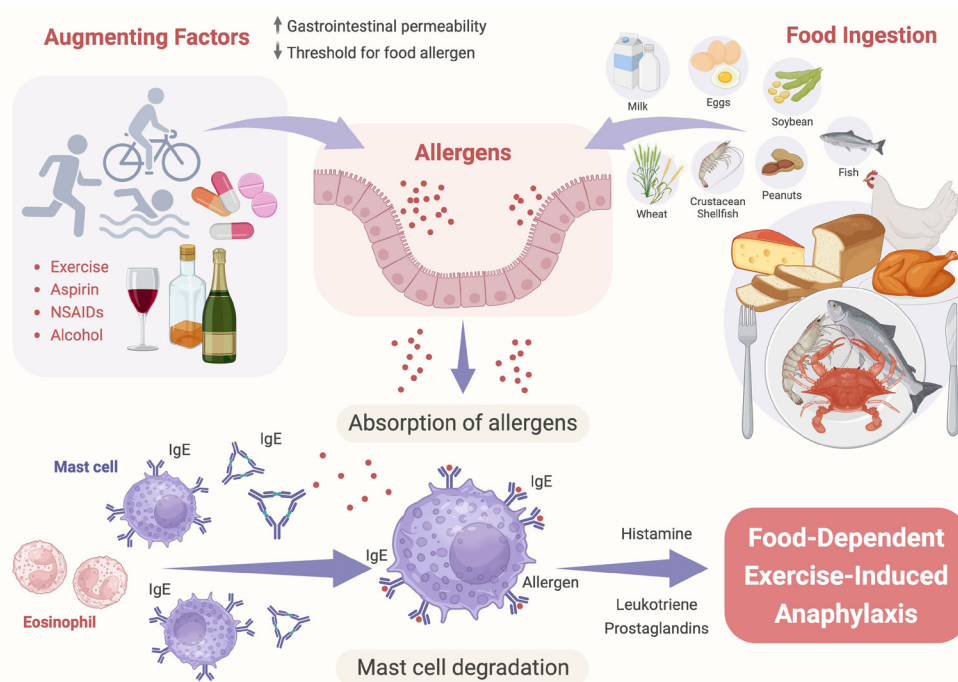


Fig 1. The pathogenesis and pathophysiology of food-dependent exercise-induced anaphylaxis. This diagram provides a visual representation of the sequential events leading to the development of FDEIA, highlighting the critical role of food allergen ingestion, exercise as an augmenting factor, and mast cell activation in the pathophysiology. Upon ingesting the culprit food, the food-allergenic proteins bind to specific immunoglobulin E (IgE) on the surface of mast cells, leading to mast cell degranulation with the release of inflammatory mediators, such as histamine and other mediators.

anaphylactic reactions, emphasizing the need to consider exercise intensity and timing relative to food ingestion.²⁰ FDEIA can develop in both well-trained athletes and individuals engaging in sporadic activities like walking.²⁰ In addition to exercise, various augmenting factors can contribute to FDEIA, including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), higher temperature, alcohol consumption, atopic dermatitis, and the menstrual cycle.^{5,21-25} These cofactors can significantly lower the food threshold needed to trigger a reaction,²⁶ enhance the severity of FDEIA episodes, and complicate diagnosis.

The interaction of allergens with IgE on sensitized mast cells^{17,18} leads to mast cell activation and the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins.¹⁰ These mediators initiate a cascade of immune responses, resulting in the clinical manifestations of anaphylaxis.

Clinical manifestations

The clinical symptoms of FDEIA typically develop when individuals engage in physical exertion within 30 to 120 minutes after ingesting the responsible food, with symptoms onset occurring between 10 to 50 minutes following exercise.¹⁴ The clinical manifestations of FDEIA encompass a broad spectrum of symptoms related to IgE-mediated reaction, ranging from mild cutaneous reactions to severe systemic anaphylaxis.²⁰ Cutaneous involvement, such as urticaria, pruritus, flushing, and angioedema, is the most common manifestation, followed by respiratory and gastrointestinal symptoms. Cardiovascular symptoms like tachycardia, hypotension, and syncope may arise, with potential progression to shock and cardiac arrhythmias. Though less common, neurological symptoms include dizziness, confusion, and loss of consciousness. The reactions could evolve into anaphylaxis involving multi-organ systems that pose life-threatening risks.²⁷ The severity of symptoms may vary between episodes and among individuals, depending on the amount of ingested culprit food, exercise intensity, and immune system sensitivity.²⁸

