

Combined effects of food and exercise on anaphylaxis

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Abstract

Food-dependent exercise-induced anaphylaxis (FDEIAN) is induced by different types and various intensities of physical activity, and is distinct from food allergies. It has been shown that consumption of allergenic food followed by exercise causes FDEIAN symptoms. Intake of allergenic food or medication before exercise is a major predisposing factor for FDEIAN. Urticaria and severe allergic reactions are general symptoms of FDEIAN. Dermatological tests and serum IgE assays are the typical prescreening methods, and have been used for several decades. However, these screening tests are not sufficient for detecting or preventing FDEIAN. It has been found that exercise may stimulate the release of mediators from IgE-dependent mast cells that can result in FDEIAN when a certain threshold level has been exceeded. Mast cell degradation might be a major factor to induce FDEIAN but this has not been determined. A number of foods have been reported to be involved in the onset of FDEIAN including wheat, eggs, chicken, shrimp, shellfish, nuts, fruits, and vegetables. It is also known that aspirin increases the occurrence of type I allergy symptoms when combined with specific foods. Moreover, high intensity and frequent exercise are more likely to provoke an attack than low intensity and less frequent exercise. In this paper, we present the current views of the pathophysiological mechanisms underlying FDEIAN within the context of exercise immunology. We also present a detailed FDEIAN definition along with etiologic factors and medical treatment for cholinergic urticaria (UC) and exercise-induced anaphylaxis (EIA).

Key Words: Food, exercise, anaphylaxis, FDEIAN

Introduction

Anaphylaxis is defined as a very serious systemic hypersensitive allergic reaction involving the skin, respiratory tract, gastrointestinal (GI) tract, and cardiovascular system [1]. This spontaneous and severe reaction is often accompanied by various signs and symptoms such as dyspnea, angioedema, and hypotension.

Anaphylaxis results from the release of bioactive mediators from basophils and mast cells. Previous studies found that the rate of food anaphylaxis is between 0.008 to 0.05% per year with a lifetime prevalence of 0.05 to 2.0% [2,3].

According to another previous investigation [3], the prevalence of food anaphylaxis has been underestimated while the occurrence has dramatically increased. Other scientific data have indicated

that up to 2% of the Western population might be affected by food anaphylaxis [4].

The difference between anaphylaxis and food-dependent exercise-induced anaphylaxis (FDEIAN) is the inclusion of physical activity as a causative factor. FDEIAN arises from a combination of allergenic food and exercise, especially high-intensity regimens. In other words, an individual who has FDEIAN will present signs and symptoms during exercise a few hours after ingesting allergenic food.

FDEIAN is a subtype of exercise-induced anaphylaxis (EIA) characterized by the onset of symptoms of anaphylaxis during or following physical exertion. This condition is less commonly known compared to other severe allergic reactions. It has been reported that FDEIAN symptoms include urticaria, respiratory

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disturbances (e.g., dyspnea, coughing, and wheezing), angioedema, GI manifestations, and even hypotension [5,6]. The symptoms of EIA can be observed at any moment during or after physical activity. However, approximately, 90% of patients develop symptoms within 30 min after exercise cessation [7]. In cases of FDEIAN, ingestion of allergenic food usually precedes exercise by several minutes or even hours. However, some research has indicated that FDEIAN may also occur if the patient ingests allergenic food soon after the completion of exercise.

Although not all the food allergens have been identified, Stellato *et al.* [8] suggested that exercising after consuming of shellfish can produce allergic reactions. There are some studies indicating that omega-5 gliadin and gluten are common allergens involved in wheat-dependent FDEIAN [9,10]. Apparently, crustaceans and wheat are foods most commonly associated with FDEIAN [11]. The prevalence of FDEIAN has not been accurately reported although this condition is thought to be an infrequent phenomenon.

While the cause of FDEIAN remains unknown, it has been surmised that allergic anaphylaxis can be initiated by the onset of exercise in patients who have low-grade type I allergies to specific foods [2]. Exercise helps increase the absorption of food allergens in the GI tract and the degranulation of mast cells. Thus, plasma histamine levels increase in patients with EIA [2,12]. It has also been reported that IgE production is increased in patients with allergies because isotype switching from type I to type II cytokines occurs during physical exercise.

Dermatological tests and *in vitro* serum food-specific IgE assays are not sensitive enough to detect IgE-mediated hyper-reactivity [10]. The importance of FDEIAN should not be overlooked because this is a life-threatening disorder. Furthermore, it is difficult to diagnose FDEIAN because many factors are involved.

The main discourse

EIA typically occurs with physical activity. This syndrome can be categorized into two distinctive forms: systemic cholinergic urticarial (CU) and EIA. The symptoms have been shown as a CU [10]. Various forms of exercise-related allergies have been described including a random rash associated with CU, a conventional form of EIA, and variant EIA [13,14]. In this review, we describe three types of EIA along with the diagnosis, pathophysiology, and treatment of this disorder.

