

Food-Dependent Exercise- and Pressure-Induced Syndromes

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KEY CONCEPTS

- Food-dependent exercise-induced anaphylaxis (FDEIA) is a physical allergy syndrome that occurs only in response to exercise preceded by food ingestion.
- The importance of food in eliciting attacks of exercise-induced anaphylaxis (EIA) in some patients may be under-recognized, and many patients diagnosed with EIA may in fact have FDEIA.
- Food-specific FDEIA has been reported with many different types of food, and in some patients, attacks follow ingestion of any food (non-specific FDEIA).
- The main treatment for FDEIA is avoidance of ingestion of implicated foods at least 4 hours before exercise.
- Convincing evidence for a role of food allergy in other physical urticaria syndromes is currently lacking.

Introduction

The body of literature describing the association between physical allergy syndromes with the ingestion of food has grown significantly in the past decade. In these food-dependent physical allergy syndromes, it appears that two or more stimuli, which independently do not provoke an allergic response, do so when combined in sufficient temporal relationship. The clinical manifestations of the allergic response range in severity from itching and hives to anaphylactic shock. The two recognized physical allergy syndromes in which food ingestion contributes a “sub-threshold” precipitating factor are food-dependent exercise-induced anaphylaxis (FDEIA) and food-dependent delayed pressure urticaria (FDDPU).

Definitions

The clinical syndrome of exercise-induced anaphylaxis (EIA) has been described in several comprehensive reviews [1–11]. It is a physical allergy syndrome with onset generally during or within minutes of completion of exercise. Initial symptoms consist of a sensation of generalized

fatigue, warmth, pruritus, cutaneous erythema, and urticaria. Progression to other systemic symptoms including angioedema, dyspnea, cough, wheezing, nausea, vomiting, abdominal cramping, diarrhea, malaise, laryngeal edema, hypotension, vascular collapse, and loss of consciousness can follow. The attack can last from 30 minutes to 4 hours. Headache may persist following an attack for 24–72 hours. Various types and intensities of exercise may precipitate attacks. Jogging is the most commonly reported provoking exercise, but walking, bicycling, racquet sports, skiing, aerobics, dancing, soccer, and swimming have also been reported. Importantly, other reported provoking activities include horseback riding, raking leaves, and shoveling snow [10,11].

In one case series evaluating the frequency of various etiologies of anaphylaxis, exercise is considered the cause of anaphylaxis in 5–10% of patients (10–12% of patients with identifiable causes) referred to allergy and immunology clinics after presenting to acute care centers with anaphylaxis [12].

EIA appears to be associated with atopy in up to 50% of patients [1]. Women with EIA appear to be at least twice as likely as men to respond to epidemiologic surveys, but whether they in fact are more likely to experience EIA, as has been stated in other reviews on the subject, is unknown [13].

Little is known about the natural history of EIA, but lifestyle modification can certainly reduce the frequency and severity of attacks. Shadick *et al.* report on the 10-year

follow-up survey results of one cohort of 279 patients with EIA [13]. The response rate of women was twice that of men. The mean age at the time of first EIA attack was 26 years, with a range of 3–66 years. Forty-seven percent of respondents reported a decrease in the frequency of attacks, and 41% reported being completely free of attacks, in the preceding year. Subjects reported reducing attacks by avoiding exercise during extremely hot or cold weather (44%), restricting exercise during allergy season (36%) or humid weather (33%), and avoiding certain foods before exercise (37%).

Though considered by some to be another example of exercise-induced urticaria and anaphylaxis [9], there is rather convincing evidence that cholinergic urticaria (CU) is clinically distinct from EIA [14,15]. First, exercise, not heat, sweat, nor rise in body temperature has been identified to be the provoking factor for EIA. Second, the hives that occur in EIA are typically larger and distinct in appearance from the classic punctuate hives seen in CU. Third, CU can be associated with bronchospasm but vascular collapse occurs rarely. Laryngeal edema and stridor can occur in EIA, but no change in pulmonary function was observed in patients with EIA who underwent exercise challenge. Finally, studies have found elevated tryptase levels following attacks of EIA, but not CU [16,17].

FDEIA refers to a physical allergy syndrome in which attacks of EIA occur only when exercise is preceded by ingestion of a specific food (specific FDEIA) or any food (non-specific EIA).

A far less common type of exercise-induced urticaria and anaphylaxis, variant-type EIA, has been identified. These patients have attacks characterized by eruptions of punctuate urticaria, progression to vascular collapse, and are precipitated by exercise only and not passive warming [1,18].

Delayed pressure urticaria is a physical urticaria characterized by the development of hives and angioedema 30 minutes to 6 hours after the application of a sustained pressure stimulus on the skin. Underlying chronic idiopathic urticaria is usually present. A few reports have suggested that food may play a role in some cases of DPU.

Food-dependent, exercise-induced anaphylaxis

Epidemiology

In recent years, it has become clearer that a subset of patients with EIA can completely prevent exercise-induced attacks by avoiding either specific foods or non-specific food ingestion in the hours before exercise. In the survey results of their cohort of 279 patients with EIA, Shadick *et al.* reported that 37% of patients were able to reduce or eliminate attacks by avoiding certain foods [13]. A report of survey results obtained from another cohort of 199 EIA patients noted 54% of patients considered food ingestion or intake of specific foods to be a factor in the development of attacks [19].

In order to determine the prevalence of FDEIA in pre-adolescent school children in Japan, Aihara and colleagues conducted a survey of junior high school nurses representing 76,226 students in Yokohama [20]. Twenty-four cases of EIA (12 boys and 12 girls) and 13 cases of FDEIA (11 boys and 2 girls) were identified, with prevalences of 0.031% and 0.017%, respectively. Ten of 12 patients with FDEIA had other allergic disorders.

In a review of 167 cases of FDEIA in the Japanese literature since 1983, Harada and colleagues [21] described several characteristics of the disease, including a recent upward trend in the number of reports of FDEIA, male predominance, adolescents accounting for more than half of the cases, and a history of atopy in 40% of affected individuals.

Clinical features

The first case of EIA associated with food ingestion was reported by Maulitz *et al.* in 1979 [22]. This case involved a runner who developed anaphylactic reactions when he ran within 8–12 hours of ingestion of shellfish. The patient ran regularly, averaging 50–130km per week. Over a 3-year period prior to diagnosis of the condition, the patient sustained approximately 10 bouts of transient facial flushing and edema, with diffuse urticaria and pruritus occurring during or immediately after exercise. Two of the reactions resulted in almost complete upper airway obstruction requiring emergency therapy with epinephrine and antihistamines. The patient had no initial suspicion of allergic sensitivity to, or clinical reactions following, shellfish ingestion, but eventually the association with exercise was made. During further evaluation, he had positive immediate reactions with epicutaneous skin testing to clams, oysters, shrimp, crab, peanuts, trees, grasses, and weeds. Once the diagnosis was made and causative foods identified, avoidance of ingestion of these foods for at least 12 hours prior to exercise resulted in almost complete elimination of any further reactions.

In all cases of FDEIA, ingestion of the implicated food or non-specific food ingestion followed by exercise provokes the attack, and neither food ingestion nor exercise alone is sufficient. The nature of the attacks in FDEIA is indistinguishable from those described in patients with EIA. In their report on the clinical characteristics of 54 patients with FDEIA, Romano *et al.* found the most common symptoms to be pruritus (94% of patients), urticaria (85%), and angioedema (83%). Other common symptoms included flushing (74%), dyspnea (70%), gastrointestinal disturbances (nausea, diarrhea, colic, vomiting: 35%), hypotension (33%), and upper respiratory disturbances (choking, throat constriction, and hoarseness: 30%) [23].

