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INVITED REVIEW ARTICLE

Food-dependent exercise-induced anaphylaxis

Eishin Morita^{a,*}, Kohno Kunie^a, Hiroaki Matsuo^b

^a Department of Dermatology, Shimane University School of Medicine, 89-1 Enya, Izumo 693-8501, Japan

^b Division of Pharmacotherapeutics, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

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High molecular weight
glutenin;
Aspirin

Summary Food-dependent exercise induced anaphylaxis (FDEIA) is a distinct form of food allergy induced by physical exercise. Symptoms are typically generalized urticaria and severe allergic reactions such as shock or hypotension. Whereas various food items are responsible for the development of FDEIA, wheat is reported to be the allergen with the highest frequency in Japan. Recently aspirin has been known to be an additional exacerbating factor. Skin tests and *in vitro* serum food-specific IgE assays are currently used, however their sensitivity and specificity are not always satisfactory. A challenge test consisting of ingestion of assumed food followed by intense physical exercise is the only reliable method to determine the causative food and to diagnose the disease. The challenge test is not always safe because in some cases the test induces an anaphylactic shock. So a reliable *in vitro* diagnostic method is necessary for the patients with FDEIA. We revealed that wheat omega-5 gliadin and high molecular weight glutenin subunit are major allergens in wheat-dependent exercise-induced anaphylaxis (WDEIA). A simultaneous detection of specific IgE to epitope sequences of both omega-5 gliadin and high molecular weight glutenin is found to achieve higher sensitivity and specificity compared with the *in vitro* serum food-specific IgE assays currently used for diagnosis of WDEIA. On the other hand, immunoreactive gliadins appeared in the sera of patients during the provocation test with both wheat-exercise and wheat-aspirin challenges in parallel with allergic symptoms. These findings suggest that FDEIA is IgE-mediated hypersensitivity reaction to foods and both exercise and aspirin facilitate allergen absorption from the gastrointestinal tract.

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* Corresponding author. Tel.: +81 853 20 2210; fax: +81 853 21 8317.
E-mail address: emorita@med.shimane-u.ac.jp (E. Morita).

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1. Introduction

Nowadays IgE-mediated hypersensitivity to foods is clearly recognized as food allergy. Limited numbers of life-threatening anaphylactoid reactions have been observed associated with exercise [1]. Within this clinical entity considerable numbers of cases show anaphylactic reactions during or in association with exercise after ingestion of foods. A case of exercise-induced anaphylaxis was first reported by Maulitz et al. in 1979 [2] as a previously undescribed late allergic reaction to shellfish induced by strenuous exercise. In 1983, Kidd et al. [3] reported four cases of exercise-induced anaphylaxis (EIA) occurring only in combination with the ingestion of food, and initially described as food-dependent exercise-induced anaphylaxis (FDEIA). Three of these four cases were proved as having celery-allergy. The first case of FDEIA in Japan was described by Kushimoto and Aoki in 1985 [4], and the cause of the food reaction was wheat. Since these initial reports, numerous foods have been implicated in FDEIA/anaphylaxis and further clinical features of the disease have been documented.

2. Epidemiology

Data regarding the incidence of FDEIA are limited. According to a study in Japanese children, 0.06% of the elementary school students, and 0.21% of the junior high school students suffer from FDEIA [5]. In a larger study the incidence in Japanese students was calculated to be 0.012% with a prevalence of 0.017% for junior high school students and 0.0086% for high school students [6].

In an analysis of 167 Japanese FDEIA cases [7], the disease was more frequent in children than in adults with a higher peak incidence in the second decade and a lower peak of incidence in the fourth decade. Men are more frequently affected than women (M/F = 2:1), although the reason for this is unknown.

