

# Diagnosis of exercise-induced anaphylaxis: current insights

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**Abstract:** Exercise-induced anaphylaxis (EIA) is defined as the occurrence of anaphylactic symptoms (skin, respiratory, gastrointestinal, and cardiovascular symptoms) after physical activity. In about a third of cases, cofactors, such as food intake, temperature (warm or cold), and drugs (especially nonsteroidal anti-inflammatory drugs) can be identified. When the associated cofactor is food ingestion, the correct diagnosis is food-dependent EIA (FDEIA). The literature describes numerous reports of FDEIA after intake of very different foods, from vegetables and nuts to meats and seafood. One of the best-characterized types of FDEIA is that due to  $\alpha$ 5-gliadin of wheat, though cases of FDEIA after wheat ingestion by sensitization to wheat lipid transfer protein (LTP) are described. Some pathophysiological mechanisms underlying EIA have been hypothesized, such as increase/alteration in gastrointestinal permeability, alteration of tissue transglutaminase promoting IgE cross-linking, enhanced expression of cytokines, redistribution of blood during physical exercise leading to altered mast-cell degranulation, and also changes in the acid–base balance. Nevertheless, until now, none of these hypotheses has been validated. The diagnosis of EIA and FDEIA is achieved by means of a challenge, with physical exercise alone for EIA, and with the assumption of the suspected food followed by physical exercise for FDEIA; in cases of doubtful results, a double-blind placebo-controlled combined food–exercise challenge should be performed. The prevention of this particular kind of anaphylaxis is the avoidance of the specific trigger, ie, physical exercise for EIA, the assumption of the culprit food before exercise for FDEIA, and in general the avoidance of the recognized cofactors. Patients must be supplied with an epinephrine autoinjector, as epinephrine has been clearly recognized as the first-line intervention for anaphylaxis.

**Keywords:** anaphylaxis, exercise-induced anaphylaxis, food-dependent exercise-induced anaphylaxis, epinephrine autoinjector

## Introduction

The term “anaphylaxis” defines an acute, life-threatening, generalized reaction with various clinical presentations that concern the skin, respiratory, gastrointestinal, and cardiovascular systems.<sup>1,2</sup> Recent epidemiological surveys have found a prevalence of anaphylaxis of less than 2% in children<sup>3</sup> and ranging from 1.6% to 5.1% in adults.<sup>4</sup> Anaphylaxis may be caused by a variety of triggers, which may be grouped under two major mechanisms: IgE-mediated and non-IgE-mediated.<sup>5</sup>

## IgE-mediated anaphylaxis

The most common cause of anaphylaxis is exposure to specific allergen to which a subject is sensitized. Allergens related to IgE-mediated mechanism are foods, insect

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venoms, latex, antibiotics, such as  $\beta$ -lactams, general anesthetics, and biological agents.<sup>6</sup>

## Non-IgE-mediated anaphylaxis

Anaphylactic reactions from nonsteroidal anti-inflammatory drugs (NSAIDs) are mostly non-IgE-mediated, while hypersensitivity reactions to chemotherapeutic drugs, general anesthetics, or biological agents may or may not be IgE-mediated.<sup>1,7–10</sup>

## Mast-cell disorders

Mast-cell disorders may sustain severe reactions in association with exposure to allergens (especially insect venoms and foods), but may also act directly in the frame of mast cell-activation syndromes.<sup>11,12</sup>

## Idiopathic anaphylaxis

The use of the term “idiopathic” refers to anaphylaxis with no identification of causes, but the number of diagnoses of this kind of anaphylaxis is declining, due to the increasing recognition of a mast-cell disorder as the actual cause. The correct diagnosis can be confirmed by measuring tryptase (the mediator exclusively produced by mast cells)<sup>13</sup> or detecting mast-cell clonality by bone marrow examination.<sup>14</sup> Unfortunately, the measurement of serum tryptase is not often feasible clinically.

## Exercised-induced anaphylaxis

The occurrence of anaphylactic symptoms after physical activity defines the type of exercise-induced anaphylaxis (EIAN).<sup>15</sup> Here, we review the updated literature on pathophysiological mechanisms and diagnosis of EIAN.