The most common implicated foods are wheat, shellfish, alcohol, and a variety of fruits and vegetables, though over 40 different foods have been reported (see Table 47.1). In Japan, wheat and shellfish are implicated in the majority of cases of FDEIA, whereas case series reports from the

Table 47.1 Foods reported to be associated with FDEIA

>10 cases reported	<10 cases reported	
Alcohol	Apple	Mushroom
Barley	Almonds	Mustard
Celery	Banana	Onion
Cheese	Beef	Orange
Milk	Cabbage	Peas
Oats	Chicken	Pear
Peach	Corn	Penicillium
Peanut	Egg	(contaminated food)
Rye	Fennel	Pistachio
Soybean	Fish	Poppy seed
Shellfish	Garlic	Pork
Strawberry	Grape	Potato
Tomato	Hazelnut	Rice
Wheat	Kiwi	Snail
	Lentil	Spinach
	Lettuce	Umeboshi
	Litchi	(combination w/wheat)
		Walnut

United States and Europe implicate a wider variety of foods [13,15,22–42].

In a subset of patients with EIA associated with food ingestion, a specific food cannot be identified. Among the 54 patients with FDEIA reported by Romano *et al.*, a causative food could not be identified by history or specific IgE testing in six subjects [23]. Another case series of 11 Japanese patients with FDEIA, 4 were not sensitive to any specific food [25].

As with EIA, a variety of types and intensities of exercise can provoke attacks. Running, jogging, walking, soccer, dancing, and racquet sports are the most commonly reported provoking exercises for FDEIA [13,23,25]. The time between food ingestion and exercise generally ranges between 30 minutes and 4 hours, with the vast majority occurring within 2 hours [23]. The distance runner first described by Maulitz *et al.* in 1979 reported attacks 5, 20, and 24 hours after shellfish ingestion [22], but no cases of food-and-exercise challenge (FEC) confirmed cases with ingestion-to-exercise intervals greater than 6 hours have been reported. Whether the intensity of exertion correlates with the severity of the attack remains unclear, but the duration of exercise necessary to provoke an attack can range from 10 to 50 minutes. A single case of FDEIA has been reported in which the attack only occurred if the food (celery) was ingested within 2 hours after exercise [30].

It is unknown whether the amount of allergen ingested has an impact on the elicitation or severity of the attacks in FDEIA. Case series reporting FEC results do not specify the amount of food ingested prior to exercise. Hanakawa

and colleagues reported a case of FDEIA in which the systemic allergic reaction depended on the amount of allergen ingested [43]. A 24-year-old woman with EIA associated with wheat ingestion had a class 2 positive radioallergo-absorbent test (RAST) for wheat and gluten, class 3 positive RAST for rye, and positive skin prick tests (SPTs) for wheat, bread, gluten, and udon (Japanese wheat noodles). Challenge tests with bread were performed. Exercise following ingestion of 64g, but not 45g, of bread induced generalized urticaria. Challenge tests with udon also provoked urticaria in a dose-dependent manner: 200g, but not 100 or 150g, elicited symptoms. They concluded that a negative challenge in patients suspected to have FDEIA may result from an insufficient amount of ingested food allergen (or sub-threshold exercise).

In some cases, a combination of two different foods followed by exercise may be required to elicit a reaction. Aihara *et al.* [28] reported a case of a 14-year-old boy with FDEIA diagnosed by provocation testing with the simultaneous ingestion of wheat and umeboshi (unripe plums pickled in brine and other ingredients, used in Japanese cooking), followed by exercise. Provocation tests with wheat or umeboshi alone failed to produce the transient increase in plasma histamine levels and drop in forced expiratory volume in 1 second (FEV1) elicited by the combination of food allergens. Again, this could partly account for negative challenge tests in patients with a strong clinical history for FDEIA. More recently, a case of FDEIA was reported in a 48-year-old woman that could only be provoked by a combination of food additives, ethanol, wheat flour, and exercise, whereas exercise challenges with or without ingestion of food additives, ethanol or wheat individually were negative [39].

Cross-reactivity of allergenic food components may also play an important role in FDEIA. Palosuo *et al.* examined the sera of 23 adult patients with wheat-dependent EIA for cross-reactivity of wheat omega-5 gliadin with other cereal proteins. They found that gamma-70 and gamma-35 secalins in rye and gamma-3 in barley cross-react with omega-5 gliadin [44]. In addition, two patients in their cohort of wheat-specific FDEIA reported exercise-induced allergic symptoms after rye ingestion. This suggests that rye and barley may also elicit exercise-induced symptoms in patients with wheat-specific EIA. Romano *et al.* noted that in their cohort of patients with FDEIA, 9 of 14 patients with tomato-specific FDEIA had positive skin tests for grasses with structural cross-reactivity with tomato. IgE cross-reactivity has also been reported in patients with mustard-specific FDEIA to mugwort pollen, celery-dependent FDEIA to mugwort pollen, and snail-dependent FDEIA to dust mite allergen [34,35,45].

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and possibly other medications may have a key role in eliciting or enhancing food-dependent, exercise-induced reactions. Dohi *et al.* described two patients who recalled that

aspirin taken 30 or 60 minutes before food intake provoked exercise-induced reactions that were more severe than without aspirin [25]. In another case series of three patients with FDEIA, Harada *et al.* found that aspirin added to FEC was required to provoke a systemic reaction in two patients, and was sufficient to provoke systemic symptoms when combined with food (without exercise) in one patient [46].

In order to investigate the effect of aspirin in provocation tests and in SPT of patients with FDEIA, Aihara *et al.* performed provocation challenges with combinations of food, exercise, and aspirin. Pre-treatment with aspirin was associated with enhanced SPT reactions to food, but not histamine, in five of eight (62.5%) patients. Of three patients who did not react to food and exercise, two reacted when challenged with the combination of food, exercise, and aspirin. In addition, two of three patients with positive challenges to food and exercise also had a positive challenge when food was combined with aspirin instead of exercise [47]. In another case series, Dohi *et al.* described three patients in whom aspirin ingestion followed by specific foods and exercise elicited more severe attacks with less exercise than when food and exercise were not preceded by aspirin ingestion [48]. Taken together, these data suggest aspirin may contribute to the severity of FDEIA reactions. Cross-reactivity of this aspirin effect on FDEIA severity with NSAIDs is supported by the finding by Romano *et al.* that three of five patients who reported taking aspirin shortly before FDEIA attacks had also taken NSAIDs before other FDEIA attacks [23].

Other factors that appear to be capable of contributing to the elicitation or severity of FDEIA attacks include psychological stress, abnormal response of the autonomic nervous system, menstruation, fatigue, lack of sleep, and seasonal variation [23,25].

Diagnostic considerations

Differentiating FDEIA from other clinical entities involving food, exercise, urticaria, respiratory symptoms, or collapse may be difficult (Table 47.2). Unless the association of exercise-induced attacks with specific or non-specific food ingestion can be identified historically, patients with FDEIA may be misdiagnosed as having EIA. Idiopathic anaphylaxis, food- and drug-induced anaphylaxis, and anaphylaxis associated with systemic mastocytosis lack a clear association with exertion.

