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Anaphylaxis (M Sánchez-Borges, Section Editor)

Food-Dependent Exercise-Induced Anaphylaxis

Maria João Vasconcelos, MD[1]
Luís Delgado, MD PhD[1,2]
Diana Silva, MD[1,2,*]

Address
[*,1]Serviço de Imunoalergologia, Centro Hospitalar de São João, EPE, Porto, Portugal
Email: disolha@gmail.com
[2]Basic and Clinical Immunology, Department of Pathology, Faculty of Medicine, University of Porto, Porto, Portugal

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Abstract

Purpose of review Food-dependent exercise-induced anaphylaxis (FDEIA) is a form of anaphylaxis that occurs associated with exercise, in which symptoms develop by the combination of food ingestion and physical activity. We aimed to review and discuss the main clinical recommendations for management of FDEIA, focusing on individual factors.
Recent findings New diagnostic strategies have been developed to optimize the accuracy of provocation challenges, taking in consideration augmenting factors, such as alcohol or non-steroidal anti-inflammatory drugs. However, FDEIA is still insufficiently diagnosed and a high index of clinical suspicion is usually required. Management is complex and based on preventing the reaction and education of the patient, followed by treatment of the acute episode. Several pharmacological strategies for prophylactic treatment have been proposed; however, they are based mainly in low quality of evidence.
Summary For management of FDEIA, the culprit food allergen should be avoided at least 4 h before exercise and the individual needs to be educated on how to practice exercise in safe conditions, particularly recognizing the importance of stopping exercise or physical activity at the earliest manifestation of symptoms. This prevention strategy should be developed accordingly to the specific characteristics of the individual and food allergen involved. Due to the difficulty in avoiding and preventing a reaction, pharmacological prophylactic treatment options, namely antihistamines, montelukast, oral cromolyn sodium, misoprostol, and omalizumab, have been proposed. However, they do not replace current recommendations. The risk and quality-of-life impact of FDEIA warrants more accurate diagnostic tools and management strategies. The improvement on the knowledge of the mechanisms mediating FDEIA will help to find new prevention and treatment targets.

Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a form of anaphylaxis that occurs associated with exercise, in which symptoms develop by the combination of food ingestion and physical activity [76]. When episodes of anaphylaxis occur after the ingestion of specific foods, to which the patient is sensitized, it is described as specific FDEIA (sFDEIA). While those occurring after the ingestion of any food are described as nonspecific FDEIA (nsFDEIA) [64, 70]. The combination of different foods and/or drugs, like non-steroidal anti-inflammatory drugs [2, 59], food processing [1], and the amount of food ingested, might have an influence on the triggering and severity of a FDEIA [13, 33].

FDEIA is uncommon but has been reported around the world and in patients of all ages [14], although adolescents and young adults make up the majority of the cases reported in the literature [3, 7, 24, 26, 27, 73]. Most cases are sporadic, although there are rare reports of family cases [26, 54]. The exact prevalence is unknown, as FDEIA seems to be underdiagnosed, since many patients with reported idiopathic anaphylaxis are not truly idiopathic when extensively studied [84]. A study with Japanese adolescents revealed a 0.02% frequency of FDEIA that was maintained after a 14-year follow-up, despite an increased awareness for the disease [3, 51]. The first described case of FDEIA was in 1979 with shellfish [53]; however, until now, several different foods have been involved.

The foods most commonly associated with FDEIA are wheat, specifically ω5-gliadin, and shrimp, but other foods may be implicated, differing accordingly to geographic distribution and cultural dietary habits [56, 73, 76]. In the Mediterranean area, vegetables are a common culprit allergen, mainly explained by the high prevalence of sensitization to lipid transfer protein (LTP) [32, 72–74]. Wheat and shellfish are prevalent in Asian populations [44, 51]. Large series of reports have expanded the number of foods responsible, including several fruits, peach [37], apple [43], orange [55], tomato [74], vegetables, cereals, nuts, fish, cow's milk, eggs, beef, pork, chicken/turkey, snails, and mushrooms [70, 74, 76]. Not only the type of food but also the intensity of exercise that is able to elicit symptoms is variable, even in the same subject [11].

