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EXERCISE-INDUCED ANAPHYLAXIS: CURRENT INSIGHTS FROM THE LITERATURE

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ABSTRACT

Background: Exercise-induced anaphylaxis (EIA) is an uncommon but potentially life-threatening disorder triggered by physical activity. Its food-dependent form (FDEIA), most frequently associated with wheat and ω -5 gliadin, is the most prevalent subtype. Despite increasing recognition, both EIA and FDEIA remain underdiagnosed due to their heterogeneous presentations and multifactorial pathogenesis.

Methods: A narrative literature review was conducted, focusing on publications from 2023–2025 retrieved through PubMed, Scopus, and Google Scholar. Emphasis was placed on recent clinical trials, case reports, and mechanistic studies addressing epidemiology, diagnosis, and management.

Results: Recent evidence highlights the interplay between allergens, exercise, and cofactors such as nonsteroidal anti-inflammatory drugs, alcohol, and infections in lowering the threshold for reactions. While wheat and ω -5 gliadin remain the dominant triggers in FDEIA, newly described allergens, including banana, shellfish, and soy, broaden the clinical spectrum. Advances in molecular allergology, particularly component-resolved diagnostics, enhance sensitivity in identifying culprit allergens, although accessibility remains limited. Management continues to rely on trigger avoidance and the availability of self-injectable epinephrine. Promising developments include hypoallergenic wheat formulations, biologics such as omalizumab, and experimental approaches targeting mast cell signaling, notably Bruton's tyrosine kinase inhibitors.

Conclusion: EIA and FDEIA are clinically significant disorders with diverse presentations and considerable diagnostic challenges. Progress in molecular diagnostics and biologic therapies suggests a shift toward proactive, disease-modifying strategies. Future priorities include standardized diagnostic protocols, validation of emerging therapies, and enhanced clinical awareness to improve patient safety and quality of life.

KEYWORDS

Exercise-Induced Anaphylaxis, Food-Dependent Exercise-Induced Anaphylaxis, Ω -5 Gliadin, Cofactors, Omalizumab, Bruton's Tyrosine Kinase Inhibitors, Molecular Allergology

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Introduction

Exercise-induced anaphylaxis (EIA) represents an uncommon but potentially severe allergic disorder in which systemic reactions are provoked by physical exertion. First described in the 1970s, EIA is now recognized as a clinically heterogeneous condition, with manifestations that may vary from mild urticaria and angioedema to severe anaphylactic shock with cardiovascular collapse. Among its variants, food-dependent exercise-induced anaphylaxis (FDEIA) has emerged as the most frequently encountered form. In this subtype, symptoms are elicited only when ingestion of specific foods is combined with exercise within a critical time window. Wheat proteins, particularly ω -5 gliadin, are the most consistently implicated triggers, although additional allergens have also been identified (Srisuwatchari et al., 2025; Veramendi-Espinoza et al., 2025).

Recent studies have reinforced the multifactorial nature of EIA. Besides food and exercise, a range of cofactors—including nonsteroidal anti-inflammatory drugs, alcohol intake, concurrent infections, and hormonal influences—can significantly reduce the threshold for anaphylaxis (Le Bon Chami et al., 2025). The clinical spectrum has continued to expand, with reports linking FDEIA not only to cereal proteins but also to fruits such as banana (Kampitak, 2023; Özdemir, 2025). Unusual manifestations, such as concomitant rhabdomyolysis, have further illustrated the diagnostic challenges of this condition (Tang et al., 2025).

Diagnostic approaches have evolved considerably. Conventional methods such as skin prick testing and measurement of allergen-specific IgE remain important, but the introduction of component-resolved diagnostics and molecular allergology has improved the accuracy of identifying sensitizing proteins and assessing patient risk (Piboonpocanun et al., 2025; Srisuwatchari et al., 2025). The development of novel gliadin extracts and the application of microarray technologies have shown promise; however, studies indicate

that certain multiplex assays may lack sufficient sensitivity and specificity for ω -5 gliadin detection, limiting their reliability in diagnosing wheat-dependent exercise-induced anaphylaxis (Miyamoto et al., 2025).

Current management still emphasizes avoidance of identified triggers and cofactors, as well as prompt self-administration of epinephrine in case of accidental exposure. Nevertheless, recent investigations suggest that new therapeutic options may emerge. A multicenter trial demonstrated tolerance to bread prepared from a hypoallergenic wheat line, without evidence of desensitization (Kohn et al., 2025). Case-based reports have described the successful use of monoclonal antibodies such as omalizumab in selected patients (Mobayed et al., 2023), while experimental data indicate that Bruton's tyrosine kinase inhibitors could provide prophylactic benefit (Callisto et al., 2024). These findings open the possibility of shifting from purely preventive strategies toward disease-modifying therapies.

