



Exercise-Induced Anaphylaxis: Literature Review and Recent Updates

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Abstract

Purpose of Review This paper will review the pathophysiology, diagnosis, and treatment of exercise-induced anaphylaxis and food-dependent, exercise-induced anaphylaxis with an emphasis on novel studies published in the past several years.

Recent Findings Exercise-induced anaphylaxis (EIAN) is a clinical syndrome characterized by anaphylaxis during or shortly after physical exertion. The syndrome is broadly grouped into two categories: exercise-induced anaphylaxis and food-dependent, exercise-induced anaphylaxis (FDEIAN). Recent literature indicates that FDEIAN is a primary IgE-mediated food allergy which is augmented by several cofactors. Cofactors such as exercise, NSAIDs, and alcohol increase intestinal permeability and allow increased antigen uptake, thereby causing symptoms. The pathophysiology of EIAN is still under investigation.

Summary EIAN and FDEIAN are rare clinical syndromes characterized by symptoms during or shortly after exercise. Despite recent advances in the understanding of EIAN and FDEIAN, the pathophysiology of both conditions is not fully understood.

Keywords Anaphylaxis · Exercise-induced anaphylaxis · Food-dependent, exercise-induced anaphylaxis · Food allergy

Introduction

Exercise-induced anaphylaxis (EIAN) is an uncommon clinical syndrome characterized by symptoms consistent with anaphylaxis provoked primarily by exercise [1]. The syndrome is often subdivided into two groups: anaphylaxis caused exclusively by exercise and anaphylaxis caused by exercise after eating a particular food [2]. The latter entity is named food-dependent, exercise-induced anaphylaxis (FDEIAN) [3].

Exercise-induced anaphylaxis was first reported in 1979 by Maulitz [4]. He described a 31-year-old male with recurrent anaphylaxis triggered by jogging after eating shellfish. The patient was able to exercise without symptoms and consume shellfish without symptoms. However, when eating shellfish prior to exercise he developed sudden onset symptoms. Maulitz then demonstrated evidence of IgE-mediated sensitivity via skin prick testing. Since this initial description of

EIAN—or more correctly FDEIAN—significant scientific progress has been made [5•].

More broadly, anaphylaxis is an acute and life-threatening clinical disorder characterized by sudden onset, multisystem involvement. Anaphylaxis is relatively common and the estimated prevalence is between 1.6–5.1% in the USA [6]. It can be caused by many triggers and is often classified based on etiology [2]. Both EIAN and FDEIAN are subtypes of anaphylaxis [2]. The purpose of this paper is to review the pathophysiology, diagnosis, and treatment of EIAN and FDEIAN with a particular emphasis on novel studies published in the past several years.

Epidemiology

There is little epidemiologic data regarding the prevalence of EIAN and FDEIAN. One group estimated prevalence in children in Yokohama, Japan, based on a written questionnaire provided to school nurses. The prevalence of exercise-induced anaphylaxis was estimated at 0.03% in Japanese junior-high students [7]. The same group reported the prevalence of FDEIAN to be 0.005% in elementary school children and 0.02% in junior-high-aged children [8, 9]. Approximately 40% (5/13) of the patients had diagnoses confirmed by provocation testing and more than half of the children suffered repeat episodes of EIAN [7].

This article is part of the Topical Collection on *Anaphylaxis and Drug Allergy*

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Anaphylaxis in general is considerably more common. Estimates of prevalence vary between 0.09–5.1% [10–12]. Exercise is an uncommon trigger of anaphylaxis. Wood et al. reports that exercise accounts for 1.5% of all cases of anaphylaxis [6].

EIAN and FDEIAN can affect patients of all ages and ethnicities. Published case reports span a wide age range, involving patients from 4 to 74 years [13–15]. There appears to be an increased incidence in young adults although this may be an artifact of lifestyle. Both females and males appear to be equally affected [16]. Affected individuals tend to have concomitant atopic disorders [7].