High-intensity exercise practice modalities, such as jogging, dancing, aerobics, and sports involving sudden burst of sprinting, like football, are most often associated, although lower levels of activity (e.g., ironing or yard work) are capable of triggering FDEIA [45•, 77].

The mainstay approach to FDEIA is to avoid the culprit food associated with exercise and identify the potential augmenting factors [27]; this strategy needs to be adapted at the light of precision medicine [17] as this approach is dependent on several individual factors. Therefore, we aimed to review and discuss the main clinical recommendations for management of FDEIA, focusing on individual factors.

Clinical presentation

Symptoms of FDEIA most commonly develop within 30 min of the onset of physical activity, but may begin at any stage of exercise and occasionally after [65]. The culprit food is usually ingested within 4 h preceding exercise, despite the ingestion of the food immediately after exercise practice might also, less frequently, trigger a reaction [73].

The clinical presentation is similar to an anaphylactic reaction [83]. A typical episode usually begins, while the patient is exercising, with a sensation of diffuse warmth and flushing, followed by itching and urticaria and, in many cases, angioedema (typically of the face and hands) [27]. If exercise continues, other symptoms can occur, namely gastrointestinal (abdominal pain, nauseas, vomiting, diarrhea), respiratory distress symptoms, like bronchospasm, laryngeal edema, followed by dizziness, tachycardia, hypotension, and vascular collapse [26, 72, 77]. If the activity is ceased

immediately after the first symptoms, there is most often improvement or resolution within minutes [26, 72, 77].

The frequency of FDEIA episodes can be unpredictable, even in the same patient [26, 27]. Not only different levels of exercise intensity can trigger a reaction, but also different foods, food processing, and other co-factors can have a role [57].

Exercise is recognized as the most common augmenting factor for food allergy. Nevertheless, several other triggers might influence the immunological mechanisms inducing an anaphylactic reaction [26]. These include the following: (a) NSAIDs [30, 34, 59]—in the Mediterranean area, NSAIDs are involved up to 58% as a cofactor-induced food-related anaphylaxis episodes [16] and in up to 33% of cases of anaphylactic reaction that are induced by LTP [66]; (b) alcoholic beverages [13, 77]; (c) premenstrual or ovulatory phases of the menstrual cycle [9]; (d) extremes of temperature (either high heat and humidity or cold exposure) [41, 77, 79]; (e) seasonal pollen exposure in pollen-sensitized patients [77] and infections [89].

Concomitant and uncontrolled diseases, such as asthma, unrecognized clonal mast cell disorders, and cardiovascular disease, can lower the threshold for symptoms and are associated with more severe reactions and increased mortality [17, 60].

Pathophysiology

The exact mechanism by which the ingestion of one or more foods, to which the patient is sensitized to, could provoke an adverse reaction only when combined with exercise is still not fully understood. The role of exercise as an augmenting factor for an allergic reaction might be mediated by the lowering of the threshold for a reaction, an increase of the severity of the reaction or by reversing acquired clinical tolerance [61]. Several hypotheses have been proposed, particularly derived from mechanisms mediating exercise-induced anaphylactic reactions [4]:

1. Exercise may induce changes on *gastrointestinal permeability* [39], induced by epithelial cell damage. This will increase the absorption of recently ingested, but incompletely digested, food proteins into the circulation, reaching higher peak concentrations of the allergen [10]. Afterwards, allergens migrate into the perivascular and tissue spaces where mast cells armed with allergen-specific IgE reside [56], inducing their activation and causing a reaction. Nevertheless, research testing this hypothesis, using current exercise physiology, lacks plausibility that only exercise load could lead to such a significant change in gastrointestinal permeability [4]. Concomitant intake of NSAIDs or alcohol, which also increases gastric permeability, might increase the likelihood of symptoms and support this mechanism [30, 34]. Another factor is that gastric acid secretion is suppressed during the exercise and only starts to rise gradually after cessation; this could consequently reduce digestion of some food allergens leading to the absorption of more structurally intact allergens absorbed across the epithelial barrier, crossing the threshold for IgE-mediated mast cell degranulation. For some allergens, such as LTPs, that are already partially resistant to digestion, this may be particularly significant [18].