Despite these advances, EIA continues to be underdiagnosed and often misinterpreted in clinical practice. Reviews have called for greater awareness among healthcare professionals, particularly in sports medicine and emergency care, where many patients first present (Landgraf, 2025). Considering the growing number of published cases, the expanding spectrum of allergens, and novel therapeutic strategies, an updated summary of current knowledge is timely.

The objective of this review is therefore to provide a comprehensive overview of the most recent literature on EIA, with emphasis on its pathophysiology, clinical features, diagnostic methods, and treatment options, drawing on latest publications.

Exercise-Induced Anaphylaxis

Definition and Clinical Characteristics

Exercise-induced anaphylaxis (EIA) is defined as a systemic hypersensitivity reaction precipitated by physical activity. Clinical manifestations typically appear during or shortly after exertion and may range from cutaneous symptoms, such as flushing, pruritus, and urticaria, to severe systemic involvement, including hypotension, bronchospasm, gastrointestinal distress, and in some cases, cardiovascular collapse (Carlisle & Lieberman, 2024; Landgraf, 2025). The onset of symptoms is variable, often occurring within minutes of initiating exercise but occasionally delayed until recovery or cooling down. Importantly, the clinical course may differ between episodes in the same individual, complicating recognition and diagnosis.

Two major forms of EIA are described: the **classic type**, in which symptoms occur in association with physical exertion alone, and the **food-dependent subtype (FDEIA)**, where reactions are elicited only when exercise is combined with the ingestion of specific food allergens within a defined time frame. FDEIA currently represents the majority of reported cases (Srisuwatchari et al., 2025; Veramendi-Espinoza et al., 2025).

Pathophysiology

The precise mechanisms underlying EIA remain incompletely elucidated, but evidence suggests a multifactorial process involving immunologic, physiologic, and environmental contributors. Proposed mechanisms include:

- **Enhanced allergen absorption during exercise:** Increased gastrointestinal permeability and altered digestion during exertion may allow greater systemic exposure to food allergens such as ω -5 gliadin (Srisuwatchari et al., 2025).
- **Activation of mast cells and basophils:** Exercise-induced changes in blood flow, pH, and osmolality have been implicated in lowering the threshold for mast cell degranulation (Ansley et al., 2015).
- **Role of cofactors:** Substances and conditions such as nonsteroidal anti-inflammatory drugs, alcohol, infections, and menstruation can amplify allergic responses by modifying gastrointestinal absorption or mast cell reactivity (Le Bon Chami et al., 2025; Zogaj et al., 2014).
- **Genetic susceptibility:** Emerging evidence suggests that specific loci encoding wheat storage proteins, particularly gliadins and glutenins, may influence the risk of sensitization and the severity of clinical reactions, providing a potential molecular explanation for disease heterogeneity (Miyamoto et al., 2025);

Triggers and Cofactors

The most consistently implicated food in FDEIA is wheat, particularly the ω -5 gliadin component. Other allergens include shellfish, peanuts, tree nuts, fruits (e.g., banana), and various plant-derived proteins (Povesi Dascola & Caffarelli, 2012). The ingestion-to-exercise interval is typically within 2–4 hours, although atypical timelines have been reported (Patel et al., 2025).

Cofactors significantly influence the occurrence and severity of EIA. NSAIDs are among the strongest enhancers, followed by alcohol and intercurrent illness. Hormonal changes, particularly those associated with the menstrual cycle, have also been described (Benito-Garcia et al., 2019; Le Bon Chami et al., 2025; Zogaj et al., 2014). The interplay between allergen exposure, exercise, and cofactors contributes to the variable clinical expression observed in practice.

Epidemiology

EIA is considered rare, with an estimated prevalence varying between 0.3 and 5.1% in population-based studies, though the true frequency is likely underestimated due to underrecognition (Sayaca, 2023). Cases have been reported across age groups, but young adults and adolescents appear most frequently affected. No consistent sex predilection has been established, although some studies suggest a slight female predominance in FDEIA, possibly related to hormonal cofactors.

Clinical Diagnosis

Diagnosis relies on a thorough clinical history, emphasizing the temporal relationship between exercise, food intake, and onset of symptoms. Confirmatory testing may include skin prick tests, specific IgE assays, and component-resolved diagnostics, particularly for ω -5 gliadin (Piboonpocanun et al., 2025; Srisuwachari et al., 2025). Exercise challenge tests combined with food ingestion may provide diagnostic clarity in specialized centers, although they carry significant risk and require careful monitoring.