CU should also be distinguished from FDEIA. As discussed above, CU is a physical urticaria syndrome characterized by small, punctate wheals that develop in response to elevation in body temperature such as through exercise, exposure to hot water, sweating, fever, or emotional stress. The symptoms are generally limited to the skin, can be associated with wheezing, but not stridor, laryngeal edema, or vascular collapse. The provocation of the other physical urticarias by

Table 47.2 Differential Diagnosis of FDEIA

Differential diagnosis of FDEIA

Anaphylaxis syndromes
Idiopathic
Food induced
Drug induced
Exercise-induced syndromes
Exercise-induced anaphylaxis
Physical urticarias
Cholinergic
Delayed pressure
Solar
Aquagenic
Exercise-induced bronchospasm
Cardiac arrhythmias
Other
Other urticaria
Idiopathic/autoimmune urticaria
Systemic mastocytosis
Vasovagal syncope–presyncope
Carcinoid syndrome
Psychogenic
Shock
Septic
Cardiogenic
Hypovolemic

exposure to sunlight, water, vibration, and pressure should be readily distinguished from FDEIA on the basis of history.

The phenomenon of exercise-induced bronchospasm that can occur in patients with asthma presents with dyspnea, cough, and wheezing provoked by exercise but is rarely associated with pruritus, urticaria, upper respiratory obstruction, or vascular collapse. Non-allergic causes of vascular collapse such as neurocardiogenic syncope and cardiac arrhythmias that can be associated with exercise and/or food ingestion also lack these characteristic features of anaphylaxis.

Diagnosing underlying food sensitivity in patients with FDEIA may prove difficult. The history is the most important diagnostic tool. Special emphasis should be placed on obtaining a detailed account of the symptoms of the attack, timing in relation to food and exercise, specific foods and/or medications (as well as quantities) ingested prior to attack, and other allergic history. The best clue comes from the presence of intermittent or sporadic exercise-induced reactions superimposed on the baseline of consistent, uneventful exercise. Although a specific food is usually implicated as a co-precipitating factor (specific FDEIA), some patients suffer from EIA after any food ingestion (non-specific FDEIA) [23]. In many cases of FDEIA, the association with food ingestion may not have been made, thereby unnecessarily restricting affected patients' ability to exercise. Some cases may

even be labeled idiopathic. A confounding factor that may complicate the process of making an accurate diagnosis may be the lag in time between ingestion and reaction. This may rarely extend to 12–24 hours, making the association with a specific food trigger extremely difficult. The association of EIA episodes with a specific food may also be missed in cases when the implicated food is a dietary staple such as wheat. Varjonen *et al.*, for example, reported a series of five patients who could only associate the attacks of anaphylaxis with exercise, but were found to have detectable IgE on SPT and were able to exercise safely by eliminating wheat from the diet [49]. The accurate diagnosis can further be obscured by the requirement, in at least a few cases, of other factors such as aspirin or NSAID ingestion, psychological stress, menstruation, and seasonal or temperature variation. Some patients considered to have exercise-induced or “idiopathic” anaphylaxis without apparent relationship to food may in fact be reacting to unidentified ingestants, a combination of allergenic ingestants, or a cross-reacting ingestant.

Specific IgE testing in the form of SPT or RAST can be quite useful, especially as an opportunity to minimize exercise restrictions for affected patients. The vast majority of cases of FDEIA with a specific food identified as a co-precipitating factor have positive SPTs to the implicated food. Based on their findings in 54 patients with FDEIA, Romano and colleagues stress the importance of both *in vivo* and *in vitro* testing to an extensive panel of foods [23]. After detailed histories, patients were subjected to SPT to 26 commercial food allergens, SPTs with 15 fresh foods, and RAST for 31 food allergens. Forty-eight patients had suspected a particular food in association with attacks; six could not recall a certain food. Fifty-two patients were positive to at least one food; two had no positive results at all. All suspect foods were positive and each of the three tests revealed varying degrees of sensitivity, with positive results not discovered by the other tests. Exercise challenges following meals lacking the foods that elicited positive results on SPT or RAST failed to elicit reactions.

In another study of 19 patients referred for evaluation for anaphylaxis that occurred during or immediately following exercise, screening SPT and/or RAST to foods ingested prior to the episode of EIA revealed sensitization in 17. Avoidance of the identified foods 5 hours prior to exercise successfully prevented recurrence in 15 of these patients during the follow-up period (median 2 years) [29].

Special consideration of the limitations of specific IgE testing in the evaluation of patients with possible wheat-dependent EIA should be noted. Omega-5 gliadin (the major allergen responsible for wheat-dependent EIA) exists in the insoluble gliadin fraction of wheat proteins, which is lacking from commercial testing reagents [44,50]. The clinical implication is that the detection of IgE sensitization to wheat with commercial test reagents is impaired and this may lead to the

incorrect diagnosis of EIA or nonspecific FDEIA, rather than wheat-specific EIA. *In vitro* IgE testing to omega-5 gliadin is not currently commercially available.

Though considered to be the gold-standard for confirming the diagnosis of FDEIA, the role of food-and-exercise provocation challenges in the clinical setting is unclear. The decision to perform such provocation challenges should include consideration of the risk of patient harm resulting from positive challenges, the possibility of a false-negative challenge, and the ease of avoidance of the suspected food prior to exercise. One approach used by some authors [23,29] is performing observed exercise challenges following meals lacking the suspected food(s), thereby providing reassurance that patients can safely exercise as long as the implicated food is eliminated from the diet.

Pathophysiology

The mechanism whereby exercise and food ingestion elicit the allergic response resulting in urticaria and anaphylaxis is not entirely understood. Food and exercise appear to act as two sub-threshold stimuli that individually are inadequate to produce mediator release from mast cells or basophils, yet when combined in a temporal relationship can produce mast cell or basophil degranulation. Support for the concept that mast cell degranulation is involved comes from studies involving electron microscopy of biopsy specimens obtained from exercise-induced urticarial lesions in patients with EIA showing ultrastructural evidence of mast cell degranulation [17]. Furthermore, a number of endogenous peptides can release histamine from mast cells both *in vivo* and *in vitro* [51]. These peptides include substance P, vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), gastrin, pentagastrin, and endorphins [51–54]. Release of these peptides occurs via various stimuli, including exercise, digestion, anxiety, pain, and local irritation. Any of these factors could be involved in physical urticarias or other allergic syndromes, including chronic urticaria, asthma, allergic rhinitis, and anaphylaxis, but studies showing increases in any of these endogenous peptides in response to exercise in patients with FDEIA are lacking.

Increased levels of histamine and tryptase have been observed after exercise in patients with EIA [3,16]. Exercise alone was sufficient to produce a rise in histamine in 6 of 11 patients with FDEIA, and exercise preceded by provocative foods was necessary in one additional patient [25].

Kivity *et al.* studied the effect of compound 48/80, a mast cell degranulating agent, on SPT in five subjects with FDEIA who had previous skin reactivity to provocative foods and five normal controls. Intradermal injection of compound 48/80 was associated with a much larger wheal response in four subjects with FDEIA as compared to controls after FECs, but not after food- or exercise-only challenges. The histamine wheal response in these subjects was not significantly changed [55]. Similar increases in exercise-induced

wheal responses have been found in other studies using compound 48/80 and codeine [56,57]. These findings suggest reactions in patients with FDEIA are produced by a direct effect of exercise and food allergen on mast cell releasability, rather than an increased sensitivity to histamine. This also implies that IgE and food antigens may interact with mast cells to lower the threshold to another stimulus, such as exercise, to produce the anaphylactic response.