## Clinical characteristics of EIAN

Physical exercise may elicit specific forms of asthma or urticaria, but the diagnosis of EIAN relies upon the development after any kind of physical activity of different symptoms that include skin symptoms (itching, flushing, hives, angioedema), respiratory symptoms (wheezing, dyspnea), gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), and cardiovascular symptoms (hypotension, collapse, loss of consciousness).<sup>15</sup> Subjects of any age are involved, with a reported age range of 4–74 years.<sup>16</sup> The exercise intensity able to elicit symptoms is variable, even in the same subject.<sup>17</sup> EIAN is relatively rare, as suggested by the largest epidemiological study available (including 76,229 adolescents), that detected a prevalence of 0.048%.<sup>18</sup> According to data from registries for anaphylaxis in European countries, about 30% of cases of EIAN are associated with cofactors.<sup>19</sup> The most important cofactor is food ingestion. The first report dates back to 1979, when the case of a patient who experienced anaphylaxis after eating shellfish and performing strenuous exercise was described.<sup>20</sup> Since then, a large series of reports have expanded the number of foods responsible, including several vegetables, cereals, nuts, fish, cow's milk, beef, pork, chicken/turkey, snails, and mushrooms,<sup>20–70</sup> as shown in Table 1. To diagnose food-dependent exercise-induced anaphylaxis (FDEIAN), it is required that physical exercise or food consumption alone do not cause any reaction, while their combination elicits anaphylactic symptoms.<sup>15</sup> Early studies reported that a meal with any food (nonspecific FDEIAN) before exercising was able to trigger reactions,<sup>71</sup> but today it is clear that such a subtype is much rarer than FDEIAN. It is similarly rare that anaphylaxis is elicited only if two different foods are simultaneously ingested.<sup>37,72</sup>

**Table 1** Food-dependent exercise-induced anaphylaxis papers in the literature are reported

Author	n	Age, years	Food/s responsible
Maulitz et al <sup>20</sup>	1	31	Shrimp, oysters
Kidd et al <sup>21</sup>	4	20–39	Celery (3 cases), any food (1 case)
Buchbinder et al <sup>22</sup>	1	24	Peach, grape
Sheffer and Austen <sup>23</sup>	3	12–54	Not identified
Kushimoto and Aoki <sup>24</sup>	3	19–67	Wheat
McNeill and Strauss <sup>25</sup>	1	19	Shrimp
Akutsu et al <sup>26</sup>	3	Data not available	Wheat (2 cases), most likely wheat (1 case)
Debavelaere et al <sup>27</sup>	1	12	Orange
Dohi et al <sup>28</sup>	11	7<20 4>30	Shellfish, grapes, wheat (7 cases), none identified (4 cases)
Fukutomi et al <sup>29</sup>	4	12–14	Shrimp (2 cases), hen's eggs (1 case), any food (1 case)
Añibarro et al <sup>30</sup>	1	12	Apple + cold
Muñoz et al <sup>31</sup>	1	13	Hazelnut
Tilles et al <sup>32</sup>	1	16	Pizza, cheese sandwich
Caffarelli et al <sup>33</sup>	4	<12	Tomato, chestnut, pea, rice, hen's eggs, beans, wheat, garlic, pine nuts
Caffarelli et al <sup>34</sup>	1	14	Cuttlefish