2. Exercise induces a *blood flow redistribution* from visceral organs to skeletal muscle and skin. This results in transport of structurally intact food allergens from the gut to the skin and skeletal muscle where there are phenotypically different mast cells, which may have a lower threshold for degranulation [4, 18, 26]. This hypothesis is still not supported by experimental evidence.
3. Exercise induces a *transient serum hyperosmolality* due to airway water evaporation, which increases histamine release from the basophils after allergen exposure [7]. Nevertheless, in the studies supporting this hypothesis, the plasma osmolality levels needed to promote histamine release and basophil activation would be clinically pathological in vivo.
4. *Autonomic nervous system dysregulation*. Intensive training may promote vagal hegemony with resting bradycardia, but increased bronchomotor tone and susceptibility to bronchospasm [26]. However, this does not explain the reactions associated with specific foods.
5. Changes in *acid–base balance* associated with exercise can occur, although only with very high work levels. This appears to induce a reduction of cellular pH. Mast cell instability has been seen associated with low levels of pH (< 7.0) [4, 88]. However, these levels are usually pathological.
6. Exercise may induce changes in the *allergen processing* within the gastrointestinal tract, leading to increased allergenicity. In patients with wheat-dependent exercise-induced anaphylaxis, exercise activates the intestinal enzyme tissue transglutaminase that is capable of binding and aggregate gliadin moieties to form large immunogenic complexes, showing increased IgE binding and thus enable them to more efficiently elicit mast cell degranulation [69]. On the other hand, contracting skeletal muscles have been shown to increase interleukin-6, an inflammatory mediator that upregulates the expression of tissue transglutaminase [18].

Until now, none of these working hypotheses have been completely validated and each mechanism alone is unlikely to be sufficient to elicit a reaction, despite these appear to be IgE-mediated reactions, given the presence of positive skin tests and/or serum-specific IgE to the foods reportedly ingested before the reaction [3, 30, 54].

Diagnosis

The diagnosis of FDEIA, is based on a careful history of events surrounding each episode and exclusion of other disorders that could present similarly [26]. A prolonged time lag (32–62 months) until the diagnosis is not uncommon [90] and a high index of clinical suspicion is required. Diagnosis of FDEIA is usually based on the previously suggested clinical criteria [27, 80] that are summarized in Table 1.

Clinical history should question the patients to list all foods (including drinks or supplements) consumed within 24 h prior to each episode and should focus on a detailed timeline of the events. Foods repeatedly eaten prior to exercise without provoking symptoms and episodes occurring while the patient was fasting should also be documented. The season of the year in which the episodes occurred should be considered, namely pollen season, as well as environmental conditions (extremes of cold/heat

Table 1. Clinical diagnostic criteria proposed for food-dependent exercise-induced anaphylaxis [15, 52]

Clinical diagnostic criteria
Signs and symptoms consistent with anaphylaxis according to World Allergy Organization criteria [64]
Onset of symptoms that occurred during or within an hour of exercise
Exercise was preceded by food ingestion (symptoms occurred within 4 h of ingesting the implicated food)
No symptoms on the ingestion of food in the absence of exercise or with exercise alone
If a specific food is implicated
Evidence of specific IgE to the implicated food (skin testing or by food-specific IgE)
No symptoms are described on the ingestion of that food in the absence of exercise
No symptoms if exercise occurs without ingestion of that food

or humidity). Concomitant medication should be enumerated (especially NSAIDs, ACE inhibitors, beta blockers).

Usually, no physical findings are specific in patients with FDEIA. Potentially relevant findings include signs of allergic diseases, such as stigmata of longstanding allergic rhinitis. A meticulous skin examination should be performed to ensure that *urticaria pigmentosa*, the characteristic skin finding in mastocytosis, is not present. Most patients develop urticaria during episodes with wheals that are larger than the ones of cholinergic urticaria.