The high prevalence of atopic diseases in patients with FDEIA and the finding that most patients with challenge-proven food-specific FDEIA have detectable IgE antibodies to implicated foods on SPT or RAST leave little doubt that IgE plays an important role in triggering attacks of FDEIA [20,21,23,25]. In addition to possible effects on mast cell releasability, exercise may also serve to facilitate increased small intestine allergen absorption. In one study of six patients with wheat-dependent EIA and four healthy controls, Matsuo *et al.* found that serum levels of gliadin, a major wheat allergen, rose in parallel with allergic responses following wheat ingestion and exercise [58]. An explanation for this observation comes from studies on the effects of exercise on intestinal function and hemodynamics showing that reduction of splanchnic blood flow from exercise causes epithelial barrier disruption and increases in intestinal permeability [59–61].

Other studies involving wheat-dependent FDEIA in Japan have provided further support for IgE-mediated food allergy in at least this subset of patients. Some of the IgE-binding epitopes for two important allergens in wheat-dependent FDEIA, omega-5 gliadin and a high-molecular-weight glutenin, have been identified [62,63]. In both cases, the epitope appears to be linear, rather than conformational. Interestingly, neither wheat-sensitive subjects with atopic dermatitis nor healthy controls demonstrated reactivity with epitope-specific IgE testing.

Of the additional cofactors that have been reported to possibly contribute to FDEIA attacks, the potential role of aspirin in enhancing FDEIA reactions has been most widely studied. Aspirin and other NSAIDs are capable of provoking or exacerbating hives in up to 30% of patients with chronic urticaria and angioedema through inhibition of cyclooxygenase-1 (COX-1) [64]. The observation that aspirin and other NSAIDs appear to provoke or exacerbate reactions in patients with FDEIA could, at least in part, also be attributable to COX-1 inhibition, but other mechanisms may also be involved. Aspirin, like exercise, appears to increase intestinal permeability through damage to gut epithelial tight junctions [65]. Matsuo *et al.* showed that co-ingestion of aspirin and wheat in patients with wheat-dependent EIA resulted in a rise in serum levels of gliadin and clinical allergic reactions [58]. Further studies are required to determine what potential role other cofactors such as medications, psychological stress, menstruation, fatigue, and lack of sleep may play in FDEIA responses.

Taken together, these observations provide some insight into the processes whereby food and exercise combine to produce anaphylactic reactions (see Fig. 47.1). In sensitized individuals, immunologically intact food antigen is absorbed, but in the absence of exercise, an immune response does not occur. When food ingestion is followed by exercise, the clinically observed reaction that follows is likely brought about by at least two key concomitant mechanisms: enhanced mast cell releasability and altered intestinal permeability. Serum levels of a number of the endogenous peptides known to induce mast cell degranulation including substance P, VIP, CGRP, gastrin, pentagastrin, and endorphins have been shown to increase in response to exercise [55–58]. In addition, intestinal epithelial barrier disruption associated with reduced splanchnic blood flow leads to altered intestinal permeability and the potential for enhanced absorption of immunologically intact food antigens [62–65]. Aspirin and

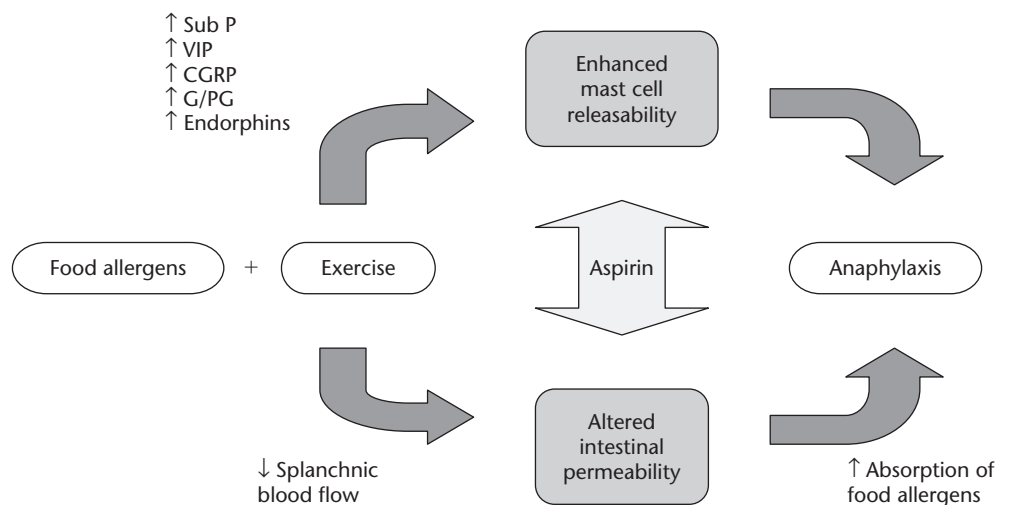


Figure 47.1 Schematic representation of role of exercise in food-specific EIA. Sub P, substance P; VIP, vasoactive intestinal peptide; CGRP, calcitonin gene-related peptide; G/PG, gastrin/pentagastrin.

NSAIDs can further potentiate these effects through COX-1 inhibition (and increased mast cell releasing factors, such as LTC₄) and disruption of intestinal epithelial tight junctions. The result is the observed clinical allergic reaction.

Treatment

Avoidance of ingestion of any implicated foods in sufficient temporal proximity to exercise is the cornerstone of management of FDEIA. Prospective, controlled studies designed to evaluate the minimal time interval between provoking foods and exercise are lacking, but for patients with specific FDEIA, avoidance of implicated foods 4–6 hours prior to exercise usually prevents an urticarial or anaphylactic reaction following exercise. In cases of non-specific FDEIA, avoidance of all foods for at least 6–8 hours prior to exercise is recommended [66]. Of 43 patients with food-specific FDEIA advised to avoid implicated foods for 4 hours prior to exercise, none had experienced reactions after a mean of over 4 years of follow-up. In addition, none of the five patients with non-specific FDEIA advised to avoid exercise for at least 4 hours after any meal had experienced reactions [23]. Because lower levels of exertion such as walking and activities not considered to be exercise such as yard work and ironing clothes have been reported to provoke EIA, some patients might prefer complete avoidance of implicated foods [31]. Inquiring about and tailoring exercise regimes as indicated to avoid co-precipitating factors such as aspirin and NSAID ingestion, menstruation, seasonal variation, and extremes of weather should also be considered [13].

The utility of various medications taken prior to exercise in patients with FDEIA has not been established. Antihistamines taken either daily or one-half hour before exercise may help blunt the attack [67]. However, no data exist to suggest that this therapy can eliminate or prevent episodes. Oral cromolyn has also been reported to successfully prevent attacks [28,68]. The leukotriene antagonists, zafirlukast and montelukast, have been shown to attenuate exercise-induced bronchoconstriction, but no studies have evaluated this class of agents in FDEIA so far [69,70].

When attacks do occur, early intervention should help decrease their severity [1]. Patients should have a clear understanding of the early signs and symptoms of anaphylaxis, and immediate cessation of exercise when they occur is recommended. Self-injectable epinephrine should be prescribed for all patients along with the recommendation to carry it during exercise. Patients with a history of life-threatening reactions should also consider wearing a medical alert bracelet and avoid exercising alone. Emergency treatment at the time of the reaction may be lifesaving, although deaths attributed to FDEIA are rare [10,71].