Author	n	Age, years	Food/s responsible
Asero et al <sup>35</sup>	1	15	Poultry, hen's eggs
Okano and Sakuma <sup>36</sup>	1	17	Matsutake mushrooms
Biedermann et al <sup>37</sup>	1	72	Pork
Longo et al <sup>38</sup>	1	14	Snail, beefsteak, ham, wheat
Kano et al <sup>39</sup>	18	9–43	Wheat (9 cases), unknown (5 cases), shrimp (2 cases), shellfish (1 case), fish (1 case)
Shimizu et al <sup>40</sup>	1	13	Wheat
Harada et al <sup>41</sup>	3	18–48	Wheat (2 cases), shrimp (1 case)
Noma et al <sup>42</sup>	1	8	Buckwheat
Romano et al <sup>43</sup>	48	13–47	Tomato (14 cases, 29.2%), wheat (8 cases, 16.7%), peanuts (8 cases, 16.7%), maize (6 cases, 12.5%), soybeans (5 cases, 10.4%), lettuce, fennel, shrimp, peas (3 cases, 6.2%), beans, lentils, garlic, walnuts, almonds, peaches (2 cases, 4.2%), pork/beef, hazelnuts, apples, rice, bananas (1 case, 2.1%)
Pérez-Calderón et al <sup>44</sup>	1	26	Onion
Mathelier-Fusade et al <sup>45</sup>	7	16–50	Wheat (2 cases), maize (1 case), barley (1 case), shrimp (1 case), apple (1 case), paprika and mustard (1 case)
García-Ara et al <sup>46</sup>	1	16	Milk
Matsuo et al <sup>47</sup>	6	15–61	Wheat
Porcel et al <sup>48</sup>	1	16	Pistachios
Tewari et al <sup>49</sup>	1	13	Peanuts, hen's eggs
Wong and Mace <sup>50</sup>	1	41	Chickpeas
Oyefara and Bahna <sup>51</sup>	1	16	Wheat
Du Toit <sup>52</sup>	2	7–14	Cashew nuts (1 case), wheat (1 case)
Orhan and Karakas <sup>53</sup>	1	17	Lentil, chickpeas
Pacharn et al <sup>54</sup>	5	8–14	Wheat
Mu et al <sup>55</sup>	1	18	Wheat
Baek et al <sup>56</sup>	1	18	Celery–mugwort–birch syndrome
Bianchi et al <sup>57</sup>	1	12	Peaches, cherries
Jo et al <sup>58</sup>	1	19	Walnuts + warm
Ahanchian et al <sup>59</sup>	1	32	Wheat
Kaneko et al <sup>60</sup>	1	13	Apples
Mobayed and Al-Nes <sup>61</sup>	2	14–15	Wheat, nuts
Pastorello et al <sup>62</sup>	3	15–21	Wheat (lipid transfer protein [LTP])
de Silva et al <sup>63</sup>	19	9–45	Wheat
Ono et al <sup>64</sup>	1	10	Citrus fruit
Iijima et al <sup>65</sup>	1	12	Japanese apricots, peaches
Kobayashi et al <sup>66</sup>	14	21–73	Wheat (sensitized by hydrolyzed wheat protein in soap)
Roberts and Ben-Shoshan <sup>67</sup>	1	17	Chickpeas
Brockow et al <sup>68</sup>	16	23–76	Gluten + exercise (4 cases), gluten + acetylsalicylic acid + alcohol + exercise (10 cases), gluten + submaximal exercise (2 cases)
Hotta et al <sup>69</sup>	1	54	Peaches (peamaclein [Pru p 7])
Asaumi et al <sup>70</sup>	20	5–22	Wheat (4 cases), wheat + shrimp (2 cases), wheat + apples (2 cases), peaches (2 cases), maize (1 case), wheat + buckwheat (1 case), wheat + maize + shrimp (1 case), wheat + shrimp + taro (1 case), carrots (1 case), carrots + oranges (1 case), oranges (1 case), tangerines (1 case), apples (1 case), shrimp (1 case), shrimp + eggs + wheat + kiwifruit (1 case), fish (1 case), chicken (1 case)

All challenges performed after administration of 10 mg/kg acetylsalicylic acid (maximum 500 mg)

Other cofactors needed to cause anaphylaxis from physical exercise have been identified in exposure to warm<sup>58</sup> or cold temperature,<sup>40</sup> menstrual cycle,<sup>28</sup> metal-containing dental amalgams,<sup>73</sup> and drug intake, especially NSAIDs. In Table 2, we summarize FDEIA cofactors reported in the literature. Concerning warm temperature, in its early phase (ie, before respiratory or cardiovascular symptoms appear), EIA must be differentiated from cholinergic urticaria, which is a form of urticaria associated with elevation of body temperature,

possibly triggered by exercise, hot showers, and ingestion of hot or spicy foods.<sup>74</sup> The role of NSAIDs was reviewed by Sheffer and Austen in 1984,<sup>23</sup> and acetylsalicylic acid is the best-investigated agent.<sup>41,47</sup> When one of the aforementioned cofactors reported is present before physical exertion, anaphylaxis symptoms develop mostly within 30 minutes from the onset of physical activity. However, a case of anaphylaxis 5 hours after intake of a wheat-containing meal has been reported.<sup>51</sup>

