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Editorial



# Food-dependent Exercise-induced Anaphylaxis: The Need for Better Understanding and Management of the Disease

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▸ See the article "Evaluation of Allergenicity on a ω-5 Gliadin-Deficient Cultivar in Wheat-Dependent Exercise-Induced Anaphylaxis" in volume 14 on page 379.



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Food-dependent exercise-induced anaphylaxis (FDEIA) is characterized by the onset of anaphylaxis during or soon after physical exercise preceded by ingestion of a causative food, while the food and exercise are each tolerated separately. The first case of FDEIA was reported by Maulitz *et al.*[1] in 1979 as a late allergic reaction to shellfish following vigorous exercise. Wheat is the most common cause of FDEIA, but other grains, seafood, peanut, egg, milk, Rosaceae fruits and vegetables have also been reported as causes of FDEIA.[2,3] In some cases, symptoms may be triggered by any meal followed by exercise regardless of the food type.[4] Although FDEIA is frequently reported in young adults, epidemiologic studies are rare. A Japanese group reported the prevalence of FDEIA at 0.017% among junior high school students and 0.0047% among elementary school students.[2,5] In a multicenter anaphylaxis registry in Korea, the proportion of FDEIA was 1.2% and 3.1% in children and adults, respectively.[6] Recently, the concept of FDEIA has been expanded and described as "food-dependent cofactor-augmented anaphylaxis" or "cofactor-induced food allergy."[7,8] Reported cofactors other than physical exercise are aspirin, other analgesics, alcohol, stress, and infections.

Although increased levels of serum histamine and tryptase levels during FDEIA attacks indicate immunoglobulin E (IgE) -dependent degranulation of mast cells, the pathophysiology of FDEIA is not fully understood. Several theories to explain the mechanism of FDEIA are as follows: (i) activation of tissue transglutaminase during exercise resulting in conjugation between food allergen peptides and tissue transglutaminase, followed by IgE binding; (ii) increased gastrointestinal permeability and facilitation of allergen absorption into the circulating blood by exercise and other cofactors such as aspirin; (iii) transport of allergens to tissues containing mast cells by blood flow redistribution during exercise; and (iv) increased plasma noradrenaline levels inducing anaphylactoid symptoms.[9-12]

In most cases the diagnosis of FDEIA is made clinically based on the history of signs and symptoms consistent with anaphylaxis that have occurred during or within hours of exercise explicitly preceded by specific food ingestion, without any diagnosis that explains the clinical presentation. Typically, no symptoms are induced by exercise alone or ingestion of the culprit food in the absence of exercise. Skin testing or *in vitro* testing for food-specific IgE is generally essential during the evaluation of FDEIA to confirm the sensitization to the causative food(s). A positive provocation testing that combines the food and exercise is the most confirmative

diagnostic method, but it is not easy to implement in an actual clinical setting. Moreover, a negative challenge does not completely exclude the diagnosis because there is significant variability among patients in the intensity and duration of exercise, the amount of food to trigger symptoms, and the presence of additional cofactors necessary to reproduce symptoms. Basophil activation test combined with appropriate allergens may provide useful information in diagnosing FDEIA,[8] but is a rather demanding procedure to be carried out in the clinical setting.

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is the most frequent type of FDEIA cases, and ω-5 gliadin was first reported in 1999 as a major allergen of WDEIA in Finnish adults by Palosuo *et al.*[13] Other studies supporting ω-5 gliadin as the major allergen in WDEIA were serially published in the early 2000s.[14,15] Consequently, the development of wheat cultivars with reduced ω-5 gliadin content and studies on their allergenicity in WDEIA patients were followed. In 2011, Altenbach *et al.*[16] reported the technique to silence the expression of genes encoding ω-5 gliadins, and a lower sensitization capacity of the deletion line lacking the ω-5 gliadin locus was reported in the guinea pig by a Japanese group.[17] Waga and Skoczowski[18] found a considerable reduction (about 30%) in the immunoreactivity of genotypes lacking all ω-gliadins, but an increase in some α- and γ-gliadins were also noted. In this issue of the *Allergy Asthma Immunol Res*, Lee *et al.*[19] demonstrated the allergenicity of the new cultivar (ω5D) which has selective deletions in the ω-5 gliadins as well as some i- and m-type low-molecular-weight glutenins and γ-gliadins in 14 WDEIA and 7 classic wheat allergic patients. The specific IgE binding to the glutenins and gliadins by ω5D was significantly attenuated to about one-fourth compared to the wild-type cultivar in WDEIA patients, while no significant difference was noticed in classic wheat allergic patients. Although some low-molecular-weight glutenin subunits, ω-5 or γ-gliadins and other glutenins remain in the ω5D cultivar as reported in this new cultivar, ω5D can be considered an alternative dietary candidate for WDEIA patients, allowing a safer consumption of wheat in patients with mild-to-moderate sensitivity.

The management of FDEIA is mainly composed of appropriate treatment in cases of acute anaphylactic symptoms and education to prevent further episodes.[20] Physical exercise should be stopped immediately at any early warning signs of anaphylaxis to prevent progression to life-threatening severe symptoms, and intramuscular epinephrine should be administered promptly. In general, it is proposed to refrain from physical exercise for 4–6 hours after causative food intake but there is no standardized recommendation for the optimal prevention of FDEIA. Patients' quality of life may be significantly impaired, especially in WDEIA patients because wheat is one of the staple foods in the human diet. For FDEIA patients to minimize the risk of recurrence and not to have excessive restrictions on their daily life due to the disease, further research toward the clarification of the disease mechanism is needed, and a specific and effective preventive plan based on evidence should be provided. Additional research on all aspects of FDEIA, including the development of hypoallergenic alternatives, will provide better treatment and improve patients' quality of life.