3. Clinical manifestation

These anaphylactic symptoms are usually induced by physical exercise after food ingestion. The typical symptoms include skin manifestations, respiratory symptoms, abdominal pain, fatigue and loss of consciousness. The skin manifestations include generalized urticaria, angioedema, and/or erythema, and these are seen in most patients. Dyspnea is experienced by approximately 60% of patients. The dyspnea is characterized as a choking sensation in the throat: therefore, this is believed to be caused not by smooth muscle spasm of the lower respiratory tract but by angioedema of the upper airway tract mucosa. Loss of consciousness is seen approximately in 30% of patients. Numerous episodes of these symptoms during exercise are common in these patients. Eighty percent of these patients have symptoms within 2 h after eating causative food types.

In many case reports strenuous exercise, such as running and playing tennis, triggers or increases the likelihood of anaphylaxis after ingesting specific allergen inducing food(s) [2–4]. However, milder exercise may also induce these symptoms. One patient has been reported performing exercise before eating food that induced these symptoms [3].

This clinical entity is clearly distinguishable from cholinergic urticaria because (1) the FDEIA patients demonstrate systemic symptoms, including loss of consciousness, upper airway obstruction, or abdominal pain, (2) urticaria observed in FDEIA patients is the more usual wheal and erythema type often progressing to diffuse erythema, and is different from the pin-head sized wheal characteristic of cholinergic urticaria, (3) FDEIA patients generally have not experienced their symptoms in response to warmth (such as a hot bath), or other condition which increases the core body temperature and (4) they have symptoms only in association with an ingestion of specific food(s).

A differential diagnosis with EIA is more controversial. EIA is recognized as a physical allergy, and is characterized by an anaphylactoid reaction induced

Table 1 Triggering factors in FDEIA

Foods (amounts, sort and combination)
Exercise (strength, type of exercise, duration and timing after meal)
General conditions (fatigue, sleep, common cold, stress and menstruation)
Drugs (aspirin and NSAIDs)
Alcohol
Atmospheric condition/seasonal

by strenuous exercise [1,8–13]. In early descriptions, however, some EIA cases showed hypersensitivity to specific foods [13,14], and thus FDEIA was considered as a variant of EIA.

Triggering factors in FDEIA include foods, exercise, the patient's general condition, drugs, alcohol, and atmospheric and seasonal conditions as listed in Table 1. Induction of anaphylaxis has clearly been demonstrated to be dependent on the amount of allergen ingested by the patient with wheat-dependent exercise-induced anaphylaxis (WDEIA) [15]. Specific combinations of food intake may be necessary for allergy induction in some FDEIA cases in provoking their symptoms [16]. Fatigue, cold, and lack of sleep appeared to affect the development of the anaphylactic symptoms [17]. Some cases of cold-induced FDEIA were described [18]. There are also cases in which stages of menstrual cycle affected the onset of FDEIA [17]. Aspirin intake has been well documented to induce symptoms or to provoke more severe symptoms compared with those without aspirin intake [17,19,20]. Aspirin also induces symptoms in combination with food ingestion even without an exercise challenge [19,20].

4. Causative foods and allergens

4.1. Causative foods

A variety of foods have been described as causal allergy inducing foods in FDEIA. These include shellfish [2,14,17,19,21], wheat products [4,14,15–20],

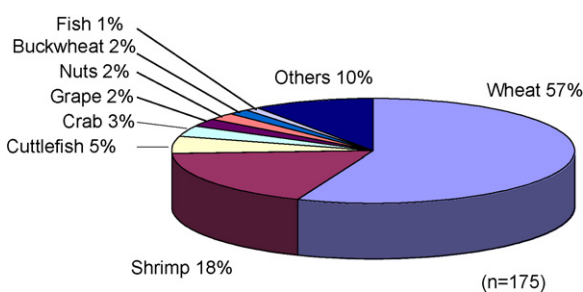


Fig. 1 Frequency of causative foods in Japanese patients with FDEIA.

vegetables [3,14,22,23], fruits [14,17,24], nuts [14], egg [14,25], mushrooms [26], corn [14,27], garlic [14], meat including pork/beef [14], and rice [14]. In European countries, vegetables are the most common food allergens. Among them tomatoes were the most frequent [14]. However, in Japan, wheat is the most frequent allergenic food as reported by Harada et al. [7] as shown in Fig. 1.