**Table 2** Cofactors of food-dependent exercise-induced anaphylaxis reported in the literature

Cofactor	References	Number of patients
Physical exercise	20–70	176
Physical exercise with cold temperature	30, 40	2
Physical exercise with warm temperature	58, 23	9
Menstrual cycle	32	1
NSAIDs	23, 28, 41, 43, 47	50
H <sub>2</sub> -receptor antagonist or PPI	–	–
Alcohol assumption	–	–
Infectious disease	–	–

**Abbreviations:** NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton-pump inhibitor.

## Mechanisms underlying EIAN

As with anaphylaxis in general, the release of mediators by mast cells is considered of critical importance, as suggested by direct observation from skin biopsies<sup>75</sup> and detection in serum of histamine<sup>76</sup> and tryptase.<sup>77</sup> This mechanism is certain in anaphylaxis when mast-cell degranulation is induced by IgE antibodies, but remains unclear in EIAN. In fact, even in FDEIAN, despite the patient being sensitized to specific foods, the food ingestion alone is unable to trigger the reaction, which occurs instead when there is physical exertion after eating the food. Therefore, other pathophysiological mechanisms are likely to be involved. The recent European Academy of Allergy and Clinical Immunology (EAACI) position statement on EIAN reviewed the current hypotheses proposed to explain this kind of anaphylaxis.<sup>78</sup> The first hypothesis concerns the increase in gastrointestinal permeability that should be caused by relaxation of the intestinal tight junctions induced by thermal injuries, NSAID intake, prolonged exercise allowing the passage of large molecules triggering EIAN,<sup>47</sup> or by impairment of gut permeability resulting in endotoxins entering the circulation, the latter being associated only with very prolonged exercise.<sup>79</sup> Another mechanism altering the gut mucosa should concern wheat as a causative food, and particularly its antigen  $\omega$ 5-gliadin, because of alterations in tissue transglutaminase, resulting in peptide aggregation and increased IgE cross-linking,<sup>80</sup> augmented production of IL-6 occurring during exercise, which increases the expression of tissue transglutaminase,<sup>81</sup> should favor this mechanism.

Other hypotheses have focused on the effect of physical exertion on blood. The redistribution of blood flow from visceral organs to skeletal muscle, skin, and heart caused by even light exercise is well known. Since this also results in

transport of allergens from the gut, where mast cells have precise functional and metabolic characteristics, to the skin and skeletal muscle, where there are phenotypically different mast cells, an altered mediator release should occur.<sup>82</sup> In addition, the known increase in plasma osmolality caused by prolonged exercise should rise basophil releasability and histamine production.<sup>83</sup> Finally, the changes in acid–base balance associated with exercise should lead to a cellular-reduced pH, triggering mast-cell degranulation.<sup>84</sup> The authors of the EAACI position statement accurately revised the available literature, concluding that all the proposed mechanisms lacked validity and recommending the development of a global research network on EIAN to gain sufficient power for scientific evaluation.<sup>78</sup>

## Diagnosis of EIAN

The diagnosis of EIAN is not simple. The first component is a history of symptoms suggesting anaphylaxis, with involvement of cutaneous, respiratory, gastrointestinal, and cardiovascular systems within 2 hours, often within 30 minutes, from exposure to a causative agent.<sup>1,2</sup> In the case of EIAN, the agent is physical exertion, regardless of its intensity, but quite frequently a cofactor is needed to elicit the reaction. Therefore, clinical history must be very accurate to identify the cofactor, with major importance for foods, followed by NSAIDs and more rarely warm or cold temperature. Concerning foods, a large array of foodstuffs may be responsible, but cereals, peanuts, tree nuts, tomatoes, and seafood are more frequently involved. Allergy testing, including skin tests and in vitro tests, is indicative of sensitization, but its results must be combined with the history to detect the culprit food.

## Laboratory testing

In vitro testing offers the advantage of assessing sensitization to single allergen molecules in place of whole-allergen extracts by the technique of component-resolved diagnosis, thus providing better precision.<sup>85</sup> For example, in ten patients with suspected FDEIAN from wheat, high levels of IgE against  $\omega$ 5-gliadin were detected in all cases.<sup>86</sup> Of interest, in a patient with wheat-dependent EIAN, the responsible allergen was identified as LTP and not  $\omega$ 5-gliadin.<sup>62</sup> On the other hand, LTPs were reported to be the most frequent primary allergens in a group of Italian patients with FDEIAN.<sup>87</sup> Also, a role for the basophil-activation test, which is based on the expression of CD203c on the basophil surface following incubation with the causative allergen, is emerging in FDEIAN.<sup>85</sup>