A recent meta-analysis found a significant association between FDEIA and coexisting atopic conditions.¹¹ Patients with FDEIA had a lower prevalence of atopy (56.9%) compared to those with food-dependent exercise-induced urticaria/angioedema without anaphylaxis (77.3%).¹¹ The most prevalent atopic conditions include allergic rhinitis, asthma, allergic conjunctivitis, and atopic dermatitis. Notably, a history of atopy, particularly allergic rhinitis, is a significant risk factor for recurrent FDEIA episodes.²⁹ Conversely, a history of urticaria was more common in FDEIA patients with wheals and/or angioedema (59.1%)

compared to those without anaphylaxis (12.5%), with chronic spontaneous urticaria being the most prevalent subtype.¹¹ Both chronic urticaria and FDEIA involve mast cells in their pathophysiology, suggesting potential shared mechanisms that warrant further investigation. The concomitant treatment for chronic urticaria may obscure or delay the recognition of IgE-mediated reactions triggered by various allergens, thereby masking symptoms.³⁰ Clinicians should remain vigilant for unexpected changes in urticaria severity or the onset of systemic symptoms, which may indicate an underlying IgE-mediated reaction, such as FDEIA.

Diagnosis

The initial step in diagnosing FDEIA involves evaluating the patient's clinical history, focusing on the temporal association between food ingestion and subsequent exercise-induced symptoms. A wide array of foods, beyond wheat, can trigger FDEIA, underscoring the importance of considering various allergenic sources. Keeping a food diary containing details of cofactors and their timing about symptoms can offer valuable diagnostic insights. It is crucial to distinguish FDEIA from chronic or acute recurrent urticaria, exercise-induced anaphylaxis, idiopathic anaphylaxis, hereditary angioedema, and mastocytosis.³¹ The World Allergy Organization criteria for wheat-dependent exercise-induced anaphylaxis can guide the diagnosis of FDEIA.²⁷ Table 1 provides an overview of commonly utilized diagnostic criteria for FDEIA, including clinical history, symptomatology, symptom timing, exclusion of alternative etiologies, and laboratory tests.

Laboratory tests, including in vivo and in vitro evaluations, can complement the diagnosis by identifying allergen sensitivities. Diagnostic tests include serum-specific IgE and skin prick tests targeting suspected trigger allergens.^{3,14,32} Prick-to-prick skin testing with fresh food can increase diagnostic accuracy due to the relatively low sensitivity and specificity of commercial food extracts.³ Identifying major allergenic components of food proteins, such as specific IgE for omega-5 gliadin in wheat, provides a valuable diagnostic marker.³³ However, the presence of food-specific IgE confirms only allergen sensitization and may not indicate clinical allergy, necessitating correlation with clinical history. For FDEIA patients experiencing recurrent anaphylaxis, measuring basal serum tryptase levels can help identify underlying mast cell disorders.³ If the suspected allergens remain unclear, an exercise-food challenge test may be necessary to ensure an accurate diagnosis.³³⁻³⁶ Provocative challenge protocols integrating multiple cofactors, such as aspirin and alcohol, have shown

TABLE 1. Diagnosis of FDEIA.⁴

Assessment	Clinical evaluation
Clinical history	History of anaphylactic reactions occurring after exercise, typically within 4 hours of food ingestion. Tolerance of the culprit food without exercise and safe exercise tolerance without ingesting the trigger food.
Symptom presentation	Manifestations of anaphylaxis, including skin, respiratory, gastrointestinal, or cardiovascular symptoms. Symptoms may range from mild cutaneous reactions to severe systemic manifestations.
Timing of symptoms	Symptoms typically occur within minutes to hours after the combination of food ingestion and exercise.
Exclusion of other causes	Rule out alternative diagnoses, such as exercise-induced bronchospasm or idiopathic anaphylaxis.
Specific diagnostic tests	Specific IgE, skin prick, and prick-to-prick tests. IgE for omega-5 gliadin for wheat-dependent exercise-induced anaphylaxis. Basal serum tryptase levels for mast cell disorders. Oral food challenge followed by physical exertion provocation.

promise in enhancing diagnostic yield.^{21,37-39} However, incorporating additional augmenting factors alongside conventional exercise-food challenges requires careful patient selection and monitoring due to the potential for severe reactions. Tailoring diagnostic strategies to individual patient profiles and utilizing advanced testing modalities can enhance diagnostic accuracy and facilitate effective management.