4.2. Allergens and epitopes

Although various foods, such as shellfish, hazel nuts, celery, corn, are reported in association with FDEIA, wheat is reported to be the most frequent allergenic food, especially in Japan [7]. Wheat comprises four classes of proteins, albumins and globulins, both of which are water and salt soluble proteins, and gliadins and glutenins, both of which are water and salt insoluble proteins [28]. Wheat allergens have mainly been analyzed in baker's asthma, a hypersensitivity to inhaled wheat flour, and several antigens were identified in both the water/salt soluble and insoluble fractions [29,30]. The identity of the main wheat allergens in FDEIA is rather complicated issue. Wheat gliadins, which are major components of the gluten fraction, were found to be the allergens in cereal-dependent exercise-induced anaphylaxis by skin test studies and immunoblotting [31–33]. Recently omega-5 gliadin has been identified as a cause of WDEIA [34,35]. Analysis with a panel of purified gliadins and glutenins revealed that 80% of the patients with WDEIA most strongly react to omega-5 gliadin and the rest of the patients to high molecular weight glutenin [36]. When IgE-binding epitopes were analyzed using arrays of overlapping peptides, seven epitopes, QQIPQQQ, QQLPQQQ, QQFPQQQ, QQSPEQQ, QQSPQQQ, QQYPQQQ and PYPP, were detected within the primary sequence of omega-5 gliadin [36]. By using sera from 15 patients, four of them, QQIPQQQ, QQFPQQQ, QQSPEQQ and QQSPQQQ, were found to be the dominant epitopes. Mutational analysis of the QQIPQQQ and QQFPQQQ peptides indicated that amino acids at position 1(Q), 4(P), 5(Q), 6(Q) and 7(Q) were critical for IgE-binding [36]. IgE-binding epitopes in the high molecular weight glutenin were identified to be QQPGQ, QQPGQGQ, and QQSGQGQ [37]. These epitopes were found to appear repetitively in these proteins, indicating multivalent allergenic property of these proteins (Figs. 2 and 3).

5. Mechanisms

The main distinctive feature of FDEIA is that some foods cause a severe systemic anaphylactic reaction

SRLLSPRGKELHTPQEQQFPQQQFPQPQQFPQQQIP
 QQHQIPQQPQQFPQQQQLQQQQIPQQHQIP
 QQPQQFPQQQFPQQHQSPQQFPQQQFPQQKL
 QQEFPPQQISQQPQQLPQQQQIPQQPQQFLQQQF
 PQQQPPQQHQFPQQQLPQQQQIPQQQQIPQQPQQI
 PQQQIPQQPQQFPQQQFPQQQFPQQQFPQQEFPPQ
 QQQFPQQIARPPQQLPQQQQIPQQPQQFPQQQF
 PQQQSPQQQFPQQQFPQQQLPQKQFPQPQQIPQ
 QQQIPQQPQQFPQQQFPQQQFPQQQEFPPQQFPQ
 QQFHQQQLPQQFPQQQFPQQQFPQQQFPQQQ
 LTQQQFPRPQQSPQQFPQQQFPQQPPQQFPQQQ
 FPIPYPPQQSEEPSYQYPPQQPSGSDVISISGL

Fig. 2 Amino acid sequence of omega-5 gliadin and distribution of four predominant IgE-binding epitopes, QQIPQQQ, QQFPQQQ, QQSPEQQ, and QQSPQQQ.

when followed by physical exercise, but are usually tolerated if not followed by exercise. The mechanisms by which exercise induces this reaction are controversial. Scheffer et al. demonstrated that exercise enhances the degranulation of mast cells in patients with exercise-induced anaphylaxis [11], and a considerable rise in plasma histamine concentration was observed during the exercise challenge tests [9]. Conversely, the reaction seen in FDEIA is generally considered to be IgE-mediated hypersensitivity to food allergens, because IgE antibodies against the causative food allergens have been detected after skin prick or radioallergosorbent tests in the majority of FDEIA patients [14,17,19,20,23]. Therefore, we have hypothesized that exercise enhances the absorption of allergens from the gastrointestinal tract in their improperly digested or undigested forms. We utilized a gliadin-specific sandwich enzyme-linked immunosorbent assay (ELISA) and tested six patients with WDEIA to evaluate their serum gliadins levels during exercise challenge tests [38]. As a result of these experiments immunoreactive gliadins appeared in the sera of patients during the wheat-exercise combination challenge provocation tests and that these gliadins were concurrent with the onset of the allergic symptoms. However, these immunoreactive gliadins were not detected in experiments using the wheat challenge or exercise challenge alone (Fig. 4), supporting the hypothesis that exercise enhances the absorption of incompletely or undigested allergen proteins from the patients' gastrointestinal tract [38].