A baseline serum tryptase level should be measured; elevated baseline values suggest clonal mast cell disorders. Elevations in serum tryptase immediately after an episode support the diagnosis of anaphylaxis, but do not provide information about exercise or food/exercise as the trigger [26].

Skin testing or in vitro testing for allergy evaluation

Allergy testing, including both in vivo (skin tests) and in vitro (total and specific IgE), chosen according to the clinical suspicion, is essential to FDEIA evaluation because sensitization to the precipitant food(s) is demonstrable, with rare exceptions [46]. Initial evaluation with commercial skin-prick tests and specific IgE immunoassays is usually followed by skin-prick-to-prick tests with fresh food, as these tests have a higher sensitivity [35]. Testing for aeroallergen sensitization could be useful in the evaluation of FDEIA if specific co-triggers are suspected, namely reactions that occur only during certain pollen seasons [27].

Recently, an immunoassay-based approach with specific IgE detection using the immuno solid-phase allergen chip (ISAC) microarray system allows to assess a vast panel of allergenic molecule panel, including panallergens, and provides a better precision [52]. In a study by Romano et al. [74], ISAC microarray allowed to identify a common allergenic determinant, LTP, as the most frequent primary allergens in a large group of Italian patients with FDEIA. Component-resolved diagnosis is useful to identify both primary and cross-reactive allergenic compounds involved in polysensitization [87].

Basophil-activation test is emerging [57], and although it allows to predict causative food allergen, it is not able to confirm diagnosis. Another test, also used to guide dietary elimination recommendations, particularly when exercise

challenge is not recommended, is the use of an in vitro immunodepletion procedure [81].

Provocation tests

The gold standard for FDEIA diagnosis is still provocation tests that include a food challenge, an exercise challenge, followed by a combined food–exercise challenge [56]. There is no established protocol for food–exercise challenge evaluation and several protocols have been used [3, 5, 70, 74, 75]. Furthermore, these procedures were not able to confirm diagnosis in up to 30% of the patients, even in those that clinically had recurrent and reproducible FDEIA [3, 13, 33, 56, 72, 73].

A positive challenge for FDEIA includes a negative isolated exercise challenge and a negative food challenge, but when food is combined with exercise, it triggers one or more allergic symptoms [83]. It is consensual that the challenges must be performed under strict medical control, with cardiopulmonary monitoring, trained personnel for emergency intervention, and prompt availability of drugs and equipment to manage anaphylaxis. A treadmill ergonometric stress test with progressively increasing speeds is typically used [74].

Many difficulties surround the use of provocation challenges in FDEIA. In subjects with multiple food hypersensitivity, probably not all the positive foods are responsible. It would be useful to establish the causative role played by each one by performing exercise challenges after their ingestion, but that approach is not only harmful but also time-consuming and costly [32, 73].

Several hypotheses are suggested to explain the high rate of false negatives: the role of co-factors, namely certain drugs (NSAIDs), alcohol, menstruation/ovulatory phase, stress, or unfavorable atmospheric conditions; the amount of food and its processing [1, 26], as well as ingestion of combined foods [2, 3, 28]. The time of the meal and the intensity of exercise need to be individualized to reproduce, as closely as possible, the events of the subject's previous reactions [72]. To improve diagnostic accuracy, different protocol changes have been tried, namely by administering greater amounts of food, ingesting the suspected foods along with aspirin, or consuming alcohol 90 min before exercise [5, 13, 47, 52, 59]. Despite some of these strategies have been proved to increase the rate of positive challenges, they have been also associated with severe reactions and an increase of epinephrine administration [5, 36].

Therefore, a positive challenge allows to establish the causative role of a particular food, but a negative response is more difficult to interpret and does not necessarily discard the suspicion [72].

Management

FDEIA management is based on preventing a reaction and treatment of the acute episode. Currently, there is no prospective data or studies on the optimal management of FDEIA; therefore, recommendations are usually individualized [75]. The prevention strategy is based on a series of clinical recommendations to patients and community that include education regarding the recognition of clinical symptoms and immediate treatment (Fig. 1).