Pathophysiology

The mechanism of EIAN and FDEIAN are not completely understood at present. As with many rare conditions, understanding of the pathophysiology advances incrementally. Recent advances in the FDEIAN literature have revised our understanding of the disease. Accumulating evidence suggests FDEIAN is actually IgE-mediated food allergy augmented by cofactors. Investigation into the mechanisms of EIAN is still ongoing.

Hypotheses and known mechanisms of EIAN and FDEIAN will be reviewed below. Both diseases, however, culminate in mast cell degranulation and release of bioactive mediators such as histamine, arachidonic acid metabolites (leukotrienes, prostaglandins, and platelet-activating factor), and tryptase [17–21]. Symptoms are caused by the effects of mast cell mediators on various organ systems. Histamine has pleiotropic effects including urticaria, flushing, tachycardia, and bronchoconstriction [22, 23]. Arachidonic acid metabolites can cause vasodilation, increased vascular permeability, and bronchoconstriction [24–26]. Tryptase is a serine protease and activates the cascade and complement pathways [27].

Food-Dependent, Exercise-Induced Anaphylaxis

FDEIAN is a mast cell-dependent phenomenon. Elevated mast cell mediators have been identified in several patients during acute symptoms [17, 20, 28]. However, the underlying mechanism of mast cell activation is not fully understood. Recent literature indicates that FDEIAN is a primary IgE-mediated food allergy facilitated by an increase in food antigens entering the bloodstream secondary to increased gut permeability [29•, 30•]. Substances that may increase intestinal permeability are termed “cofactors” [3]. A recent publication by Brockow et al. described 16 patients with a history of wheat-dependent, exercise-induced anaphylaxis [30•]. The authors were able to induce symptoms *in the absence of exercise* with high doses of oral gluten, acetylsalicylic acid (ASA) coingestion, and/or alcohol coingestion. This has since

been replicated and suggests FDEIAN may be more appropriately named cofactor-induced food allergy, blurring the line between primary food allergy and FDEIAN [31, 32].

Exercise is a common cofactor in FDEIAN and can often elicit symptoms without additional factors. Pals et al. showed that small intestinal permeability is increased after 60 min of exercise at 80% of peak exercise [33]. Peak serum gliadin levels also increase in patients with wheat-dependent, exercise-induced anaphylaxis [34]. In mice, exercise to exhaustion induces damage of surface epithelium and transit of protein across the small intestinal epithelium [35]. Although exercise increases intestinal permeability, the effects appear to be significant only during high intensity or prolonged exercise [34–36]. It is important to note that EIAN and FDEIAN can both occur without high intensity exercise.

Non-steroidal anti-inflammatory drugs are also reported as common cofactors [13]. Two mechanisms explain the effect of NSAIDs on the intestinal mucosa: direct irritation of the mucosa and decreased prostaglandin synthase activity [37–39]. Mucosal irritation and erosion is caused directly by NSAIDs [40–43]. Modulation of the intestinal barrier increases permeability and allows for increased transit of food antigens into the bloodstream [34]. Separately, NSAIDs may also contribute to urticaria via COX-1 inhibition [44, 45].

Several other cofactors have been described in case reports. Alcohol ingestion prior to food consumption can lower the threshold for reaction [29•, 46•, 47]. Infection and increased temperature (not related to exercise) have also been reported as cofactors [48, 49]. Pollen season and premenstrual or ovulatory phase have been described [13, 49, 50]. Finally, psychological stress has been implicated in several reports [51, 52].

Although the above view of primary food allergy enhanced by cofactors has a reasonable amount of supportive data, it cannot account for all cases of FDEIAN. Kidd et al. report a case of FDEIAN that occurs with ingestion of any food prior to exercise [53]. In the absence of definitive data, alternative theories of FDEIAN have been proposed. These include an exercise-dependent redistribution of blood away from the gut [5•]. This may expose non-intestinal and less tolerogenic mast cells to food antigens and trigger symptoms [54, 55]. Increased activity by tissue transglutaminase during exercise may increase ω -5 gliadin cross-linking and subsequent IgE recognition [56]. Both hypothesis are based on case reports and require further study.