The enhancing effects of exercise were also investigated in four healthy subjects monitoring the levels of serum gliadins before and after eating wheat. Serum gliadin levels also increased under the same exercise and wheat challenge conditions in the healthy subjects, although they exhibited no

EGEASEQLQCERELQELQERELKACQQVMDQQLRDISPECHPVVSP
 VAGQYEQQIVPPKGGSFYGETTPPQQQLQQRIFWGIPALLKRYPSV
 TCPQVSYYPGQASPRPGQQGQQGQQGYYTSPQQPGQWQQ
 PEQGGQGYPTSPQQPGQLQQPAQGGQPGQGGQGGQGGQGG
 YPTSSQLQPGQLQQPAQGGQGGQPGQAQQGQQPGQGGQGGQ
 QGGQPGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 PTLQQLGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 QGGQPGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 PTSSQPTQSQQPGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 YYTSPQQSGGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 GGGQPGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 QPGQWQQPGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 GQLQQPAQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 QGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 QPGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 LTFSAARTGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 PKLSGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 QGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQGGQ
 KAQQLAAQLPAMCRLEGGDALSASQ

Fig. 3 Amino acid sequence of HMW-glutenin and distribution of three IgE-binding epitopes, QQPQGQ, QQPQGQGGQ, and QQSGGGQ.

allergic symptoms [38]. This indicates that exercise-enhancement of antigen absorption occurs not only in allergic patients but also in healthy subjects.

Only limited data are available shedding insight into the mechanisms of exercise-induced enhancement of intestinal absorption of food allergens into the blood circulation. In the investigation using rats sensitized to horseradish peroxidase, the protein was shown to across epithelia cells by a process comprising two phases [39]. The initial phase was the endocytotic uptake of the antigen into the enterocytes and its rapid transcytosis into the lamina propria. The second phase occurred with marked increase of antigen flux through tight junctions by a paracellular route after mast cell activation by cross-linking of IgE bound to FcεRI receptors. Several studies have shown an increased flux of certain antigens during intestinal anaphylaxis [40,41], but the specific route of enhanced uptake has not been clearly delineated. Our findings that exercise-enhanced antigen-absorption occurs even in healthy subjects suggests that there may be a mechanism independent of mast cell activation [38]. On the other hand, Katsunuma et al. reported a case of FDEIA, in which pretreatment with sodium bicarbonate inhibits the reappearance of anaphylactic symptoms as well as an elevation in plasma histamine levels following wheat and exercise provocation, suggesting a decrease in blood pH associated with exercise may play some role in mast cell activation [42].

Aspirin is another well-known trigger for anaphylaxis in FDEIA patients [17,19,20]. Harada et al. first confirmed the effects of aspirin in the induction of food anaphylaxis, even in patients with FDEIA who had no previous history of aspirin hypersensitivity or