CU

CU manifests as a skin rash induced by an elevated body temperature. This reaction is mainly caused by active heat generation or passive heating, but is rarely associated with angioedema, bronchospasm, or hypotension. The characteristics of CU are well known; however, the specific mechanism underlying this condition has not been elucidated in detail [15].

Likewise, the exact pathophysiology governing the release of histamine has not been identified [16]. Exercise-induced CU has to be distinguished from EIA, which is a potential life-threatening condition and a challenge for medical providers. Pinpoint-sized wheals on the skin are lesions typically observed.

The subtypes of urticaria most commonly seen in athletes are acute forms induced by exercise, temperature, sunlight, water, or certain levels of external pressure. CU is the most common type of urticaria seen in young athletes [17]. Figure skaters, skiers, ice hockey players, and speed skaters exposed to a cold environment frequently suffer from dermatological injuries. Cold urticaria is another type of physical urticaria defined as urticaria and angioedema arising after exposure to the cold [18]. Effective management of cold urticarial includes patient education, antihistamine administration, and avoidance of precipitating triggers such as hot showers, strenuous exercise, or prolonged exercise. Exercise modification such as changing exercise type, duration, intensity, and frequency is commonly recommended for patients with anaphylaxis.

Conventional EIA

Cases of urticaria or angioedema and hypotension induced by intense physical activity are classified as conventional EIA. Temperature elevation induced by exercise causes EIA, which is unaffected by food intake. EIA is associated with other disorders including atopic eczema, atopic asthma, exercise-induced asthma, and seasonal rhinitis [19]. Exercise-induced asthma that is related to exercise and allergenic food intake is associated with typical asthma symptoms, but these symptoms are limited to the lower airways [19]. Vigorous exercise such as jogging and running have been identified as activities that can trigger EIA [7,19]. Other high- and/or low-intensity exercises such as soccer, tennis, swimming, basketball, snowboard, and walking have also been identified as activities linked to EIA. Signs and symptoms generally last at least 30 min and up to 4 h after exercising [20].

EIA occurs as a result of mast cell degranulation leading to the release of histamine and other mediators into the circulation [20]. An exaggerated pathologic response to increased temperature seems to provoke mast cell degranulation in individuals with CU [20]. In cases of conventional EIA, exercise is considered a physical stimulus that induces mast cell degranulation through an unknown mechanism. Treatment of acute EIA includes the administration of epinephrine and antihistamines. In addition, airway maintenance and preserving normal cardiovascular function is very important for preventing further complications. Prophylactic treatment includes exercise avoidance, abstinence from specific foods and medications, pretreatment with antihistamines, caffeine, and cromolyn (used to prevent exercise-induced asthma); and the induction of tolerance to CU through regular physical activity [14].

Variant EIA and FDEIAN

The typical signs of variant EIA are punctate erythematous papules and symptoms similar to those of CU. These signs are related to increased plasma histamine levels. Only physical activity can be a factor which causes the variant forms of EIA. Anaphylaxis can occur when patients consume a particular food and participate in exercise within a few hours of eating. During physical activity, cardiovascular problems such as sudden cardiac death can be a unique sign or symptom of exercise-induced food allergies [21]. Approximately 10% of EIA cases have been diagnosed as variant EIA [22].

FDEIAN occurs in both adults [23] and children [24]. The exact mechanisms underlying FDEIAN have not been elucidated. However, it is expected that food allergens, exercise, and subsequent IgE action reduce the mast cell release threshold. Exercise can also promote mast cell degranulation and cause physical anaphylaxis.

FDEIAN should be differentiated from CU and EIA. FDEIAN is provoked by the combination of allergenic food and physical exercise whereas for EIA is caused by exercise alone while CU is induced by stress, heat, and exercise. Vascular collapse and laryngeal edema can also occur with FDEIAN unlike CU.

Severity of an allergic reaction can be determined based on the amount of allergenic food that has been consumed. Therefore, food intake and exercise need to be carefully evaluated. The most common trigger foods for FDEIAN are eggs, milk, wheat products, cheese, tomatoes, peaches, and shellfish. Epinephrine is the most common treatment for allergy anaphylaxis while H1 antagonists and salbutamol can be used to relieve secondary symptoms. The combination of H1 and H2 may also ameliorate symptoms [25].

Diagnosis, pathophysiology, and treatment of FDEIAN

It is well known that the clinical symptoms of EIA include pruritus, urticaria, angioedema, respiratory distress, and syncope. To diagnose FDEIAN, the medical history of the patient is first reviewed to find a specific cause of the symptoms and/or signs. This is followed by allergy tests including skin prick tests or immunoglobulin E assays [26]. Physical allergies are a group of reactions caused by physical stimuli such as low temperature, heat, exercise, sunlight, and mechanical pressure. It has also been reported that alcohol consumption can provoke a variety of hypersensitive reactions. Furthermore, alcohol intake may increase total serum IgE levels. Alcohol consumption could also attenuate sensitivity to environmental allergens [27].

CU and EIA are generally categorized as exercise-induced allergies. EIA related to food intake is known as FDEIAN [28]. Patients with FDEIAN are divided into two groups. One group includes patients whose symptoms are induced by particular food allergens. IgE specific for different foods can be detected by either an immediate skin test or radioallergen sorbent test (RAST)

in these patients [29]. The other group consists of patients who do not respond to a specific food allergen. Not surprisingly, specific IgE is not detected in these patients.