## REFERENCES

1. Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. J Allergy Clin Immunol 1979;63:433-4.
PUBMED | CROSSREF
2. Manabe T, Oku N, Aihara Y. Food-dependent exercise-induced anaphylaxis in Japanese elementary school children. Pediatr Int 2018;60:329-33.
PUBMED | CROSSREF

3. Adachi A, Horikawa T, Shimizu H, Sarayama Y, Ogawa T, Sjolander S, et al. Soybean beta-conglycinin as the main allergen in a patient with food-dependent exercise-induced anaphylaxis by tofu: food processing alters pepsin resistance. Clin Exp Allergy 2009;39:167-73.
PUBMED | CROSSREF
4. Karadan U, Manappallil RG, Zacharia IP, Anand T. Nonspecific food dependant exercise-induced anaphylaxis with seizure: a case report. Asian J Med Sci 2020;11:94-7.
CROSSREF
5. Aihara Y, Takahashi Y, Kotoyori T, Mitsuda T, Ito R, Aihara M, et al. Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. J Allergy Clin Immunol 2001;108:1035-9.
PUBMED | CROSSREF
6. Jeong K, Ye YM, Kim SH, Kim KW, Kim JH, Kwon JW, et al. A multicenter anaphylaxis registry in Korea: clinical characteristics and acute treatment details from infants to older adults. World Allergy Organ J 2020;13:100449.
PUBMED | CROSSREF
7. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Wheat-dependent cofactor-augmented anaphylaxis: a prospective study of exercise, aspirin, and alcohol efficacy as cofactors. J Allergy Clin Immunol Pract 2019;7:114-21.
PUBMED | CROSSREF
8. Gabler AM, Gebhard J, Eberlein B, Biedermann T, Scherf KA, Brockow K. The basophil activation test differentiates between patients with wheat-dependent exercise-induced anaphylaxis and control subjects using gluten and isolated gluten protein types. Clin Transl Allergy 2021;11:e12050.
PUBMED | CROSSREF
9. Palosuo K, Varjonen E, Nurkkala J, Kalkkinen N, Harvima R, Reunala T, et al. Transglutaminase-mediated cross-linking of a peptic fraction of omega-5 gliadin enhances IgE reactivity in wheat-dependent, exercise-induced anaphylaxis. J Allergy Clin Immunol 2003;111:1386-92.
PUBMED | CROSSREF
10. Robson-Ansley P, Toit GD. Pathophysiology, diagnosis and management of exercise-induced anaphylaxis. Curr Opin Allergy Clin Immunol 2010;10:312-7.
PUBMED | CROSSREF
11. Kato Y, Nagai A, Saito M, Ito T, Koga M, Tsuboi R. Food-dependent exercise-induced anaphylaxis with a high level of plasma noradrenaline. J Dermatol 2007;34:110-3.
PUBMED | CROSSREF
12. Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. J Allergy Clin Immunol 2017;140:335-48.
PUBMED | CROSSREF
13. Palosuo K, Alenius H, Varjonen E, Koivuluhta M, Mikkola J, Keskinen H, et al. A novel wheat gliadin as a cause of exercise-induced anaphylaxis. J Allergy Clin Immunol 1999;103:912-7.
PUBMED | CROSSREF
14. Morita E, Matsuo H, Mihara S, Morimoto K, Savage AW, Tatham AS. Fast omega-gliadin is a major allergen in wheat-dependent exercise-induced anaphylaxis. J Dermatol Sci 2003;33:99-104.
PUBMED | CROSSREF
15. Matsuo H, Morita E, Tatham AS, Morimoto K, Horikawa T, Osuna H, et al. Identification of the IgE-binding epitope in omega-5 gliadin, a major allergen in wheat-dependent exercise-induced anaphylaxis. J Biol Chem 2004;279:12135-40.
PUBMED | CROSSREF
16. Altenbach SB, Allen PV. Transformation of the US bread wheat 'Butte 86' and silencing of omega-5 gliadin genes. GM Crops 2011;2:66-73.
PUBMED | CROSSREF
17. Kohno K, Takahashi H, Endo TR, Matsuo H, Shiwaku K, Morita E. Characterization of a hypoallergenic wheat line lacking ω-5 gliadin. Allergol Int 2016;65:400-5.
PUBMED | CROSSREF
18. Waga J, Skoczowski A. Development and characteristics of ω-gliadin-free wheat genotypes. Euphytica 2013;195:105-16.
CROSSREF
19. Lee J, Kim SR, Park JH, Park KH, Jeong KY, Lee JH, et al. Evaluation of allergenicity on a ω-5 gliadin-deficient cultivar in wheat-dependent exercise-induced anaphylaxis. Allergy Asthma Immunol Res 2022;14:379-92.
CROSSREF
20. Asaumi T, Ebisawa M. How to manage food dependent exercise induced anaphylaxis (FDEIA). Curr Opin Allergy Clin Immunol 2018;18:243-7.
PUBMED | CROSSREF