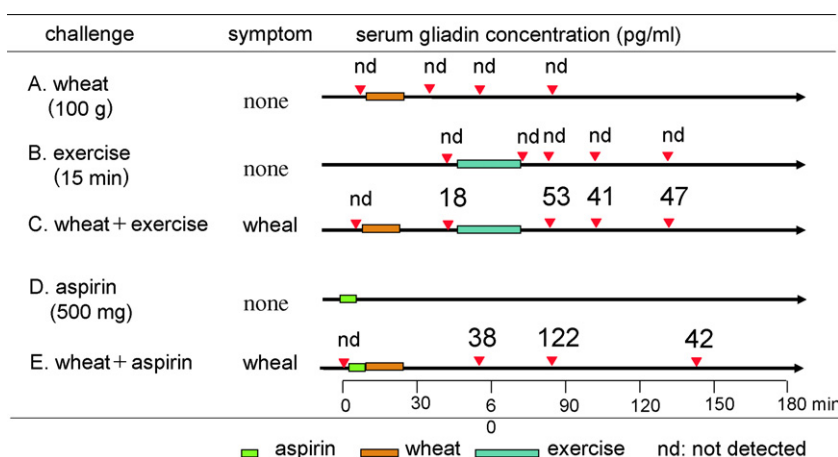


Fig. 4 Serum gliadin levels during provocation tests for the patient with WDEIA.

precipitation of symptoms by non-steroidal anti-inflammatory drugs [19]. The fact that a combined intake of causative food and aspirin could induce anaphylaxis without apparent exercise suggests two possible mechanisms in the elicitation of symptoms: (1) aspirin may upregulate antigen uptake across the intestinal epithelium and into the circulating blood, and/or (2) aspirin itself may activate mast cells in combination with IgE cross-linking through unknown mechanism(s). We demonstrated for the first time that blood gliadin levels correlate well with clinical symptoms induced by aspirin in FDEIA patients [38]. These findings support the first hypothesis that aspirin as well as exercise may both facilitate allergen absorption from the gastrointestinal tract. However, the latter possibility is also supported by the fact that skin prick tests with a causative food allergen were enhanced by pretreatment with oral aspirin in five out of eight FDEIA patients [20].

6. Diagnosis

A detailed clinical history of exercise-induced anaphylactic symptoms, especially a preceding history of all food-intake, is of particular importance for the correct diagnosis of FDEIA. Following this procedure EIA as well as cholinergic urticaria can be ruled out, and candidate causative foods can be identified.

Currently, the most useful diagnostic tests for food allergy are skin tests, *in vitro* serum food-specific IgE assays, and oral food challenges. Skin tests (a skin prick test is usually performed) and *in vitro* serum food-specific IgE assays provide some important information, however a positive reaction in skin prick test or a positive value in *in vitro* serum food-specific IgE assays do not necessarily indicate the causative foods as described above. An enzymatic immunoassay for specific IgE detection

(CAP-FEIA, Phadia, Sweden) is an accurate and standardized procedure of determination of allergen-specific IgE and is now widely used for the diagnosis of food allergy [43]. The usefulness of food-specific IgE concentrations in predicting clinical reactivity has been reported for egg, milk, peanut, and fish allergy. Cereal allergy, especially WDEIA, is not easily diagnosed using this test. Measurement of gluten-specific IgE is possible for the diagnosis of WDEIA using the CAP-system, however approximately 30% of patients with definite cases of WDEIA are also negative for gluten [37]. In addition, a considerable number of patients with atopic dermatitis have positive CAP scores for gluten, although the patients have experienced no episodes of type I allergic reactions after ingestion of wheat products. Thus, the measurement of food-specific IgE using the CAP-system alone is not a satisfactory diagnostic marker for FDEIA.

When the IgE-binding epitopes of omega-5 gliadin and HMW-glutenin were tested in the CAP-FEIA-system to determine the specific IgE to those epitope peptides, 97% (29/30) of the patients with WDEIA were found to be positive, whereas the gluten-specific IgE test positively recognized only 80% (24 of 30) of the patients as shown in Fig. 5 [37]. In addition, specific IgE binding levels in the epitope peptide-specific CAP-system were much higher than that in the gluten-specific test in most WDEIA patients, indicating a higher sensitivity using the epitope-specific system. This is due to a higher amount of epitope peptides used in the epitope-specific CAP-system than in the gluten-specific CAP-test. Ten out of 25 patients with atopic dermatitis who had no obvious allergic reaction after wheat product ingestion showed positive CAP-tests for epitope peptides indicating a low specificity of the test. When the cutoff value for a positive test was set at 1.0 kUa/L, sensitivity and specificity of