FDEIAN is marked by the onset of anaphylaxis during or soon after exercise preceded by the intake of allergenic foods [11]. Numerous foods have been reported to be allergens associated with FDEIAN [30]. Physical activities that provoke symptoms include marathon running, ball sports, and swimming. FDEIAN may be allergen-specific or non-allergen-specific.

As previously stated, FDEIAN is a rare disease in which postprandial exercise causes anaphylaxis. However, several other factors such as physical and mental stress, fatigue, dry air, insufficient sleep, the common cold, humid weather, low temperature, and non-steroidal anti-inflammatory drugs (NSAIDs) are reported to aggravate anaphylaxis [31]. If a patient is suspected to suffer from FDEIAN, a diagnostic physical stress test can be performed. This can be accomplished on a treadmill or cycle ergometer in a manner similar to graded exercise testing.

Previous animal studies demonstrated that exercise intensity and duration is positively correlated with FDEIAN severity. The FDEIAN score is increased with high exercise intensity and duration compared to low intensity and duration. This is because intense and prolonged exercise converts Th1 lymphocytes into Th2 lymphocytes caused by Th2 cytokine production [32-34]. Exercise also induces the release of mediators from mast IgE-dependent cells. It was found that exercise lowers the mast cell degranulation threshold. Therefore, more intense and prolonged episodes of exercise provoke a more severe allergic reaction. Moreover, vigorous exercise facilitates allergen absorption from the GI tract, leading to FDEIAN.

Skin vasoactive mediators are major factors that cause EIA symptoms. Additionally, increased plasma histamine levels are a typical indicator of variant and conventional forms of EIA and CU.

The exact pathophysiology underlying FDEIAN is also unknown. It has been hypothesized that physical exercise reduces the mast cell degranulation threshold [35]. Other research indicated that physical exercise disrupts the digestion and absorption of allergenic food, leading to a rise in allergenic proteins in the blood [36]. This results in IgE-mediated mast cell sensitization, and the release of heparin and histamine in response to the allergenic food that was consumed [36]. Histamine leukotriene stimulates smooth muscle constriction, causing difficulties in breathing and GI symptoms. Histamine also induces vasodilation, and leads to urticaria and angioedema, decreased blood pressure, and syncope [35]. The course of EIA is very similar to that of other types of anaphylaxis. Once EIA develops, patients need to cease physical activity. This is the most crucial factor for avoiding further progression of the disease [37].

The best treatment for FDEIAN is to prevent the intake of causative foods and reduce exercise intensity. For cases of specific FDEIAN, patients should not consume causative foods before physical activity. For cases of non-specific FDEIAN, individuals should not participate in exercise within 1-6 h after

consuming allergenic food. Avoidance of medications including NSAIDs is also recommended. Patients who participate in exercise are also encouraged to have an individualized emergency kit that includes epinephrine, antihistamines, and corticosteroids [38]. Prophylactic use of antihistamine, corticosteroid, β -stimulant, and theophylline has been documented [38]. The use of cromolyn, a mast cell stabilizer and antihistamine, has been shown to be effective for the prophylactic treatment of FDEIAN. This reagent prevents the degranulation of mast cells, plasma histamine efflux, and the production of pro-inflammatory factors [38]. Modification of exercise regimes, detraining, and cross-training are also important for treating patients suffering from FDEIAN.

Individuals with FDEIAN should avoid causative allergenic foods and not exercise until 4 to 6 h after eating. Additionally, NSAIDs should not be taken before participating in exercise. If patients have any signs or symptoms while exercising, they should stop their exercise and seek medical aid if the symptoms persist [39,40]. For management of acute anaphylaxis, an open airway should be maintained. Vascular collapse and angioedema should be treated with epinephrine.

Conclusions

FDEIAN is a clinically distinct form of anaphylaxis in which symptoms occur only when the patient exercises within a few hours of eating allergenic food. The precise mechanism underlying this disease remains unclear and has been reported to have a wide variety of factors.

FDEIAN is characterized by symptoms of anaphylaxis due to the consumption of allergenic foods that manifest during or soon after exercising. Several exercises predispose individuals to FDEIAN. These include running, tennis, basketball, soccer, swimming, and even brisk walking. Numerous foods (e.g. certain fruits, shrimp, shellfish, chicken, wheat, nuts, eggs, and vegetables) have been identified as allergens associated with FDEIAN.

Individuals may be diagnosed with EIA if a reaction occurs with physical exertion alone without any food intake. However, CU should be distinguished from EIA. To prevent the occurrence of FDEIAN, patients should not eat any causative food within 4 h before exercising and should avoid vigorous physical activities. However, limited intake of causative food has been found to be a reliable method for preventing FDEIAN. In this review, we described three types of EIA including CU. Further research on the specific mechanisms underlying FDEIAN along with the development of effect treatment and diagnostic techniques are urgently needed.

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