## In vivo testing

In diagnosing food allergy, the in vivo test to be considered as a reference standard is challenge with the suspected food.<sup>70,88</sup> In patients with suspected EIAN or FDEIAN, the challenge must be performed under strict medical control, with blood pressure and lung-function monitoring and prompt availability of drugs and equipment to manage anaphylaxis. First, an exercise test on fasting should be performed. If positive, the diagnosis of EIAN is achieved; if negative, an exercise test after 1 hour from the assumption of the suspected food should follow.<sup>15</sup> Still, the test may give false-negative results.<sup>43</sup> The need of concomitant factors, such as cold or warm temperature<sup>58,40</sup> or other particular characteristics of the environment where EIAN occurred, may partly account for such outcome.<sup>16</sup> Also, in 34 patients with wheat-dependent EIAN, a positive challenge was obtained only by using oral gluten flour (four patients) or gluten plus consumption of acetylsalicylic acid and alcohol as cofactors (ten patients), which were associated with significantly increased plasma gliadin levels.<sup>68</sup> Regardless of the food suspected, when the results of the open challenge in patients with FDEIAN are positive but doubtful, a double-blind placebo-controlled combined food–exercise challenge is indicated.<sup>89</sup>

## Treatment and prevention of EIAN

The acute treatment of EIAN does not differ from the treatment of anaphylaxis in general, being based as first-line intervention on epinephrine 1:1,000 (1 mg/mL) at a dose of 0.2–0.5 mg in adults and 0.01 mg/kg in children, by the intramuscular route. The role of corticosteroids and antihistamines, though they are more used than epinephrine, is ancillary.<sup>1,2</sup> Also, patients with EIAN must carry with them an epinephrine autoinjector to be used quickly in case of a reaction, following detailed instructions by physicians on how to use it.<sup>1,2</sup> Another important factor in anaphylaxis is that the patient must be placed or place themselves in the Trendelenburg position (lying on the back with legs elevated), in order to prevent the “empty-ventricle syndrome” and to favor blood flow to the heart.<sup>90</sup>

The best prevention is educating the patients in avoiding the triggers, ie, physical exercise when EIAN without a cofactor is concerned or avoiding the various cofactors. If the cofactor is a food, its ingestion before exercise or within 1 hour after exercise in FDEIAN must be abolished.<sup>16</sup> Concerning prophylactic drug treatment, there are reports suggesting the utility of chromones, antihistamines, leukotriene antagonists, and corticosteroids, but scientific evidence supporting their recommendation is lacking.<sup>15,16</sup> The effectiveness

of prevention measures was evaluated in a study on 279 patients with EIAN with an average duration of 10.6 years of anaphylactic reactions (most frequently triggered by such activities as jogging or brisk walking). It was found that the frequency of EIAN attacks had decreased (47% of patients) or stabilized (46% of patients) compared to the onset of the disease; 41% of patients reported they were completely free of attacks in the past year. The frequency of the attacks was reduced by avoiding exercise during extremely hot or cold weather (44%), avoiding eating certain foods before exercise (37%), and restricting exercise during seasonal allergy (36%) or humid weather (33%). The most common pharmacologic agents used to manage symptoms were H<sub>1</sub> antihistamines (56%) and/or epinephrine (31%), but 28% of patients did not use any treatment.<sup>91</sup>

In FDEIAN, desensitizing the patient to the causative food(s) should have a critical role in preventing the reactions, comparable to immunotherapy with Hymenoptera venom in patients with anaphylaxis from insect stings. However, though an increasing number of studies on oral, sublingual, and recently also epicutaneous immunotherapy have been published, immunotherapy for foods is not yet approved in a consensus document, and due to the unavailability of commercial preparations is not included in clinical practice.<sup>92</sup>

## Conclusion

EIAN and FDEIAN are rare disorders that need a careful diagnosis, because they are associated with a risk of life-threatening anaphylactic reactions. The diagnostic workup is quite demanding, and (especially for FDEIAN) requires thorough investigation to identify the culprit food. The two mainstays of management are early treatment of the reaction by epinephrine, especially through patient self-administration using an autoinjector, and prevention of further episodes. The latter needs adequate information and education of patients on how to keep away from the specific triggers.

## Disclosure

The authors report no conflicts of interest in this work.

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