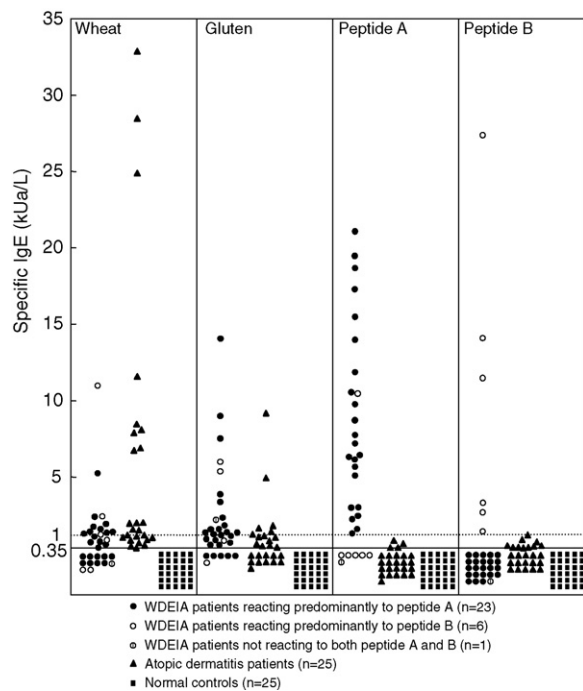


Fig. 5 Specific IgE levels to gluten and combined epitope peptides of omega-5 gliadin and high molecular weight glutenin (peptide A: KPQQSPQQFPQQIPQQQ, containing epitope peptides of omega-5 gliadin and peptide B: PTSPQQSGQGQPGQGQQ, containing epitope peptides of HMW glutenin).

the epitope peptide-specific CAP-test was satisfactory because sensitivity and specificity of the test reached to 97% (29/30) and 98% (1/50), respectively [37].

Recently, the use of recombinant food allergens, which are of a more consistent quality and quantity, have been tried to optimize the diagnostic process for many food allergies [44–46]. The efficacy of the CAP-system incorporating the new recombinant wheat allergen protein has been investigated. Matsuo et al. cloned a omega-5 gliadin gene that encodes a 439 amino acid-long protein with a calculated mass of 53 kDa and, by means of the expression system in *Escherichia coli*, constructed a water soluble recombinant C-terminal half-protein (178 amino acids) of the omega-5 gliadin that includes all IgE-binding epitopes [46]. The recombinant omega-5 gliadin was found to have an IgE antibody-binding ability comparable to natural omega-5 gliadin. When the levels of specific IgE antibodies to recombinant omega-5 gliadin were measured with CAP-FEIA-system, the value was well correlated with those of specific IgE antibody to the synthetic peptide epitopes of omega-5 gliadin conjugated to CAP-system (Fig. 6).

Challenge tests will give a definite diagnosis of FDEIA in patients with a history of occasional

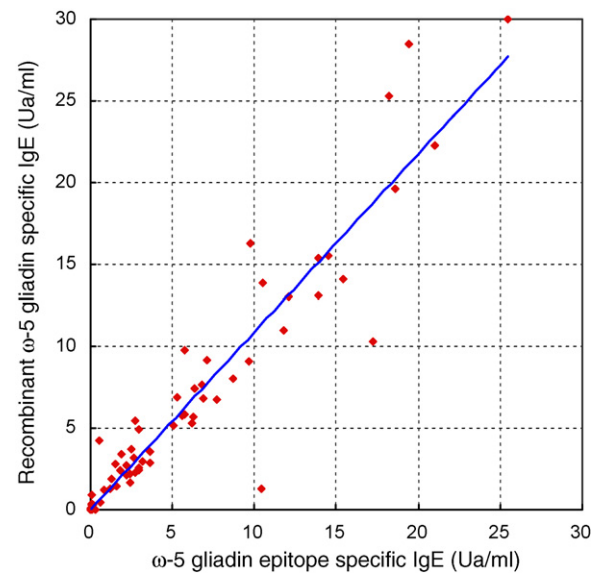


Fig. 6 Correlation between IgE values using recombinant omega-5 gliadin-CAP-system and those using omega-5 gliadin epitope peptide-CAP-system in WDEIA patients' sera.