Exercise-Induced Anaphylaxis

The mechanism of EIAN in the absence of a food trigger is not well understood. Several hypotheses have been presented which involve physiologic changes during exercise that activate mast cells.

The best-described hypothesis states that physical activity and/or dehydration causes changes in plasma osmolarity.

Vigorous exercise and dehydration can cause plasma osmolality to increase above 301 mOsm/L (baseline 288 mOsm/L) [57]. Perivascular mast cells and basophils may recognize these changes and degranulate, causing acute symptoms [58, 59]. There is also support for this hypothesis from the exercise-induced asthma literature, where acute changes in airway mucosal osmolality can drive mast cell mediator release and bronchoconstriction [60, 61].

Several alternative mechanisms have also been proposed. Acid-base disturbances can occur during strenuous exercise and may precipitate mast cell degranulation [62]. Release of gastrin and endogenous opioids during exercise may directly activate mast cells [63–65].

Clinical Manifestations and Diagnosis

Clinical Manifestations

The hallmark manifestation is symptom onset during, or shortly after, exercise [4]. Prodromal symptoms include dyspnea, flushing, generalized pruritus, cough, abdominal pain, and rhinorrhea [66]. Cessation of exertion generally results in an improvement in symptoms. However, persistent exercise may lead to generalized urticaria, angioedema, bronchospasm, and hypotensive syncope [67].

EIAN and FDEIAN have been reported at varying activity levels. Intense activity such as jogging is most common. Symptoms have also been reported with mild activity such as yardwork and walking [49]. Onset of symptoms varies significantly between patients, and may even vary within the same patient.

Evaluation and Diagnosis

EIAN and FDEIAN are clinical diagnoses. Symptoms of EIAN begin during or within an hour of exertion [3]. Furthermore, two or more organ systems must be involved to meet criteria for anaphylaxis [2]. Table 1 reviews the proposed diagnostic criteria for exercise-induced anaphylaxis. The diagnosis of food-dependent, exercise-induced anaphylaxis must meet the above criteria *and* have an associated food trigger. The patient must be able to consume the culprit food in the absence of exercise and vice-versa without symptoms. Additionally, there must be evidence of IgE-mediated sensitivity to the culprit

Table 1 Proposed criteria for exercise-induced anaphylaxis (EIAN)

1. Signs and symptoms compatible with anaphylaxis that occurred during (or within an hour) of exercise.
2. There is no alternative diagnosis to better explain the patient's symptoms.

Table 2 Proposed criteria for food-dependent, exercise-induced anaphylaxis (FDEIAN) [3]

1. Signs and symptoms compatible with anaphylaxis that occurred during (or within an hour) of exercise, but only when exercise was preceded by specific food ingestion.
2. Evidence of allergic sensitivity to the implicated food. This may include either positive serum-specific IgE or positive skin prick test
3. No symptoms upon ingestion of the food in the absence of exercise.
*Symptoms may occur in the presence of cofactors such as aspirin and/or ethanol.
4. There is no alternative diagnosis to better explain the patient's symptoms.

food. Table 2 describes the proposed diagnostic criteria for food-dependent, exercise-induced anaphylaxis as published by Feldweg [3].

As both entities are clinical diagnoses, a detailed history is critical. Initial evaluation should focus on type of activity, intensity of activity, onset of symptoms, food consumption, medication use, and time of year. Additional details include substances that can cause anaphylaxis (NSAIDs, known food allergy, etc.) and known cofactors for FDEIAN (NSAIDs, alcohol, pollen, temperature changes, and menses). As food is often involved, history regarding consumption of common culprit foods is important. Table 3 summarizes the most common culprit foods in FDEIAN.