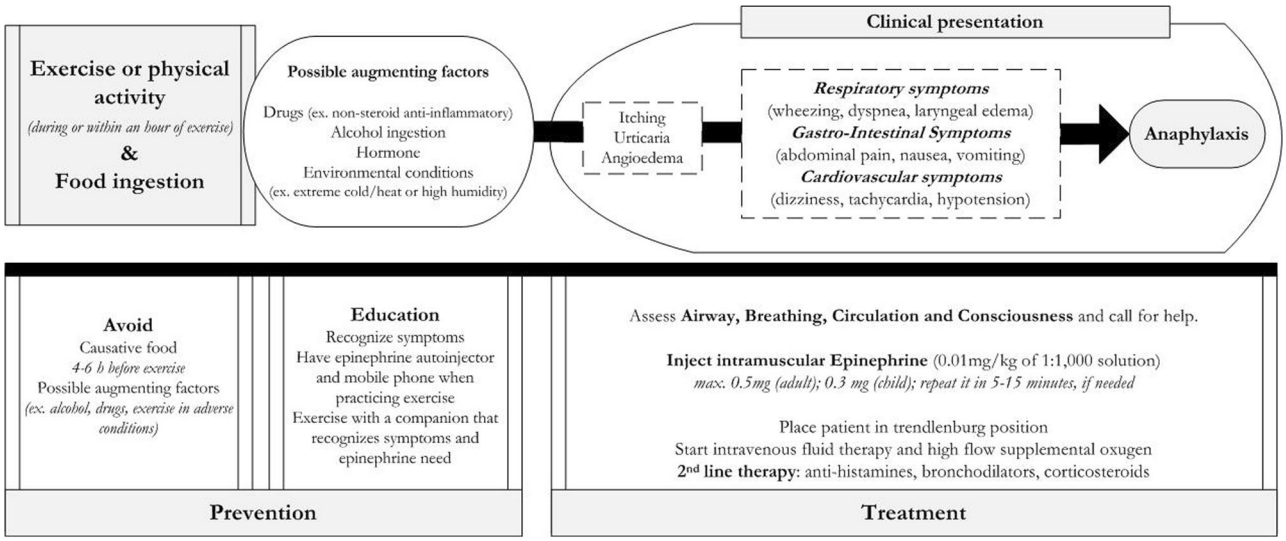

Fig. 1. Integrated management of food-dependent exercise-induced anaphylaxis

Prevention and education

Management does not involve advising the patient to refrain from exercise on a permanent basis. Avoidance of the triggering activity often is prudent in the period between the onset of symptoms and the initial evaluation, but it should not be necessary after complete diagnostic workup [26]. Until triggers that induce symptoms are identified and avoided, exercise should be performed with a partner that is informed to recognize early signs and administer epinephrine [27]. Once evaluation has been completed and recommendations established, patients may resume exercise gradually, starting with a low-level exertion and gradually increase their activity over weeks to months [26].

For patients diagnosed with nsFDEIA, avoidance of any type of meals 4 to 6 h before exercise and within 1 h after [70] is recommended. Time may be reduced, but not under a minimum of 2 to 3 h [27]. A strategy frequently recommended is to exercise in the morning before eating anything [27]. If a specific food allergen was confirmed, or is highly suspected, all foods that contain that food allergen should be avoided during the same period. Using the clinical history and recognizing foods that have been repeatedly consumed prior to exercise without causing reactions might help to provide a list of "safe" foods that can be suitable to eat before [72]. In children, who are usually active throughout the day, athletes that need to eat before exercise practice, or those that have physically active jobs, it is often suitable to remove completely the causative food/food allergen from the diet [27].

Patients, athletes, and amateurs at risk for FDEIA should learn to recognize their first symptoms and have an action plan to deal with future events [6, 26]. That includes stopping the exercise immediately at the first sign of symptoms. This might be challenging to follow, particularly in individuals that regularly practice high level of physical activity, like military personnel. Therefore, it might be needed to change work conditions or strictly avoid the food allergen from the diet.