Emerging diagnostic tools include novel gliadin-based reagents and expanded allergen panels on multiplex platforms, which may improve sensitivity and specificity (Piboonpocanun et al., 2025). However, current evidence suggests that not all multiplex assays reliably detect ω -5 gliadin sensitization, highlighting the importance of targeted testing (Park et al., 2025).

Food-Dependent Exercise-Induced Anaphylaxis

Food-dependent exercise-induced anaphylaxis (FDEIA) represents the best-characterized and most frequently reported subtype of EIA. Unlike the classic form, where exercise alone can act as the precipitant, FDEIA requires a synergistic interaction between food ingestion and physical activity. The allergen consumed is typically tolerated under resting conditions, but when combined with exertion—often within a 2–4 hour time frame—it provokes systemic allergic reactions (Srisuwachari et al., 2025).

Distinctive Clinical Features

FDEIA is characterized by greater reproducibility of reactions compared with classic EIA, often presenting with more severe systemic involvement. Importantly, its clinical spectrum has recently been expanded: case reports document unusual manifestations such as exertional rhabdomyolysis triggered by wheat ingestion followed by exercise (Tang et al., 2025). The variability of symptom onset and severity, strongly influenced by cofactors, complicates recognition in clinical practice.

Allergen Spectrum

Wheat remains the prototypical trigger, with ω -5 gliadin consistently implicated as the dominant allergenic protein. Advances in molecular allergology confirm its central role, making component-resolved diagnostics particularly valuable (Piboonpocanun et al., 2025). Nonetheless, FDEIA is not limited to wheat: shellfish, peanuts, soy, and fruits such as banana have been increasingly reported as causative agents, reflecting the global diversity of dietary exposures (Le Bon Chami et al., 2025).

Modifying Role of Cofactors

Cofactors are particularly relevant in FDEIA, where they can transform otherwise tolerated food–exercise combinations into life-threatening reactions. Nonsteroidal anti-inflammatory drugs, alcohol, acute infections, and hormonal fluctuations are the most frequently reported enhancers (Le Bon Chami et al., 2025; Zogaj et al., 2014). Their presence not only lowers the reaction threshold but also modulates severity, highlighting the importance of individualized patient counseling.

Diagnostic Challenges

The diagnosis of FDEIA requires integrating dietary history with exercise timing. Unlike in classic EIA, history-taking must include detailed assessment of food intake, cofactor exposure, and the precise interval before physical activity. Traditional allergy tests are often insufficient: standard IgE and skin prick tests may be negative despite convincing histories. Consequently, advanced diagnostics—including ω -5 gliadin-specific IgE, novel gliadin reagents, and targeted allergen microarrays—have become essential tools (Srisuwatchari et al., 2025). Exercise–food challenge protocols remain the gold standard for confirmation but are associated with significant risk and are reserved for specialized centers (Asaumi et al., 2016).

Clinical and Practical Implications

FDEIA poses unique challenges compared with classic EIA. Its reliance on multiple interacting triggers makes it more difficult to predict and prevent, while the expanding range of allergens requires tailored diagnostic approaches across populations. Increased awareness among clinicians—particularly in emergency medicine and sports settings—is crucial to reduce misdiagnosis and delayed recognition (Landgraf, 2025).

Management and Emerging Therapies

Current Standard of Care

The management of exercise-induced anaphylaxis (EIA) and its food-dependent subtype (FDEIA) remains largely preventive. The cornerstone of therapy is avoidance of identified triggers, including both allergenic foods and recognized cofactors. Patients are advised to abstain from exercise for several hours after consuming suspected foods, particularly wheat and other high-risk allergens, and to avoid known enhancers such as nonsteroidal anti-inflammatory drugs, alcohol, or intercurrent illness (Le Bon Chami et al., 2025).

Emergency preparedness is essential: self-injectable epinephrine is recommended for all patients with a confirmed diagnosis, and education on its timely use is a critical component of management (Bennett, 2015). Adjunctive measures include carrying medical alert identification and ensuring access to trained first responders, particularly in athletic or school settings.

Preventive and Interventional Approaches

Recent studies highlight potential strategies beyond strict avoidance. A phase II clinical trial investigating hypoallergenic wheat bread demonstrated that regular consumption was well tolerated in patients with wheat-dependent FDEIA, although it did not confer desensitization or long-term protection (Kohno et al., 2025). This suggests a possible role for food modification in reducing accidental exposures.