anaphylaxis after food-ingestion. If a definite food has not been identified as the cause of the reaction, a food challenge test is necessary because identification of the causative food might be life-saving. Since food challenge alone usually fails to elicit anaphylactic symptoms, food ingestion combined with exercise is needed to confirm the causative food as well as the diagnosis [17,23]. The challenge includes food challenge alone, exercise alone, and a combination of food ingestion and exercise. The exercise challenge has typically been performed according to the protocol of Bruce et al. [47] that has been used for the diagnosis of ischemic heart disease. However, intake of a specific food followed by exercise does not always provoke the anaphylactic symptoms. Consequently, the challenge tests can only confirm the diagnosis of FDEIA in up to 70% of patients, even in the patients who have had a history of recurrent episodes of anaphylaxis during exercise after ingestion of specific foods [17,23]. Induction of anaphylactic symptoms was shown to be dependent on the amount of food allergen ingested [15], indicating that an insufficient amount of food allergen might be ingested in cases of false-negative clinical responses to allergen challenge and exercise tests. Another possible factor causing the false-negative test is an inappropriate type of exercise employed in the tests. Some other conditions such as fatigue, lack of sleep, or low temperature are believed to affect the development of the anaphylactic symptoms.

Aspirin intake has been well documented to provoke or exacerbate symptoms in several patients [17,19,20,23], thus food challenge with aspirin-pretreatment has been performed for diagnosis. In fact, several patients elicited anaphylactic symptoms after a combined challenge with aspirin and food, even without exercise, despite there being no history of patients ever experiencing any anaphylactic symptoms induced by aspirin or any other non-steroidal anti-inflammatory drugs (NSAIDs).

7. Patient education

Education regarding avoidance and management of accidental ingestion of the foods causing allergy is crucial because neither medications nor immunotherapy are presently available to continuously or consistently prevent the anaphylactic symptoms. When patients consume the causative foods either accidentally or intentionally, avoidance of exercise for 4 h after eating might be helpful to prevent the occurrence of symptoms in many cases, however this is not always safe because some patients experience anaphylaxis even after mild exercise such as walking. Individuals with a history of a life-threatening reaction are strongly recommended to carry epinephrine [48,49]. Antihistamines (H_1 -antagonists) are helpful in the treatment of urticaria/angioedema caused by food allergy and might be useful to prevent urticaria/angioedema reactions [49]. However, antihistamines show much less effectiveness in treating anaphylactic shock than epinephrine, and therefore should be never administered alone as treatment for anaphylaxis.

8. Concluding remarks

FDEIA is known as a distinct form of food allergy which is specifically induced by exercise, however our intensive investigations have revealed that exacerbating factors such as aspirin intake as well as exercise can facilitate allergen absorption from the gastrointestinal tract, indicating that FDEIA is not a special subtype of allergy but is a consequence of exercise-induced increased allergen intake and routine food allergy. Interestingly facilitation of allergen absorption into the blood circulation by intensive exercise and intake of aspirin is not a specific phenomenon for the patients with FDEIA but is likely to also occur in normal healthy subjects. Food allergy including FDEIA is now showing increasing prevalence in developed countries

[50]. Wide-use of medicines such as aspirin, which cause intestinal side effects, might be related to this increase in disease prevalence. Further research is required to prove a causal relationship between aspirin use and the development of food allergies.

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Eishin Morita graduated and received the MD degree from Hiroshima University School of Medicine in 1982. He was at the Department of Dermatology Hiroshima University School of Medicine from 1982 to 1986. He was employed as a

visiting research fellow at the Department of Dermatology, University of Kiel, the Federal Republic of Germany from 1986 to 1990. In 2002, he moved to Shimane Medical College, where he was an associate professor in the Department of Dermatology. In 2004, he was promoted to a chief professor in the Department of Dermatology, Shimane University School of Medicine. His research interests include allergic skin diseases and food allergy.

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