At all exercise settings, patients should carry and know how to administer an epinephrine auto-injector, as it should be used if symptoms do not immediately improve with the cessation of exercise. Further important component in the management of FDEIA are the following: ensuring that exercise takes place under safe conditions, identifying causative foods, avoiding augmenting factors or co-triggers (e.g., alcohol, NSAIDs, high humidity) [76]. NSAIDs should be avoided for 24 h before exercise in patients with FDEIA [30]. Avoidance of β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be considered, because these drugs may increase the severity of anaphylaxis [82]. Optimizing the management of coexisting allergic disorders seems to be helpful in reducing the patient's overall reactivity.

Treatment

The acute treatment of FDEIA includes immediate termination of exercise at the earliest warning signs. Subsequently, it does not differ from the treatment of anaphylaxis, which has been addressed in previous guidelines [83].

The first-line intervention is epinephrine 1:1000 (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 [83] (Fig. 1). It reverses symptoms of airway edema, hypotension mediated by its α-1-vasoconstrictor effects, and induces bronchodilation and decrease of mediators release by its β-2-agonist action [82]. Depending of the initial response and the severity of the reaction, the dose can be repeated every 5 to 15 min, as needed [82, 83]. The patient should positioned and maintained in the supine position, while elevating the lower extremities, in order to preserve fluid in the circulation and prevent an empty vena cava syndrome [82]. Second-line medications can also be used, but should not delay the administration of epinephrine [82].

For further treatment of anaphylaxis symptoms, second-line treatments have been recommended, namely antihistamines, β-2-adrenergic agonists, and corticosteroids [82]. Inhaled short-acting β-2-agonists can be given for airway obstruction symptoms, namely wheezing or shortness of breath that are not completely relived after epinephrine injection. Antihistamines mitigate only cutaneous symptoms; although they are frequently used, they do not prevent or relieve hypotension or upper airway obstruction [82]. Corticosteroids are mainly used to prevent biphasic anaphylaxis and do not have a significant effect on initial symptoms [83]. Currently, there is no strong evidence that supports the use of these second-line treatments [21, 78]. After a reaction, the patient should be transported to the hospital, where further treatment can be performed, particularly if refractory anaphylaxis occurs [82]. The duration of observation should be risk-stratified and adapted to the clinical characteristics and severity [49].

Pharmacological treatment as a prophylaxis for FDEIA

There are no randomized trials of medications to prevent episodes of FDEIA, and recommendations are mainly based on case reports and clinical experience. Prophylactic medications are not needed in cases in which behavior can be modified and triggering foods and augmenting factors identified and avoided.

However, this is not feasible in all cases [27]. The patient should always be advised that this medication is not a reliable alternative to avoidance of the culprit food, but an additional protective measure.

Several published case reports suggest that high-dose *cromolyn sodium*, a mast cell stabilizer and antihistamine, taken orally before food ingestion can be useful in preventing FDEIA [1, 2, 42]. It acts by reducing the degranulation of mast cells, plasma histamine efflux, and the production of pro-inflammatory factors [50]. However, without controlled studies, it is unclear whether it is helpful for all patients and to what extent [27]. In a case report of an adult with wheat-dependent exercise-induced anaphylaxis (WDEIA), oral administration of disodium cromoglycate before ingestion of bread and exercise challenge prevented FEV1 decrease, symptoms, and increase in plasma histamine [42]. Similarly, in two children, the ingestion of sodium cromoglicate before lunch prevented new episodes of WDEIA [85]. Doses used in children were 100 mg and in adults 200 mg, taken with water 30 min before any meal that could be followed by exertion and up to four times a day [42, 85]. The oral formulation of sodium cromoglicate is not available in all countries, particularly in Europe [25]; therefore, access might not be easy.