Biologic Therapies

Biologic agents targeting IgE or mast cell activation pathways are increasingly explored in refractory cases. Omalizumab, an anti-IgE monoclonal antibody, has shown efficacy in patients with recurrent or severe FDEIA unresponsive to avoidance strategies (Mobayed et al., 2023). Case series and pilot studies report reduced reaction severity and improved quality of life, although controlled trials remain limited.

Novel immunomodulators are under investigation. Early mechanistic studies suggest that Bruton's tyrosine kinase (BTK) inhibitors, which interfere with mast cell and basophil activation, may have potential in preventing exercise-induced anaphylaxis (Callisto et al., 2024). While promising, these findings are preliminary and require validation in clinical trials.

Patient-Centered Management

Given the heterogeneity of EIA, a personalized management plan is recommended. This includes identifying individual triggers and cofactors, tailoring dietary restrictions, and developing an emergency action plan. For competitive athletes, collaboration with sports physicians and trainers is particularly important, as symptom onset often occurs during training or competition (Landgraf, 2025).

Future Directions

Emerging diagnostic tools—such as component-resolved diagnostics and allergen microarrays—may allow better risk stratification, potentially guiding targeted preventive strategies. Combined with biologic therapies and dietary innovations, these advances represent a shift from reactive to proactive disease-modifying management. However, long-term efficacy and safety data are still lacking, underscoring the need for multicenter trials and standardized management guidelines.

Discussion

Exercise-induced anaphylaxis (EIA) and its food-dependent subtype (FDEIA) represent unique and complex manifestations within the spectrum of allergic disorders. Although relatively rare, their unpredictable onset and potential severity necessitate a high index of suspicion among clinicians. This review highlights recent advances in understanding their pathophysiology, clinical spectrum, diagnostic approaches, and management.

A key finding across recent literature is the multifactorial nature of disease expression, where food allergens, cofactors, and physical exertion interact in a dynamic and individualized manner. While wheat and ω -5 gliadin remain the most prominent triggers worldwide, newly reported allergens—including banana and other regionally relevant foods—suggest that FDEIA is more heterogeneous than previously thought. This diversity underscores the importance of considering local dietary habits and allergen prevalence in both diagnosis and patient counseling.

From a diagnostic perspective, traditional tools such as skin prick testing and serum-specific IgE remain cornerstones, but their limitations are increasingly recognized. Advances in component-resolved diagnostics and the development of novel allergen reagents are reshaping the diagnostic landscape, particularly for wheat-dependent FDEIA (Piboonpocanun et al., 2025; Srisuwatthari et al., 2025). However, the gold standard—exercise–food challenge—remains underutilized due to its inherent risks and lack of standardized protocols. Establishing safer and reproducible diagnostic algorithms remains an urgent priority.

In terms of management, avoidance of triggers and the availability of self-injectable epinephrine remain fundamental. Yet, new therapeutic avenues are emerging. Biologic agents such as omalizumab, and mechanistic approaches targeting mast cell signaling pathways (e.g., BTK inhibitors), open the possibility of disease-modifying strategies (Callisto et al., 2024; Mobayed et al., 2023). While still in early phases, these interventions may eventually complement or replace strict avoidance regimens, which are often burdensome for patients.

Despite these advances, important gaps remain. The epidemiology of EIA and FDEIA is not well established, partly due to underrecognition and misdiagnosis. Moreover, heterogeneity in clinical presentation and cofactor involvement complicates both diagnosis and management. Large, multicenter prospective studies are needed to clarify prevalence, standardize diagnostic testing, and evaluate long-term outcomes of emerging therapies.

Conclusions

Exercise-induced anaphylaxis, particularly its food-dependent form, remains an underdiagnosed but clinically significant disorder. Recent advances have expanded our understanding of its allergen spectrum, highlighted the central role of cofactors, and improved diagnostic accuracy through molecular allergology. Novel therapeutic strategies—including dietary modification and biologic agents—offer promising alternatives to traditional management focused on strict avoidance and emergency preparedness.

However, challenges persist: diagnostic tools remain imperfect, patient education is inconsistently delivered, and evidence supporting new interventions is still preliminary. To improve patient outcomes, future efforts must focus on raising clinical awareness, standardizing diagnostic protocols, and conducting robust interventional studies.

By integrating recent scientific insights with clinical practice, the field is moving toward a more nuanced and proactive approach to EIA and FDEIA. Such progress has the potential not only to reduce morbidity and mortality but also to significantly improve quality of life for affected individuals.

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