The potential role of other treatment modalities such as anti-IgE therapy or other immunomodulatory agents requires investigation. Whether induction of tolerance to exercise following food ingestion can be achieved remains

unknown. In their report on the results of a survey of patients with EIA, Wade *et al.* reported one patient who remained free from exercise-induced attacks while walking 5 miles per day, but EIA symptoms recurred following resumption of exercise after a several month period of inactivity. Other patients have described a “refractory period” following an attack of EIA, during which time they could exercise without risk of subsequent attack [19].

Delayed pressure urticaria

Clinical features

DPU is another syndrome in which the association has been made between the ingestion of food and the development of a physically induced cutaneous reaction [72–80]. This unusual disease, which is more prevalent than previously appreciated, is characterized by the delayed onset of deep cutaneous swellings in areas exposed to prolonged pressure of variable intensity. The appearance of the pressure-induced swelling of the hands and feet is indistinguishable from that of angioedema. The onset of lesions can occur within 30 minutes to 9 hours of application of pressure from a variety of stimuli (e.g. for the feet, prolonged walking on a hard surface; for the shoulder, carrying luggage; and for the hands, hammering nails). The lesions usually peak 6–9 hours after pressure and may last as long as 36 hours. There may be a refractory period for development of new lesions in locations with recent urticaria [81]. In 30–90% of patients, DPU can be associated with chronic idiopathic urticaria [75,77,79]. Some patients develop “flu-like” symptoms (malaise, arthralgias, and fever) in association with the skin lesions. Almost half patients with DPU have an elevated erythrocyte sedimentation rate (ESR) and mild leukocytosis with or without eosinophilia. Usually the delayed pressure symptoms and reactivity parallel the activity of the chronic urticaria and can persist up to 30 years. The condition often creates a significant functional disability, especially in individuals whose occupations require heavy physical labor, such as carpenters, construction workers, and auto mechanics [75].

Diagnosis

DPU is best diagnosed by a thorough history. Many patients have been incorrectly diagnosed as having refractory angioedema in association with their chronic urticaria. The diagnosis can be confirmed using several tests [74–77,80,81]. The simplest and most reliable test utilizes 15 lb of weight split into two sandbags connected by a thin strap. This device is then suspended over the shoulder for a period of 15 minutes while the patient is walking [74]. The shoulder is examined 4–8 hours after challenge for the development of a deep, often painful, erythematous swelling. In most cases the test is positive initially. In patients with a good history and a negative initial test, a follow-up

test at least 48 hours later may be positive. The test can be negative when the disease is quiescent or in remission.

Pathophysiology

The pathogenesis of DPU remains unclear. Lesions can be induced by injections of compound 48/80 into the skin, suggesting that release of mast cell mediators may be important in lesion induction [82]. Increased histamine levels have been shown in skin blisters above the lesions [77]. Biopsy specimens reveal mild mononuclear perivascular infiltrates with some eosinophils and a small number of polymorphonuclear leukocytes [83]. Fibrin deposition and edema among the collagen fibers at the pressure challenge site suggest a similarity between the lesions of DPU and those generated by the cutaneous late-phase reaction seen after allergen injection [84]. Barlow [85] proposes a lower threshold in DPU patients to form wheals compared to control subjects. Hermes and colleagues noted endothelial cell upregulation of tumor necrosis factor (TNF)- α and IL-3 in non-lesional skin of patients with DPU, and upregulation of TNF- α production in perivascular cells [86]. They suggest a role for these cytokines in the pathogenesis of DPU by an induction of sub-threshold inflammation in endothelial cells of uninvolved skin. Kallikrein generation [77], leukotriene production [77], and cytokine release in lesions [82] have been hypothesized but, to date, not confirmed. As with other causes of urticaria, aspirin appears to have a potentiating effect on the development of urticarial lesions in DPU [87,88].

Treatment

The pressure-induced lesions of most patients with DPU respond poorly to standard drugs used in the treatment of chronic urticaria and angioedema. The only medications that consistently relieve the delayed pressure symptoms are systemic corticosteroids [74–76,79]. Some patients require relatively high doses of these agents and prolonged therapy to remain functional and able to work. The delayed pressure component often does not respond to conventional H1 antihistamine alone or to a combination of H1 and H2 antihistamines [71–76,79]. Cetirizine reportedly has been effective in some patients [88,89]. Leukotriene antagonists have been shown effective in chronic idiopathic urticaria but are poorly studied in DPU [91–95]. Berkun and colleagues [94] reported the first case of a patient with steroid-dependent DPU responding to the leukotriene antagonist montelukast. One small randomized, double-blind study of 20 patients with DPU comparing loratadine to loratadine plus montelukast found the combination to be more effective at suppressing pressure-induced reactions than loratadine alone [95]. Another small study showed the addition of theophylline to cetirizine to be more effective than cetirizine monotherapy [96]. Sulfasalazine, at doses used in inflammatory bowel disease, was found to be an effective steroid-sparing

agent for angioedema in two patients with refractory DPU [97]. Some patients [75] respond partially to NSAIDs, but this has not been observed consistently [79]. Limited studies have demonstrated the effectiveness of higher potency topical corticosteroids [98,99]. High-dose intravenous immunoglobulin induced remission or improved symptoms in five of eight patients with DPU considered to be severe and refractory to other therapies or responding only to oral corticosteroids [100]. The role in DPU of other agents used with some success in chronic idiopathic urticaria such as antimalarials [101], hydroxychloroquine [102], cyclosporine [103], dapsone [104,105], pentoxifylline [105], methotrexate [106], stanazolol [107], and calcineurin inhibitors [108] remains to be seen.

Food-related delayed pressure urticaria

Specific causal factors for DPU are rarely identified; however, Davis and colleagues [109] identified specific food ingestion as an exacerbating factor. In this report, six selected patients with challenge-proven DPU and chronic idiopathic urticaria were studied, all of whom required daily prednisone for symptomatic control. The patients either fasted, receiving only water, or were given a diet of unflavored Vivonex for a minimum of 48 hours. In five of the six patients, both spontaneous urticarial lesions and pressure-induced symptoms cleared after 24–48 hours of fasting. A control group of patients with chronic urticaria was treated in the same way, but none responded to the fast. All patients who had resolution of urticaria with fasting had at least one positive delayed cutaneous reaction (measured at 6 hours) on SPT with food antigens. Ingestion of foods producing a positive delayed cutaneous reaction was followed within 2–24 hours by recurrence of spontaneous and pressure-induced urticaria. Interestingly, RAST to foods causing positive delayed cutaneous reactions and recurrence of urticaria were negative.

A subsequent report described two patients with DPU in whom lesions could be elicited when they had eaten typical foods but not when they had been on at least 5 days of an elimination diet [110]. Skin testing was not described, however. In another study by Czarnetzki *et al.* [111], 13 patients with DPU and positive cutaneous prick testing responses to foods failed to respond to elimination diets. All of the subjects underwent testing to a large battery of common allergens, including food extracts. Seven of these patients had positive early cutaneous reactions (15 minutes), and six developed positive late cutaneous reactions (after 6 hours). None of the patients, however, showed any improvement on diets that eliminated those food antigens to which they developed a late cutaneous reaction. It is not clear whether any of the patients fasted for any prolonged period of time to exclude other allergens that were not part of the skin test battery.