Premedication with *antihistamines* has not been systematically studied. Clinical experience suggests that antihistamines do not prevent symptoms and some clinicians prefer not to initiate antihistamines due to concern for masking early symptoms [26]. There are case reports where oral taking of ketotifen or terfenadine before wheat consumption was associated with a negative exercise challenge in patients with WDEIA [20, 31]. However, this might also be due to the low reproducibility of provocation test. Two studies showed an effect when antihistamines were used in association with other drugs. In a case of an adolescent with peach-induced FDEIA, previous treatment with cetirizine associated with montelukast, a leukotriene receptor antagonist, induced a negative food–exercise challenge to peach and apples [67]. In another study, the association of fexofenadine with oral sodium cromoglicate avoided the symptoms of food–exercise-induced anaphylaxis with cold water as a cofactor [8]. Oral glucocorticoids alone or in association have not been studied [27].

Misoprostol, a prostaglandin E1 analogue [38, 86], has been used in a patient with aspirin-induced WDEIA. Pre-treatment with this drug inhibited symptoms with wheat-exercise challenge and the increase of serum gliadin levels [86]. The efficacy might be due to upregulation of gastrointestinal breakdown of allergic particles.

Omalizumab, a monoclonal antibody against IgE [12], has been used in exercise-induced anaphylaxis (EIA). Bray et al. reported a case in a 14-year-old boy, which had attempted montelukast, fexofenadine, or sodium cromoglicate before exercise without success, but tolerated exercise challenge after omalizumab administration [12]. Recently, two case reports published similar positive results [22]. A 17-year-old male racing cyclist with no prior history of allergy or food sensitization had a negative exercise challenge after 16 weeks of treatment with omalizumab [22]. Another patient, a 39-year-old man treated with omalizumab, had resolution of exercise-induced anaphylaxis episodes, but when omalizumab was stopped, episodes resumed; after omalizumab treatment was restarted, a 5-year efficacy without new episodes was seen [68]. It is possible that these results, might be similar in FDEIA.

Food *immunotherapy* could have a critical role in preventing the reactions [70]. However, though an increasing number of studies on oral, sublingual, and epicutaneous immunotherapy have been published, it is not yet approved to be used in regular clinical practice [91]. Furthermore, a few reports of individuals who developed FDEIA during or after food immunotherapy have been published [15••, 23••, 48]. While it can suppress allergic reaction induced by food ingestion, it does not alter the additional mechanisms that induce FDEIA. In two case reports of WDEIA, oral immunotherapy with interferon gamma allowed patients to acquire tolerance for wheat ingestion associated with exercise [62]. However, important side effects were described and it is not recommended in clinical practice.

Prognosis

Few fatalities have been attributed to FDEIA [29, 63]. It seems to be a persistent disorder but most patients do well reporting fewer attacks over time [44, 77]. Improvement may be attributable to a combination of recognition of early symptoms, modifications of exercise habits, and avoidance of culprit foods and/or other augmenting factors [26]. The long-term treatment focused on avoidance of the offending food can have an important impact on quality of life (QoL). Previous studies have showed that restrictions imposed on the patients with food allergy had a negative impact on health-related QoL in adults [40], in adolescents [71], and in children and its parents [58]. Only one study has evaluated QoL in patients with WDEIA, showing that it was more severely impaired in WDEIA patients than in patients with other food allergies [19].

Conclusions

FDEIA is a relatively rare, but an extremely complex form of food allergy, potentially life-threatening and insufficiently diagnosed. It is an unpredictable disease that usually affects otherwise healthy and active individuals with potentially high impact on patient's quality of life. Diagnosis is challenging, as it needs a high index of clinical suspicion. Provocation tests might not be able to confirm diagnosis, as a negative result might not discard the suspicion.

Management should be individualized, depending on the severity and frequency of symptoms, the food or other co-factors, and the patient's desire to continue participating in sports or specific types of exercise that might trigger symptoms. The cornerstone of treatment is educating the patient, preventing new reactions, and providing adequate conditions for acute treatment.

Improved strategies to ensure accurate diagnosis are needed, namely improving the accuracy of provocation tests, avoiding unnecessary dietary and exercise restrictions, and minimizing the impact of FDEIA on patient's quality of life.

Compliance with ethical guidelines

Conflict of interest
Maria João Vasconcelos declares that she has no conflict of interest.
Luís Delgado declares that he has no conflict of interest.
Diana Silva declares that she has no conflict of interest.

Human and animal rights informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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