Management

General management of FDEIA

Effective management of FDEIA involves both preventive and emergency strategies, as shown in Table 2. The cornerstone of prevention is identifying and avoiding trigger foods, along with minimizing physical exercise after ingesting such foods.⁴⁰ Patients must be educated about FDEIA triggers, symptoms, and emergency action plans, emphasizing the importance of carrying and utilizing self-injectable epinephrine. While completely avoiding physical activity may not be practical, individuals with FDEIA should avoid consuming culprit allergens at least four hours before and one hour after exercise to reduce the risk of reactions.⁴¹ Proper management by healthcare providers is essential to prevent unnecessary dietary and exercise restrictions, helping patients maintain a balanced lifestyle.⁴² Patients should always carry anaphylaxis identification cards and self-injectable epinephrine to be prepared for emergencies.⁴⁰

Specific management of FDEIA

Managing acute anaphylactic reactions in FDEIA involves timely administration of epinephrine, with dosages tailored to the patient's weight and age.⁴⁰ In cases with cardiovascular involvement, early intravenous fluid administration is crucial to restore circulatory volume. Adjunctive therapy, like antihistamines and corticosteroids, may be used, although their efficacy is limited.^{43,44} Inhaled β 2-agonists are indicated for predominant bronchial obstruction,⁴⁰ while inhaled adrenaline via a nebulizer is recommended for suspected laryngeal/pharyngeal edema.⁴⁵

Premedication with antihistamines, corticosteroids, and leukotriene receptor antagonists before culprit food ingestion or exercising is not recommended due to insufficient evidence of effectiveness.⁴⁰ Although immunotherapy and anti-IgE monoclonal antibodies may be considered for patients with IgE-mediated food allergies, their efficacy in FDEIA remains limited and requires further research.⁴⁶

CONCLUSION

FDEIA presents a complex and potentially life-threatening challenge, characterized by IgE-mediated reactions triggered by specific food ingestion combined with physical exertion. Our systematic review synthesizes current literature to highlight key aspects of FDEIA epidemiology, pathogenesis and pathophysiology,

TABLE 2. Treatment modalities for FDEIA.⁴⁰⁻⁴⁶

Treatment modalities	Description
Epinephrine	Intramuscular epinephrine as first-line management of anaphylaxis. Dosage of 0.01 mg/kg for children (max 0.3 mg) and 0.3 mg for adults. Administered promptly upon recognition of symptoms related to anaphylaxis.
Antihistamines	Adjunctive therapy to reduce histamine-mediated symptoms such as itching and hives. May be administered in conjunction with epinephrine.
Corticosteroids	Administered after epinephrine and fluid replacement to prevent late-phase reactions; however, the benefit of corticosteroids remains inconclusive.
Allergen avoidance	Avoidance of trigger foods before exercise. Patients should be educated about potential sources of allergens and how to read food labels.
Emergency action plan	Development of personalized plans outlining steps to take in case of anaphylaxis. Includes instructions on how to use self-injectable epinephrine and when to seek medical attention.

diagnosis, and management. Despite its rarity, FDEIA poses significant risks if not promptly recognized and managed. Our data underscores the importance of integrating clinical history assessment, specific laboratory testing, and exercise–food challenge tests for precise diagnosis and optimal patient care. However, the literature reviewed exhibits limitations, including small sample sizes, variability in diagnostic criteria, and potential biases such as reliance on self-reported data. These limitations highlight the necessity for more rigorous and standardized research methodologies in future investigations. Key areas for advancement involve enhancing diagnostic tools, investigating biomarkers, and refining treatment strategies to improve diagnostic accuracy and optimize therapeutic results for individuals with FDEIA.

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