Although a role for food ingestion in the causation of DPU has been suggested, it has not been well documented or proved. In over 20 years since the report by Davis *et al.* [109]

summarized above, few studies convincingly implicating food ingestion as a possible cause of DPU have been published. Vidal *et al.* reported one additional case of delayed pressure urticaria that appeared to occur only in association with egg ingestion [112]. Whereas none of the patients reported in the case series by Davis *et al.* had detectable IgE to the suspected foods, this patient did have egg-specific IgE detected on RAST and SPT.

Thus, while efforts to exclude specific foods as contributing factors to cutaneous eruptions in patients with DPU appear unlikely to contribute significantly, given the high morbidity of DPU in some patients, including the potential requirement for long-term systemic corticosteroid therapy, it may be worthwhile to consider ingestants as aggravating factors in almost any patient with DPU.

Other food/physical syndromes

Strong evidence for the role of food in eliciting other physical allergy syndromes is lacking. Zuberbier and colleagues [113] describe the case of a 43-year-old woman with angioedema resulting from a combination of non-specific food intake and elevation of body temperature. Pseudoallergic reactions to hot, cold, or spicy foods may elicit CU responses, but true allergic responses involving food ingestion have not been reported to contribute to other physical urticaria syndromes including dermatographism, solar urticaria, aquagenic urticaria, or vibratory angioedema.

Conclusions

Of the physical allergy syndromes, food allergy appears to play a role in a significant subset of patients with EIA and possibly DPU. In the case of FDEIA, the historical association of specific or non-specific food ingestion with the exercise-induced attacks may not be readily apparent but may not be uncommon. As a result, in patients with EIA in whom the possibility that food may be contributing to anaphylaxis attacks cannot be excluded historically, a thorough investigation including specific IgE testing to a variety of common foods should be considered. Because nearly all patients with specific FDEIA are able to prevent attacks of EIA by avoiding suspected foods 4 hours before exercise, this approach may contribute significantly to the quality of life in patients who may otherwise impose disabling restrictions on their physical activity in an effort to avoid attacks. Though the role of food allergy in DPU is less clear, the significant morbidity of pressure avoidance and lack of proven non-toxic therapies for this condition also warrant consideration of foods as potential co-precipitants. Future studies are clearly needed to help guide clinicians in the management and treatment of these chronic conditions.

References

- 1 Sheffer AL, Austen KR. Exercise induced anaphylaxis. *J Allergy Clin Immunol* 1980;66:106–11.
- 2 Lewis J, Lieberman P, Treadwell G, Erffmeyer J. Exercise induced urticaria, angioedema, and anaphylactoid episodes. *J Allergy Clin Immunol* 1981;68:432–7.
- 3 Sheffer AL, Soter NA, McFadden ER, Austen KR. Exercise induced anaphylaxis: a distinct form of physical allergy. *J Allergy Clin Immunol* 1983;7:311–16.
- 4 Kapla AP, Natbony SE, Tawil AP, *et al.* Exercise-induced anaphylaxis as a manifestation of cholinergic urticaria. *J Allergy Clin Immunol* 1981;68:319–24.
- 5 Songsiridej V, Busse WW. Exercise-induced anaphylaxis. *Clin Allergy* 1983;13:317–21.
- 6 Casale TB, Kehey TM, Kaliner M. Exercise-induced anaphylactic syndromes: insights into diagnostic and pathophysiologic features. *JAMA* 1986;255:2049–53.
- 7 Tilles S, Schocket A, Milgrom H. Exercise-induced anaphylaxis related to specific foods. *J Pediatrics* 1995;127:587–9.
- 8 Tilles SA, Schocket AL. Exercise-induced anaphylaxis. *Pact Allergy Immunol* 1994;9:64–7.
- 9 Volcheck GW, Li JT. Exercise-induced urticaria and anaphylaxis. *Mayo Clin Proc* 1997;72:140–7.
- 10 Lieberman P, Kemp SE, Oppenheimer J, *et al.* The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115:S483–523.
- 11 Castells MC, Horan RE, Sheffer AL. Exercise-induced anaphylaxis. *Curr Allergy Asthma Rep* 2003;3:15–21.
- 12 Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol* 2006;97:39–43.
- 13 Shadick NA, Liang MH, Partridge AJ, *et al.* The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study. *J Allergy Clin Immunol* 1999;104:123–7.
- 14 Kaplan A. Urticaria and angioedema. In: Adkinson NE, Yuninger JW, Busse WW, Bochner BS, Holgate ST, Simons FER (eds.) *Middleton's Allergy Principles and Practice*, 6th edn. Philadelphia, PA: Mosby, 2003:1537–58.
- 15 Perkins DN, Keith PK. Food- and exercise-induced anaphylaxis: importance of history in diagnosis. *Ann Allergy Asthma Clin Immunol* 2002;89:15–23.
- 16 Schwartz H. Elevated serum tryptase in exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1995;95:917–19.
- 17 Sheffer AL, Tong AKF, Murphy GE, *et al.* Exercise-induced anaphylaxis: a serious form of physical allergy associated with mast cell degranulation. *J Allergy Clin Immunol* 1985;75:479–84.
- 18 Sheffer AL, Austen KF. Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1984;73:699–703.
- 19 Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiologic observations. *Prog Clin Biol Res* 1989;297: 175–82.
- 20 Aihara Y, Takahashi Y, Kotoyori T, *et al.* Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol* 2001;108:1035–9.