An assessment for other diagnoses is recommended. Mastocytosis, in particular, can cause unprovoked (or provoked) episodes of anaphylaxis [71]. Evaluation should include a serum tryptase and skin examination for cutaneous stigmata of mastocytosis [72, 73].

Evaluation for food-specific sensitization is critical in patients with a suspected food trigger [68]. Initial testing can be conducted with commercially available food extract and/or food specific IgE. In many cases, initial evaluation is negative [74, 75]. Hofmann et al. reported 17 patients with wheat-dependent, exercise-induced anaphylaxis; 29% of patients were positive to wheat extract and 80% positive to wheat flour [69]. However, when testing for specific IgE to ω -5 gliadin, specificity/sensitivity increases considerably [69, 74–76]. In patients with refractory symptoms, one report indicates patients may improve after elimination of all sensitized foods

Table 3 Foods most commonly involved in FDEIAN [46, 51, 66, 68–70]

Most common	Less common
Wheat	Other grains (maize, buckwheat, etc.)
Shellfish (particularly shrimp)	Vegetables (lettuce, celery, pepper)
Legumes (peanut, soy)	Garlic
Tree nuts	
Tomato	

[77]. Food testing is generally guided by clinical history. However, in patients with refractory symptoms, it is reasonable to test to a panel of the most common culprit foods. The most common foods implicated in FDEIAN are reviewed in Table 3.

Utility of Exercise Challenge

Exercise challenge can confirm a diagnosis of EIAN or FDEIAN, but cannot definitively exclude either condition [1, 3]. In one review, 81 patients with a clinical diagnosis of FDEIAN underwent exercise challenge and 29/81 (36%) failed to develop symptoms [78]. In a separate study of patients with clinically diagnosed FDEIAN, food and exercise reproduced symptoms in only 3/14 (21%) of patients [79]. However, all of the patients improved after elimination of culprit foods (follow-up was 6 months–5 years) [79].

Exercise challenge has not been standardized for the purposes of EIAN and FDEIAN [1].

Several groups advocate for using the Bruce protocol as this is well established in the cardiology literature [7, 42]. The Bruce protocol is a treadmill-based maximal exercise test that involves increasing speed and incline in increments of 3 min [80]. It is standardized and easy to replicate which has led to widespread use [81]. Alternative protocols use a fixed amount of aerobic and/or aerobic exercise [30•]. There is also literature to support using other cofactors such as ASA and alcohol in place of exercise [29•, 32, 47].

Finally, exercise challenges must be conducted in a controlled environment. Vital signs should be continuously monitored. Adequate medical supervision is mandatory to treat anaphylaxis.

Management

Management of EIAN and FDEIAN focuses on recognition of symptoms and limitation of activities that may precipitate anaphylaxis. All patients should be prescribed epinephrine autoinjectors and given an anaphylaxis action plan [82]. This should include patient education regarding triggers, symptom progression, and treatment [83].

Many patients will continue to exercise despite previous episodes of anaphylaxis. This should be encouraged, assuming proper precautions are taken. First, physical activity should resume slowly. Second, all patients should exercise with an “exercise partner.” This person should be aware of the diagnosis, comfortable administering IM epinephrine, and alerting 911 if necessary. Third, in the case of FDEIAN, patients should be cognizant of cofactors. This includes avoiding food consumption for 4–6 h prior to exercise [2, 68]. Aspirin should be avoided for 24–48 h prior to exercise. Caution should be used if exercising outdoors during peak

pollen season and/or high temperature and humidity. Finally, patients should always stop exertion at the first sign of symptoms. Continuing through symptoms may precipitate fulminant anaphylaxis.