- 21 Harada S, Horikawa T, Ichihashi M. A study of food-dependent exercise-induced anaphylaxis by analyzing the Japanese cases reported in the literature. *Aerugi* 2000;49:1066–73.
- 22 Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979;63:433–4.
- 23 Romano A, Di Fonso M, Guiffreda F, *et al.* Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects. *Int Arch Allergy Immunol* 2001;125:264–72.
- 24 Silverstein SR, Frommer DA, Dobozin B, Rosen P. Celery dependent exercise-induced anaphylaxis. *J Emerg Med* 1986;4:195–9.
- 25 Dohi M, Suko M, Sugiyama H, *et al.* Food-dependent exercise induced anaphylaxis: a study on eleven Japanese cases. *J Allergy Clin Immunol* 1992;87:34–40.
- 26 Anibarro B, Domíquez C, Díaz JM, *et al.* Apple-dependent exercise-induced anaphylaxis. *Allergy* 1994;49:482.
- 27 Munoz MF, Lopez CJM, Villas F, *et al.* Exercise-induced anaphylactic reaction to hazel-nut. *Allergy* 1994;49:314–16.
- 28 Aihara Y, Kotoyori T, Takahashi Y, *et al.* The necessity for dual food intake to provoke food-dependent exercise-induced anaphylaxis (FEIAN): a case report of FEIAN with simultaneous intake of wheat and umeboshi. *J Allergy Clin Immunol* 2001;107:1100–5.
- 29 Guinépain MT, Eliot C, Raffard M, *et al.* Exercise-induced anaphylaxis: useful screening of food sensitization. *Ann Allergy Asthma Immunol* 1996;77:491–6.
- 30 Kidd JM, Cohen SH, Sosman AL, Fink JN. Food-dependent exercise induced anaphylaxis. *J Allergy Clin Immunol* 1983;71:407–11.
- 31 Biederman T, Schopf P, Rueff F, Przybilla B. Exertion-induced anaphylaxis after eating pork and beef. *Dtsch Med Wochenschr* 1999;124:456–8.
- 32 Novey HS, Fairshter RD, Salness K, *et al.* Postprandial exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983;71:498–504.
- 33 Fiocchi A, Mirri GP, Santini I, *et al.* Exercise-induced anaphylaxis after food contaminant ingestion in double-blinded, placebo-controlled, food-exercise challenge. *J Allergy Clin Immunol* 1997;100:424–5.
- 34 Figueroa J, Blanco C, Dumpierrez AG, *et al.* Mustard allergy confirmed by double-blind placebo-controlled food challenges: clinical features and cross-reactivity with mugwort pollen and plant-derived foods. *Allergy* 2005;60:48–55.
- 35 Longo G, Barbi E, Puppini F. Exercise-induced anaphylaxis to snails. *Allergy* 2000;55:513–14.
- 36 Senna G, Mistrello G, Roncarlo D, *et al.* Exercise-induced anaphylaxis to grape. *Allergy* 2001;56:1235–6.
- 37 Garcia-Ara MC, Sanchez AV, Boyano Martinez MT, *et al.* Cow's milk-dependent, exercise-induced anaphylaxis: case report of a patient with previous allergy to cow's milk. *J Allergy Clin Immunol* 2003;111:647–8.
- 38 Pauls JD, Cross D. Food-dependent exercise-induced anaphylaxis to corn. *J Allergy Clin Immunol* 1998;101:853–4.
- 39 Fiedler EM, Zuberbier T, Worm M. A combination of wheat-flour, ethanol and food additives inducing FDEIA. *Allergy* 2002;57:1090–1.
- 40 Kutting B, Brehler R. Exercise-induced anaphylaxis. *Allergy* 2000;55:585–6.
- 41 Perez-Pimiento AJ, Moneo I, Santaolalla M, *et al.* Anaphylactic reaction to young garlic. *Allergy* 1999;54:626–9.
- 42 Porcel S, Sanchez AB, Rodriguez E, *et al.* Food-dependent exercise-induced anaphylaxis to pistachio. *J Investig Allergol Clin Immunol* 2006;16:71–3.
- 43 Hanakawa Y, Tohyama M, Shirakata Y, *et al.* Food-dependent exercise-induced anaphylaxis: a case related to the amount of food allergen ingested. *Br J Dermatol* 1998;138:898–900.
- 44 Palosuo K, Alenius H, Varjonen E, *et al.* Rye-gamma-70 and gamma-35 secalins and barley gamma-3 hordein cross-react with omega-5 gliadin, a major allergen in wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2001;31:466–73.
- 45 Dreborg S. Food allergy in pollen-sensitive patients. *Ann Allergy* 1988;61:41–6.
- 46 Harada S, Horikawa T, Ashida M, *et al.* Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis. *Br J Dermatol* 2001;145:336–9.
- 47 Aihara M, Miyazawa, Osuna H, *et al.* Food-dependent exercise-induced anaphylaxis: influence of concurrent aspirin administration on skin testing and provocation. *Br J Dermatol* 2002;146:466–72.
- 48 Dohi M, Suki M, Sugiyama H, *et al.* 3 cases of food-dependent exercise-induced anaphylaxis in which aspirin intake exacerbated anaphylactic symptoms. *Arerugi* 1990;39:1598–604.
- 49 Varjonen E, Vainio E, Kalimo K. Life-threatening, recurrent anaphylaxis caused by allergy to gliadin and exercise. *Clin Exp Allergy* 1997;27:162–6.
- 50 Paluoso K. Update on wheat hypersensitivity. *Curr Opin Allergy Clin Immunol* 2003;205–9.
- 51 Foreman JC, Piotrowski W. Peptides and histamine release. *J Allergy Clin Immunol* 1984;74:127–31.
- 52 Miadonna A, Tedeschi A, Leggeri E, *et al.* Activity of substance P on human skin and nasal airways. *Ann Allergy* 1988; 61:220–3.
- 53 Wallengren J, Moller H, Ekman R. Occurrence of substance P vasoactive intestinal peptide, and calcitonin gene-related peptide in dermographism and cold urticaria. *Arch Dermatol Res* 1987;279:512–15.
- 54 Tharp MD, Thirlby R, Sullivan TJ. Gastrin induces histamine release from human cutaneous mast cells. *J Allergy Clin Immunol* 1984;74:159–65.
- 55 Kivity S, Ephraim S, Greif J, *et al.* The effect of food and exercise on the skin response to compound 48/80 in patients with food associated exercise induced urticaria angioedema. *J Allergy Clin Immunol* 1988;81:1155–8.
- 56 Errington G, Mekori Y, Silvers W, Schocket A. Altered mast cell threshold in exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1985;75:193.
- 57 Lin RY, Barnard M. Skin testing with food, codeine, and histamine in exercise-induced anaphylaxis. *Ann Allergy* 1993;70:475–8.
- 58 Matsuo H, Morimoto K, Akaki T, *et al.* Exercise and aspirin increase levels of circulating gliadin peptides in patients with

- wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2005;35:461–6.
- 59 Pals KL, Chang RT, Ryan AJ, *et al.* Effect of running intensity on intestinal permeability. *J Appl Physiol* 1997;82:571–6.
 - 60 Ryan AJ, Chang RT, Gisolfi CV. Gastrointestinal permeability following aspirin intake and prolonged running. *Med Sci Sports Exerc* 1996;28:698–705.
 - 61 Otte JA, Oostveen E, Geelkerken RH, *et al.* Exercise induces gastric ischemia in healthy volunteers: a tonometric study. *J Appl Physiol* 2001;91:866–71.
 - 62 Matsuo H, Kohno K, Niihara H, *et al.* Specific IgE determination to epitope peptides of omega-5 gliadin and high molecular weight glutenin is a useful tool for diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Immunol* 2005;175: 8116–22.
 - 63 Battais F, Mothes T, Moneret-Vautrin DA, *et al.* Identification of IgE binding epitopes on gliadins for patients with food allergy to wheat. *Allergy* 2005;60:815–21.
 - 64 Mathison DA, Lumry WR, Stevenson DD, *et al.* Aspirin in chronic urticaria and/or angioedema: studies of sensitivity and desensitization. *J Allergy Clin Immunol* 1982;69:135.
 - 65 Somasundaram S, Hayllar H, Rafi S, *et al.* The biochemical basis of non-steroidal anti-inflammatory drug-induced damage to the gastro-intestinal tract: a review and a hypothesis. *Scand J Gastroenterol* 1995;30:289–99.
 - 66 Tilles S, Schocket A, Milgrom H. Exercise-induced anaphylaxis related to specific foods. *J Pediatr* 1995;127:587–9.
 - 67 Fujimoto S, Kurihara N, Hirata K, *et al.* Successful prophylaxis of wheat-dependent exercise-induced anaphylaxis with terfenadine. *Intern Med* 1995;34:654–6.
 - 68 Juji F, Suko M. Effectiveness of disodium cromoglycate in food-dependent, exercise-induced anaphylaxis: a case report. *Ann Allergy* 1994;72:452–4.
 - 69 Dessanges J, Prefaut C, Taytard A, *et al.* The effect of zafirlukast on repetitive exercise-induced bronchoconstriction: the possible role of leukotrienes in exercise-induced refractoriness. *J Allergy Clin Immunol* 1999;104:1155–61.
 - 70 Pearlman DS, van Adelsberg J, Philip G, *et al.* Onset and duration of protection against exercise-induced bronchoconstriction by a single oral dose of montelukast. *Ann Allergy Asthma Immunol* 2006;97:98–104.
 - 71 Noma T, Yoshigawa I, Ogawa N, *et al.* Fatal buckwheat dependent exercise-induced anaphylaxis. *Asian Pac J Allergy Immunol* 2001;19:283–6.
 - 72 Kalz M, Bower C, Prichard H. Delayed and persistent dermographia. *Arch Dermatol Syph* 1950;61:772–80.
 - 73 Baughman RD, Jillson OE. Seven specific types of urticaria: with special reference to delayed persistent dermographism. *Ann Allergy* 1963;21:248–55.
 - 74 Ryan TJ, Shim-Young N, Turk JL. Delayed pressure urticaria. *Br J Dermatol* 1968;80:485–90.
 - 75 Warin R, Champion RH. *Urticaria*. London: WB Saunders, 1974.
 - 76 Sussman GL, Harvey RP, Schocket AL. Delayed pressure urticaria. *J Allergy Clin Immunol* 1982;70:337–42.
 - 77 Czarnetzki B. *Urticaria*. Berlin: Springer-Verlag, 1986.
 - 78 Czarnetzki B, Meentken J, Rosenbach T, Pokropp A. Clinical, pharmacological and immunological aspects of delayed pressure urticaria. *Br J Dermatol* 1984;111:315–23.
 - 79 Dover JS, Black AK, Ward AM, Greaves MW. Delayed pressure urticaria: clinical features, laboratory investigations, and response therapy of 44 patients. *J Am Acad Dermatol* 1988;18: 1289–98.
 - 80 Lawlor F, Kobza Black A. Delayed pressure urticaria. *Immunol Allergy Clin North Am* 2004;24:247–58.
 - 81 Estes SA, Yung CW. Delayed pressure urticaria: an investigation of some parameters of lesion induction. *Am Acad Dermatol* 1981;5:25–31.
 - 82 Davis K, Mekori Y, Kohler P, Schocket A. Late cutaneous reactions in patients with delayed pressure urticaria. *J Allergy Clin Immunol* 1984;73:810–12.
 - 83 Czarnetzki B, Meentken J, Kolde G, Brocket E. Morphology of the cellular infiltrate in delayed pressure urticaria. *J Am Acad Dermatol* 1985;12:253–9.
 - 84 Mekori Y, Dobozi B, Schocket A, *et al.* Delayed pressure urticaria histologically resembles cutaneous late-phase reactions. *Arch Dermatol* 1988;124:230–5.
 - 85 Barlow RJ. Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. *J Am Acad Derm* 1999; 29:954–8.
 - 86 Hermes B, Prochazka AK, Haas N, *et al.* Upregulation of TNF-alpha and IL-3 expression in lesional and uninvolved skin in different types of urticaria. *J Allergy Clin Immunol* 1999;103: 307–14.
 - 87 Doeglas H. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol* 1975;93:135–44.
 - 88 Murdoch RD, Pollock L, Young E. Effects of food additives on leukocyte histamine release in normal and urticaria subjects. *J Roy Coll Phys Lond* 1987;21:251–6.
 - 89 Kontou-Fili K, Maniatakou G, Paleologos G, Atom K. Cetrizine inhibits delayed pressure urticaria (part 2): skin biopsy findings. *Ann Allergy* 1990;65:520–2.
 - 90 Kontou-Fili K, Maniatakou G, Demaka P, *et al.* Therapeutic effects of cetrizine in delayed pressure urticaria (part 1): effects on weight tests and skin window cytology. *Ann Allergy* 1990; 65:517–19.
 - 91 Chu TK, Warren MS. Zafirlukast (Accolate) in the treatment of chronic idiopathic urticaria – a case series. *J Allergy Clin Immunol* 1998;101:s155.
 - 92 Spector S, Tan TA. Leukotrienes in chronic urticaria. *J Allergy Clin Immunol* 1998;101:572.
 - 93 Ellis MH. Successful treatment of chronic urticaria with leukotriene antagonists. *J Allergy Clin Immunol* 1998;102:876–7.
 - 94 Berkun Y, Shalit M. Successful treatment of delayed pressure urticaria with montelukast. *Allergy* 2000;55:203–4.

- 95 Nettis E, Pannofino A, Cavallo E. Efficacy of montelukast, in combination with loratadine, in the treatment of delayed pressure urticaria. *J Allergy and Clin Immunol* 2003;112:212–13.
- 96 Kalogeromitros D, Kempuraj D, Katsorou-Katsari A. Theophylline as “add-on” therapy in patients with delayed pressure urticaria: prospective self-controlled study. *Int J Immunopathol Pharmacol* 2005;18:595–602.
- 97 Engler RJ, Squire E, Benson P. Chronic sulfasalazine therapy in the treatment of delayed pressure urticaria and angioedema. *Ann Allergy Asthma Immunol* 1995;74:155–9.
- 98 Vena GA, Cassano N, D’Argento, *et al.* Clobetasol propionate 0.05% in a novel foam formulation is safe and effective in the short-term treatment of patients with delayed pressure urticaria: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006;154:353–6.
- 99 Barlow R, Macdonald DM. The effects of topical corticosteroids on delayed pressure urticaria. *Arch Dermatol Res* 1995;287:285–8.
- 100 Dawn G, Urcelay M, Ah-Weng A, *et al.* Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. *Br J Dermatol* 2003;149:836–40.
- 101 Koranda FC. Antimalarials. *J Am Acad Dermatol* 1981;4:650–5.
- 102 Lopez LR, Davis KC, Kohler PF, Schocket AL. The hypocomplementemic urticarial-vasculitis syndrome: therapeutic response to hydroxychloroquine. *J Allergy Clin Immunol* 1984;73:600–3.
- 103 Loria MP, Dambra PP, D’Oronzio L, *et al.* Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol Immunotoxicol* 2001;23:205–13.
- 104 Boehm I, Bauer R, Bieber T. Urticaria treated with dapsone. *Allergy* 1999;54:765–6.
- 105 Nurnberg W, Grabbe J, Czarnetzki BM. Urticarial vasculitis syndrome effectively treated with dapsone and pentoxifylline. *Acta Derm Venereol* 1995;75:54–6.
- 106 Gach JE, Sabroe RA, Greaves MW, Kobza-Black A. Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. *Br J Dermatol* 2001;145:340–3.
- 107 Parsad D, Pandhi R, Juneja A. Stanazolol in chronic urticaria: a double-blinded placebo controlled trial. *J Dermatol* 2001;28:299–302.
- 108 Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. *J Am Acad Dermatol* 2005;52:145–8.
- 109 Davis K, Mekori Y, Kohler P, Schocket A. Possible role of diet in delayed pressure urticaria – preliminary report. *J Allergy Clin Immunol* 1986;77:566–9.
- 110 Rajka P, Mork NJ. Clinical observations of the mechanisms of delayed pressure urticaria. In: Chamion RH, Greaves MW, Black AK, Pye RJ (eds.) *The Urticarias*. New York: Churchill Livingstone, 1985:191–3.
- 111 Czarnetzki B, Cap H, Forck G. Late cutaneous reactions to common allergens in patients with delayed pressure urticaria. *Br J Dermatol* 1987;117:695–701.
- 112 Vidal C, Moreno E, Rodriguez M, *et al.* Delayed pressure urticaria and egg allergy. *Int J Dermatol* 1991;30:674.
- 113 Zuberbier T, Bohm M, Czarnetzki B. Food intake in combination with a rise in body temperature: a newly identifiable cause of angioedema. *J Allergy Clin Immunol* 1993;91:1226–7.