Data for medical therapy of EIAN and FDEIAN is limited. There are no randomized controlled trials and data is limited to case reports. Antihistamines are generally prescribed as first-line therapy. H1-antagonists may delay progression and severity but are unlikely to prevent episodes [49, 84]. Antihistamines may be used as needed (at least 1–2 h prior to exercise) or regularly depending of frequency of symptoms and/or exercise. Sodium cromolyn has been reported to be effective in several case reports [85–87]. Based on the limited data, cromolyn is most effective when used 20–30 min before meals.

Omalizumab has also been used for EIAN. Omalizumab improves other types of anaphylaxis such as idiopathic and mastocytosis-associated anaphylaxis [88–90]. Several case reports note improvement in patients refractory to other medications [91, 92]. Peterson and Coop describe a patient with complete resolution of symptoms which recurred upon discontinuation of omalizumab. He has since been symptom free on omalizumab for more than 5 years [93].

There is limited data regarding the natural history of EIAN and FDEIAN. The largest longitudinal study reported a decrease from 14.5 to 8.3 events per year over 10 years [49]. The mechanism is likely multifactorial: increased awareness of symptoms, proper medical therapy, and avoidance of triggers. Finally, although fatalities are exceedingly rare, there are two case reports of fatal FDEIAN [94, 95]. Each case was complicated by an additional variable: severe asthma in the first patient, and lack of IM epinephrine in the second.

Gaps in the Literature

The pathophysiology of EIAN and FDEIAN are not fully understood and therapy has not been rigorously studied. There is a significant unmet need for additional research. The limited prevalence of both disorders has been a barrier to research and well-controlled clinical trials.

There is a need for mechanistic studies, particularly in EIAN. A more detailed understanding of the pathophysiology will lead to better management and treatment strategies. As above, several hypotheses have been proposed, but all are limited to case reports and case series. Regarding FDEIAN, there is a need for research investigating the mechanism and potency of cofactors. Aspirin (and other NSAIDs), ethanol, and exercise have been proven to impact severity of anaphylaxis. Are these cofactors dose dependent? Are there other cofactors? Do all impact symptoms by increasing intestinal permeability?

Another area for investigation is therapy of EIAN and FDEIAN. Current management relies on avoiding food and/or limiting exercise. Antihistamines, cromolyn, and omalizumab have been reported to reduce symptoms although none of these medications have been studied in a prospective manner. In particular, omalizumab appears to be a promising treatment option but warrants further evaluation in a controlled trial.

The main barrier to research has been limited disease prevalence and lack of an organized research network. The European Academy of Allergy and Clinical Immunology (EAACI) has proposed a global research network to pool patients and adequately power studies to better understand the pathophysiological mechanisms in EIAN and FDEIAN [5]. Progress to date has been slow although an organized global or nationwide network may accelerate research efforts.

Conclusions

Exercise-induced anaphylaxis and food-dependent, exercise-induced anaphylaxis are rare disorders characterized by symptoms of anaphylaxis associated with physical exertion. The pathophysiology of these conditions is not completely understood. Accumulating evidence indicates FDEIAN is a primary IgE-mediated food allergy augmented by cofactors (exercise, NSAIDs, alcohol) which modulates intestinal permeability and increases antigen availability in the bloodstream. The mechanism of EIAN is poorly understood.

Both conditions are clinical diagnoses. Symptoms must occur during or shortly after exercise. Proper workup to exclude other conditions is recommended. In the case of FDEIAN, it is necessary to demonstrate evidence of food sensitivity via prick test or serum-specific IgE.

The mainstay of treatment is modification of exercise and avoidance of trigger foods. All patients should exercise with a partner and carry IM epinephrine at all times. Recommendations for patients with FDEIAN include avoidance of food 4–6 h prior to exercise and avoiding other cofactors such as NSAIDs and alcohol.

The mechanism of these conditions is incompletely understood. There is a clear need for additional research to understand the mechanism of disease. In addition, data regarding efficacy of treatment is limited. Prospective studies investigating the efficacy of specific treatments are necessary.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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